HHS Public Access

Author manuscript

*Child Neuropsychol*. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

*Child Neuropsychol*. 2023 November ; 29(7): 1128–1154. doi:10.1080/09297049.2023.2173162.

# Trajectories of Neurodevelopment and Opportunities for Intervention Across the Lifespan in Congenital Heart Disease

**Jacqueline H. Sanz**[1,2], **Stephany Cox**[3], **Mary T. Donofrio**[4,5], **Nobuyuki Ishibashi**[5,6], **Patrick McQuillen**[3], **Shabnam Peyvandi**[3], **Sarah Schlatterer**[5,7,8]

[1]Division of Neuropsychology, Children's National Hospital, Washington, D.C.

[2]Departments of Psychiatry and Behavioral Sciences & Pediatrics at The George Washington University School of Medicine

[3]Department of Pediatrics, Division of Developmental Medicine, Benioff Children's Hospital, University of California, San Francisco, CA

[4]Division of Cardiology, Children's National Health System, Washington, D.C.

[5]Department of Pediatrics at The George Washington University School of Medicine

[6]Center for Neuroscience Research, Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Hospital, Washington D.C.

[7]Prenatal Pediatrics Institute, Children's National Hospital, Washington, D.C

[8]Department of Neurology, The George Washington University School of Medicine and Health Sciences, Washington, D.C

## Abstract

Children with congenital heart disease (CHD) are at increased risk for neurodevelopmental challenges across the lifespan. These are associated with neurological changes and potential acquired brain injury which occur across a developmental trajectory, and which are influenced by an array of medical, socio-demographic, environmental and personal factors. These alterations to brain development lead to an array of adverse neurodevelopmental outcomes, which impact a characteristic set of skills over the course of development. The current paper reviews existing knowledge of aberrant brain development and brain injury alongside associated neurodevelopmental challenges across the lifespan. These provide a framework for discussion of emerging and potential interventions to improve neurodevelopmental outcomes at each developmental stage.

### Keywords

Congenital Heart Disease; Neurodevelopmental Outcomes; Neurodevelopmental Interventions

**Conflict of Interest**: The authors have no conflicts of interest to disclose.

## Introduction

Advances in prenatal diagnosis, neonatal and perioperative care, and medical, educational and psychosocial care have led to increased survival rates and improved outcomes for individuals with Congenital Heart Disease (CHD). Within the context of these remarkable gains, there are clear patterns of changes in brain development, brain injury risk, and associated neurodevelopmental challenges observed across the lifespan, particularly for those children requiring surgery within the first year of life (Marino et al., 2012).

These neurological differences have been referred to as a unique 'encephalopathy of CHD,' with intertwined influences of alterations in typical brain development and acquired brain injury (Volpe, 2014). That is, changes to the trajectory of brain development begin in the fetal period and are further compounded by neonatal and perioperative brain injury. There are a multitude of medical, environmental, personal, and sociodemographic risk factors that impact these trajectories. This is reflected in the resulting spectrum of neurodevelopmental outcomes associated with CHD, which are heterogenous but impact a characteristic set of skills (Cassidy et al., 2017; Sanz et al., 2021).

Most notably, neurological changes and associated neurodevelopmental challenges in CHD occur over the course of development, likely in a developmental cascade, with earlier delays or impairments impacting the continued course of both skill development and brain development (Sanz et al., 2021). This paper will review our existing knowledge of brain development, injury, and recovery over the course of the lifespan in individuals with CHD, along with associated neurodevelopmental challenges. These are used as a frame to explore potential key timepoints for interventions that might interrupt the cascade of changes described, and to review those care strategies and interventions that are currently in use or under investigation, and to reveal understudied opportunities for change.

## Prenatal Brain Development in CHD

Human brain development is a complex process with morphologic events occurring across developmental stages, and a prolonged period of refinement of connections that occurs in the third trimester and extends into the early postnatal period. Technical advancements in brain magnetic resonance imaging (MRI) have revealed an increased frequency of structural and developmental abnormalities of the fetal and neonatal brain in the setting of CHD (Peyvandi et al., 2019). It was long thought that developmental abnormalities in children with CHD were secondary to surgical and peri-operative factors, such as the need for cardio-pulmonary bypass in infancy. However, in one of the first neonatal brain MRI studies performed, Miller et al. observed that neonates with complex forms of CHD (d-transposition of the great arteries and single ventricle physiology) have evidence of delayed brain development even before going to the operating room (S. P. Miller et al., 2007). Subsequently, Limperopoulos et al. observed these same patterns in the 3$^{rd}$ trimester fetus with complex CHD, demonstrating that delayed brain development begins in late gestation (Limperopoulos et al., 2010). Importantly, this divergence from typical patterns of brain development begins in the 3$^{rd}$ trimester of fetal life—a time of rapid brain growth and development that presumably requires a significant increase in oxygen and substrate

delivery. Overall, late gestation fetuses and newborns with significant CHD have smaller brains (Limperopoulos et al., 2010) with simplified cortical gyrification (Clouchoux et al., 2013), less organized white matter tracts (Miller et al., 2007), and immature biochemistry (Limperopoulos et al., 2010). With advancements in fetal MRI, including technology to account for fetal and maternal motion, there is new evidence that fetuses with CHD have decreased cerebral oxygenation (Peyvandi et al., 2021). Importantly, perinatal impairments in brain growth appear to affect subsequent brain growth trajectories (Ortinau et al., 2018) and neurodevelopmental outcomes in infancy (Sadhwani et al., 2022). The etiology of delayed brain development in the late gestation fetus with CHD is likely multi-factorial, with contributions from genetic abnormalities, cardiovascular physiology, and environmental factors.

## Cardiovascular physiology

The third trimester of fetal life is marked by a period of rapid brain growth and refinement of connections. Consequently, blood flow to the fetal brain increases and is estimated to be approximately 25% of the combined ventricular output in the third trimester (Rudolph, 2018). In the normal fetus, cerebral blood flow is supplied by highly oxygenated blood from the ductus venosus preferentially streaming across the foramen ovale to the left atrium and ventricle. Depending on the sub-type of CHD, cerebral blood flow and thus oxygen delivery can be impaired. For example, in D-transposition of the great arteries, the aorta and pulmonary artery are transposed, and thus the higher oxygenated blood reaches the pulmonary vasculature as opposed to the aorta. In hypoplastic left heart syndrome, inadequate left heart structures lead to reversal of blood flow in the foramen ovale, with mixing of oxygenated and deoxygenated blood in the right ventricle and in the cases of aortic atresia, retrograde flow in the ascending aorta.

Multi-modal fetal imaging techniques have demonstrated how this altered circulation can lead to flow disturbances affecting in-utero growth and brain development. Cerebral Doppler ultrasound can assess cerebral vascular resistance in the middle cerebral artery (MCA). Several studies have observed altered cerebral blood flow patterns in the fetus with CHD (Donofrio et al., 2003; Kaltman et al., 2005). In particular, fetuses with hypoplastic left heart syndrome consistently have the most abnormal patterns, with decreased resistance in the MCA thought to be an autoregulatory phenomenon in response to decreased flow and oxygenation to the brain, similar to the growth restricted fetus. However, it is unclear if fetuses with CHD have normal autoregulatory capacities of the brain. A recent study measuring MCA vascular resistance at baseline and after brief administration of maternal hyperoxia demonstrated variable response across different sub-types of CHD (Hogan et al., 2021). This may reflect differences in cerebral autoregulatory capacities in the setting of complex CHD. More recently, novel fetal cardiac MRI techniques have been developed, which enables measurements of flow and oxygen saturation in fetal blood vessels. By combining fetal brain MRI and cardiovascular magnetic resonance, Sun et al. found a correlation between fetal cerebral oxygen consumption and brain size (estimated brain weight) among fetuses with complex CHD in late gestation (Sun et al., 2015). Specifically, there was a direct correlation between estimated brain weight and cerebral oxygen consumption and a modest association between cerebral oxygen delivery and brain

size. Both ultrasound and MRI based studies support the hypothesis that aberrations in cardiovascular physiology can result in decreased perfusion and oxygen delivery to the brain affecting brain development and increasing susceptibility to brain injury (Peyvandi et al., 2019).

### Environmental influences on the developing fetal brain and the role of the placenta

Natural experiment studies and other observational studies have demonstrated a link between prenatal maternal stress and developmental outcomes in offspring among children without congenital anomalies (Scheinost et al., 2016, 2017). The biological mechanism of these findings is hypothesized to be through epigenetic mechanisms at the level of the placenta acting as a mediator of maternal and environmental signals to the developing fetus (Bale, 2015; Nugent & Bale, 2015). Not surprisingly, maternal stress levels are noted to be significantly higher after the diagnosis of a fetal anomaly including fetal CHD (Rychik et al., 2013). In a study of pregnant women carrying a fetus with CHD, 65% experienced significant stress, 44% reported anxiety and 29% reported depression. Furthermore, maternal stress and anxiety was associated with smaller hippocampal and cerebellum volumes in the fetus with CHD (Wu et al., 2020).

Placental pathology is known to be abnormal in pregnancies affected by significant CHD, and there is a relationship between cardiac development and placental health which in combination can contribute to in utero brain development. Common abnormalities on pathologic exam have included thrombosis, infarction, chorangiosis, immature villi and abnormal placental perfusion (Rychik et al., 2018; You et al., 2020). In addition, recent studies demonstrate abnormalities in placental vasculature in the setting of CHD with high rates of vascular malperfusion lesions (Leon et al., 2022). It is unclear whether placental abnormalities precede the development of CHD or if the placental pathology develops secondary to abnormal cardiovascular physiology. There is likely a complex interplay between maternal health, placental function, and developmental programming in the fetus that can have long term effects on outcomes such as neurodevelopment, though future studies are necessary to identify these causal pathways.

## Possible prenatal intervention strategies

Given the multi-factorial nature of delayed fetal brain development in utero, identifying an intervention to optimize outcomes is challenging. For certain complex forms of CHD, fetal cardiac interventions to change the natural history of disease have been in use for several years (Schidlow et al., 2017), though the impact of altering cardiovascular physiology on long term developmental outcomes remains unclear (Laraja et al., 2017). Trials and experiments are underway to assess the utility of maternal hyper-oxygenation therapy, which is thought to increase oxygen flow to the brain, though it is unclear if this therapy holds promise given the potential impact on the placenta as well as flow patterns in the fetus (Edwards et al., 2019; Li et al., 2022). Behavioral interventions in utero to manage maternal stress hold great promise in the general population (Li et al., 2022) and can be applied to mothers with a fetal anomaly. Finally, animal models are underway to understand complex and cumulative events in the developing cortex and white matter and

for development of potential neuroprotective approach (Leonetti et al., 2019; Morton et al., 2015). Studies using a large animal model found that neural stem/progenitor cells contribute to perinatal corticogenesis, and suggest that restoration of neurogenic potential of the unique cell population is a candidate therapeutic target for improving cortical growth (Morton et al., 2017). In a rodent model of chronic hypoxia, treatment with tetrahydrobiopterin (BH4) mitigated the deleterious effects of chronic hypoxia on the developing white matter (Romanowicz et al., 2019). Because BH4 is already approved by the FDA and shown to be safe during pregnancy, there is translational potential for BH4 to become a new neuroprotective therapy for fetuses with CHD. In addition, genetic etiologies are now recognized as a very important contributor. Integrative approaches involving genetics, cell biology, and molecular biology to model brain development in CHD will play a key role in defining the underlying causes of brain dysmaturation and optimal windows for treatment to improve neurodevelopmental outcomes in CHD.

## Neonatal Brain Development and Injury in CHD

As outlined previously, differences in brain development begin in the fetal period in CHD, and may be related to alterations in brain perfusion and oxygenation (Petit et al., 2009; Sethi et al., 2013). Neonates with TGA, ToF, and HLHS have significantly smaller head circumference (HC) than children without CHD (Barbu et al., 2009; Manzar et al., 2005; Rosenthal, 1996; Shillingford et al., 2007), which may be related to these differences in fetal brain development. Newly acquired brain injury is common among neonates with critical CHD, and this population is known to be at high risk for neurologic and neurodevelopmental differences (Donofrio et al., 2011; Licht et al., 2009; S. P. Miller et al., 2007; Sarajuuri et al., 2012; Shillingford et al., 2007). Brain injury and neurologic outcomes are due to multiple, cumulative influences beginning in the fetal period and extending throughout a survivor's lifetime (Donofrio & Massaro, 2010; Limperopoulos et al., 1999, 2000; Mulkey et al., 2013). .

### Trouble Transitioning: Fetal Predictors of Brain Injury

Delayed brain development, in particular, has been shown to correlate with abnormal postnatal brain development and pre-and postoperative brain injury in neonates with CHD (Andropoulos et al., 2010; Beca et al., 2013; Brossard-Racine et al., 2016; Claessens, Khalili, et al., 2019; Dimitropoulos et al., 2013). Preoperative brain injury in CHD appears to be strongly related to microstructural and metabolic brain development (Dimitropoulos et al., 2013), and may be related to differences in the cerebral circulation (Ortinau et al., 2012). Specific markers of delayed brain development, including enlarged ventricular and extra-axial CSF spaces (Brossard-Racine et al., 2016; Claessens, Khalili, et al., 2019), brain maturation scores (Andropoulos et al., 2010; Beca et al., 2013), and abnormal microstructural and metabolic brain development (Dimitropoulos et al., 2013) are associated with more severe pre-and post-operative brain injury.

Cardiac physiology and timing of diagnosis have also been associated with the degree of brain injury (Peyvandi et al., 2016; Peyvandi, Kim, et al., 2018). Single-ventricle physiology has been most clearly associated with a higher risk for postoperative brain injury compared

to newborns with TGA (Beca et al., 2013; Limperopoulos et al., 2000; Mcquillen et al., 2007; Mulkey et al., 2013; Peyvandi, Kim, et al., 2018). Interestingly, prenatal diagnosis of single-ventricle heart disease or transposition of the great arteries may be protective, as prenatally diagnosed neonates with CHD have a less severe postnatal brain injury than postnatally diagnosed neonates (Peyvandi et al., 2016).

## Contributing Factors to Neonatal Brain Injury

There are multiple risk factors for pre-and postoperative brain injury in neonates with CHD (Table 1). Physiologic factors that have been most commonly associated with brain injury include hypoxemia and time to surgery (Lynch et al., 2014; Petit et al., 2009), hypotension (Dimitropoulos et al., 2013; Galli et al., 2004; Mcquillen et al., 2007), and decreased regional cerebral oxygen saturation (rSO2) (Dent et al., 2005; Mcquillen et al., 2007). Lower preoperative oxygen saturation has been associated with more severe preoperative brain injury in studies evaluating neonates with heterogeneous CHD diagnoses, and in TGA, specifically (Block et al., 2010; Dimitropoulos et al., 2013; Petit et al., 2009). Preoperative hypotension is predictive of preoperative brain injury score in CHD (Dimitropoulos et al., 2013). Autonomic function is immature in infants with CHD (Mulkey et al., 2019), and worse autonomic function correlates with preoperative brain injury scores in this population (Schlatterer et al., 2021).

Aberrant electrocortical activity, as measured by EEG and amplitude-integrated EEG (aEEG), is common among neonates with CHD, and is associated with abnormal brain development and brain injury (Mebius et al., 2018; Mulkey et al., 2015). Abnormal background activity on aEEG is highly associated with pre-operative brain injury (60% in one study)(3,4) as well as brain atrophy (low brain volume) prior to surgery (Mulkey et al., 2015). Immature structural and microstructural brain development also correlates with abnormal brain electrical activity (Birca et al., 2016). Neonates with immature structural brain development and pre-operative brain injury had increased high-frequency connectivity on EEG, and neonates with delayed microstructural brain development had weaker low-frequency connectivity on EEG (Birca et al., 2016). Moreover, failure to recover continuous background activity on aEEG by 48 hours post-operatively is associated with mortality and worse neurodevelopmental outcomes on BSID-III at age two years (Gunn et al., 2012). Thus, early differences in aEEG and EEG are highly associated with developmental outcomes and mortality, indicating long-term impact (Birca et al., 2016; Gunn et al., 2012; Mebius et al., 2018; Mulkey et al., 2015).

Postoperatively, brain injury is associated with lower postoperative oxygen saturation (Galli et al., 2004), hypotension in the first 24–48h following surgery (Dimitropoulos et al., 2013; Galli et al., 2004; Mcquillen et al., 2007), and lower postoperative regional cerebral rSO2 (Galli et al., 2004; Mcquillen et al., 2007). However, one recent study did not find an association between lower postoperative cerebral rSO2 and postoperative brain injury (Claessens, Jansen, et al., 2019).

Surgical considerations associated with neonatal brain injury in CHD include time to surgery (Lynch et al., 2014; Petit et al., 2009), need for balloon atrial septostomy (BAS) (Block et al., 2010; Dimitropoulos et al., 2013; Kelly et al., 2019; Mcquillen et al.,

2006), and prolonged bypass and circulatory arrest times (Beca et al., 2013). Both pre- and postoperative white matter injury are associated with a longer time between birth and surgery (Lynch et al., 2014; Petit et al., 2009). This association may be explained by a progressive decrease in cerebral tissue oxygenation between birth and surgery in TGA or HLHS (Lynch et al., 2018). BAS is associated with stroke in several studies (Block et al., 2010; Dimitropoulos et al., 2013; Kelly et al., 2019; Mcquillen et al., 2006), and prolonged cardiopulmonary bypass and circulatory arrest times correlate with new postoperative white matter injury (Beca et al., 2013). Overall, infants with CHD undergo a complex clinical course during which they are likely to experience multiple physiologic changes that may contribute to development of brain injury.

## Neuroimaging predictors of later outcomes

Neonates with CHD may experience two separate but related processes that contribute to neurodevelopmental outcomes, namely, delayed brain development and brain injury. Structural brain immaturity during the neonatal period is associated with neurodevelopmental outcomes in survivors of CHD at 2 years of age (Beca et al., 2013), and another study revealed an association between smaller cortical gray matter and cerebellar volumes and lower fine motor scores at 9 and 18 months (Stegeman et al., 2022).

The relationship between brain injury and neurodevelopmental outcomes in CHD is an area of active investigation. Neonatal white matter injury, particularly involvement of the posterior limb of the internal capsule, is associated with lower IQ and more severe motor and attention deficits in school-age survivors of CHD (Claessens et al., 2018). One study showed that preoperative white matter injury correlates with lower Bayley Scales of Infant and Toddler Development III scores at age 12 months in CHD (Andropoulos et al., 2012). Another study found that moderate to severe WMI before or after surgery is associated with lower motor scores at 2.5 years, but not 12 months (Peyvandi, Chau, et al., 2018). Clinically silent, small neonatal strokes were not associated with adverse ND outcomes and even trended to better outcomes in TGA (Peyvandi, Chau, et al., 2018). However, there does appear to be an association between acute ischemic stroke in the corticospinal tract and abnormalities of muscle tone and gross motor delay, and severe ischemic brain injury is associated with a diagnosis of cerebral palsy in CHD (Stegeman et al., 2022). In addition, less is known regarding the association between early alterations in brain development or brain injury and longer-term neurodevelopmental outcomes in school age, adolescence, or adulthood.

## Genetic Influences on Neurodevelopment

CHD has strong heritability, and a genetic abnormality can be identified in up to 50% of syndromic CHD and 10% of non-syndromic sporadic cases (Homsy et al., 2015). Genetic anomalies include chromosomal duplication or deletion (aneuploidy, 13%), copy number variation (10%), de novo single nucleotide variant (10%) (Zaidi & Brueckner, 2017). Aneuploidies were the earliest genetic anomalies to be linked to CHD and have well described association with adverse neurodevelopmental outcome (e.g., Down, Turner syndrome). Gaynor et al. were first to focus on the importance of patient specific factors, including genetic syndromes and ApoE genotype for neurodevelopmental outcome in early

single center studies (Gaynor et al., 2007) subsequently confirmed in secondary analyses of prospective trials (Newburger et al., 2012). Review of published outcome studies over two decades, found the presence of genetic/extracardiac anomaly as a significant risk factor for worse neurodevelopmental outcome (Gaynor et al., 2015). With improvements in genomic sequencing technology, multicenter projects have embarked on large scale sequencing efforts (Hoang et al., 2018). De novo variants in genes with high heart and brain expression were identified in 20% of subjects with CHD and neurodevelopmental delay but only 2% with isolated CHD (Homsy et al., 2015). Rare de novo variants in isolated CHD overlap substantially with those identified in children with autism (Jin et al., 2017). These include genes involved in chromatin remodeling, cilia genes and signaling pathways involving Notch and Ras known to be important for both brain and heart development (Zaidi & Brueckner, 2017). Additionally, de novo damaging variants were associated with post-operative outcomes in CHD (Boskovski et al., 2020). Together, this suggests that genetic variants can affect neurodevelopmental outcomes independently, but also as potential modifiers of neurodevelopmental outcomes in CHD patients. This highlights the need for a systematic search and inclusion of genetic risk factors in neurodevelopmental outcome prediction models in CHD.

### Neurobehavioral Outcomes in the Neonatal Period

Neurodevelopmental impairments are present even in the earliest stages of development. Neonatal evaluations have suggested a range of impairments, that are present even prior to surgical intervention. Compared with typically developing term neonates, neonates with CHD are known to have poorer automatic and motor regulation, lower attention and arousal scores, poorer self-regulation, and poor feeding (Butler et al., 2017, 2019; Desai et al., 2023; Hogan et al., 2018). Neonatal attentional and self-regulation scores have been of particular interest, since they may relate to improved feeding at discharge (Gakenheimer-Smith et al., 2019) and to later motor delays, but not later cognitive or language delays (Campbell et al., 2022). Poor feeding also predicts worse motor outcomes (Medoff-Cooper et al., 2016).

## Interventions in the Neonatal and Perioperative Period

Identified risk factors for brain injury and altered development can suggest opportunities for neuroprotective interventions that may prevent injury and promote development, leading to improved neurodevelopmental outcomes.

Potential roles of acute and chronic hypoxic ischemic and inflammatory mechanisms have led to trials of maternal progesterone in the fetal period (NCT02133573) and perioperative allopurinol (NCT04217421). An initial single center trial of allopurinol before, during and after surgery did not show significant benefit to infants with two ventricle physiology but may have decreased adverse cardiovascular events (Clancy et al., 2001). The consistent finding that increased time to surgery is associated with risk of WMI in both TGA and HLHS newborns (Lim Jessie Mei et al., 2019; Lynch et al., 2014; Petit et al., 2009) suggests that early surgery, when feasible, would be an effective non-pharmacologic intervention.

Lower postoperative blood pressure has been associated with increased risk of new postoperative white matter injury (Galli et al., 2004; Mcquillen et al., 2007), suggesting

the simple intervention of targeting higher blood pressures with preload, inotropic support or vasopressors. While this is likely to be well tolerated and beneficial in newborns with TGA, concern arises for postoperative management of HLHS where intraoperative and postoperative afterload reduction have improved survival after the Norwood procedure by preventing episodes of elevated systemic vascular resistance and low cardiac output syndrome (Hoffman et al., 2021). To achieve the optimal balance between cerebral perfusion and overall cardiac output with single ventricle physiology will likely require individualized precision therapy guided by new methods for bedside monitoring of cerebral blood flow, oxygenation and autoregulation along with cardiac output.

A final area of concern and opportunity relates to exposure of the vulnerable neonatal brain to repeated anesthetics, narcotics and benzodiazepines that have been associated with neurotoxicity and programmed neuronal cell death (Ing et al., 2022; Sarić et al., 2022). These findings, while well established in animal models, are a topic of multiple clinical research studies to establish their significance in humans (Andropoulos et al., 2014; McCann et al., 2019). Nevertheless, neuroprotective clinical trials have been proposed using putative non-neurotoxic and possibly directly neuroprotective anesthesia and sedation with dexmeditomidine. Trials are also underway examining the delivery of mesenchymal stromal cells through cardiopulmonary bypass as a neuroprotective measure, as this has been shown to protect stem/progenitor cells in the subventricular zones, and to promote migration of neuroblasts in animal models (Maeda et al., 2020). A major challenge to neuroprotective trials in CHD newborns is the need for early surrogate outcome measures that reliably predict long-term childhood and adult neurodevelopmental outcomes.

## Developmental care for Neonates and Infants

Recently, more focus has been placed on neurodevelopmental care in the CICU setting (Lisanti et al., 2016; Torowicz et al., 2012). Individualized developmental care in the ICU setting is known to improve neurobehavioral functioning and structural development in preterm infants (Als et al., 2004). Currently, developmental care is variable among CICUs within North America (Sood et al., 2016), in part because critically ill infants with CHD face unique challenges (Lisanti et al., 2019). Proposed models for developmental care in the CICU include the following elements: parental engagement/family-centered care; an individualized, cue-based plan; and an emphasis on a supportive hospital environment, with particular attention to circadian rhythms, noise/light levels, feeding, social interaction/play, kangaroo care, and developmentally considerate approaches to medical procedures (Desai et al., 2023; El-Farrash et al., 2020; Lisanti et al., 2019; Peterson & Evangelista, 2017). Interdisciplinary engagement, including parents, speech/language pathologists, physical/occupational therapy, child/family life therapists, psychology, social work, dieticians, nurses, and physicians is critical for implementation of any successful developmental care program in the CICU (Butler et al., 2017; Peterson & Evangelista, 2017), and a well-planned process of implementation with a strong commitment from leadership and staff is necessary for success (Sood et al., 2016). The inclusion of parents, families, and children with CHD in the design of supportive psychosocial interventions is also critically important to ongoing research (Sood et al., 2022). Many CICUs are beginning to implement their own

developmental care programs based on the above ideas, and the community of caregivers and families of CHD patients await further studies to determine their long-term impact.

## Neurodevelopmental Outcomes from Infancy to Adulthood

The broad range of influences on the brain, beginning in fetal life and continuing through the neonatal and perioperative periods, fundamentally alter the trajectory of brain development and associated neurodevelopmental skills. Just as CHD is heterogeneous, outcomes can be quite varied, and often involve a range of neurocognitive domains (Cassidy et al., 2017).

For infants and toddlers, early difficulties with feeding, motor development, language acquisition, and self-regulation are observed (Brosig et al., 2007; Clancy et al., 2020; Latal, 2016; Ware et al., 2020). As children enter school, which presents increased cognitive, academic, and social-emotional demands, additional challenges become evident. Specifically, weaknesses in attention, executive functioning, visual-spatial processing, and academic achievement emerge (Bellinger & Newburger, 2010; Cassidy et al., 2015, 2017; Griffin et al., 2003; Sanz et al., 2017), as well concerns for social cognition, mood, emotional and behavioral regulation, and/or anxiety (Bellinger et al., 2009; Kovacs et al., 2009; Wilson et al., 2015). There are also higher rates of neurodevelopmental disorder diagnoses (ADHD, autism spectrum disorder, learning disabilities) in children with CHD compared to the general population (Loblein et al., 2022; Razzaghi et al., 2015; Ryan et al., 2019; Tsao et al., 2017; Verrall et al., 2019), with increased risks and poorer outcomes for those with comorbid genetic conditions (Latal, 2016; Marino et al., 2012; Wernovsky, 2006). Further, deficits in these areas can hinder the development of daily living (adaptive) skills needed to successfully navigate the transition to adulthood and ultimately achieve independence (Cassidy et al., 2017; Ilardi et al., 2017).

In addition, with improving care, there is now a growing population of adults with CHD, and adults with CHD now outnumber children with CHD (Marelli et al., 2014). Despite this, we have an extremely limited understanding of the continued evolution of neurodevelopmental concerns over the lifespan, particularly during the aging process. Though mechanisms are poorly understood, underlying disease factors present increased risk for vascular problems and acquired cardiovascular events (Keir et al., 2019; Melazzini et al., 2019). These presumably contribute to substantially increased rates of dementia and neurocognitive decline in older adults with CHD, a topic which remains woefully understudied (Keir et al., 2019).

Though research up to this point has generally focused on specific skills sets or diagnoses in a cross-sectional fashion, researchers and clinicians have been encouraged to shift their conceptual framework away from static models that define a unitary, “neurodevelopmental signature,” towards a dynamic conceptual framework that includes a broader range of outcomes that interact and evolve over time, in a developmental cascade (Sanz et al., 2021). When viewed this way, interventions across the lifespan become important to interrupting these cascades and promoting improvement in neurodevelopmental trajectories. An emerging lifespan perspective also becomes critically important.

## Interventions Across the Lifespan

Despite this, to date there has been notably less focus on the development and implementation of interventions for the CHD population, with only a small number of single-center investigations focused on interventions for children, adolescents, and young adults with CHD (Calderon & Bellinger, 2015; Cassidy et al., 2021). The efficacy of intervention programs developed and implemented for high-risk populations such as children born preterm and those diagnosed with chronic medical conditions and/or neurodevelopmental disorders is well documented in the literature (Case-Smith, 2013; Spittle et al., 2007). As there are many specific areas of concern that are shared between chronic medical conditions, including CHD, these interventions offer a reasonable starting point for developing intervention strategies.

### Interventions in Infancy and Early Childhood

The importance and efficacy of direct early intervention services (e.g., physical therapy, occupational therapy, speech and language therapy) for children who are at increased risk for or diagnosed with neurodevelopmental disability is well established (Majnemer, 1998; Nores & Barnett, 2010). While these services are frequently utilized by young children with CHD, little is known about the longitudinal impact of these child-directed therapies for this specific population. Parent-oriented psychoeducational interventions for young children with CHD, investigated through a series of controlled trials conducted as part of the Congenital Heart Disease Intervention Project (CHIP), have demonstrated improved cognitive development, maternal adjustment, and family functioning (McCusker et al., 2010, 2012; van der Mheen et al., 2019).

### Interventions for Attention/Executive Function

Across medical and neurodevelopmental disorder populations, there is a growing interest in neurocognitive interventions, particularly to address executive functioning deficits; however, to date, the effectiveness of these programs is mixed (Diamond & Ling, 2016; Melby-Lervåg & Hulme, 2013). A single-center study examining the effectiveness of a computerized neurocognitive intervention (Cogmed) for adolescents with CHD found no improvement in the primary outcome measure (working memory), but improvements in inhibitory control and parent-report of cognitive regulation were reported at 3-month follow-up (Calderon et al., 2020). Pharmacological treatment of symptoms of ADHD (inattention, hyperactivity, impulsivity) is often the most effective treatment for children and adolescents (Wolraich et al., 2019). The AHA released a scientific statement in 2008 (Vetter et al., 2008), with considerations for individuals with CHD recommending thorough evaluation and continued monitoring due to the cardiovascular effects of stimulant medication. However, to date there have not been any studies investigating the efficacy of these medications for individuals with CHD with or without diagnosis of ADHD. This is also the case for pharmaceutical treatment of mood and anxiety disorders in this population, which has not been directly studied.

### Social-Emotional Functioning and Transition to Adulthood

Interventions to address social-emotional functioning are especially crucial during adolescence and adulthood given the bidirectional relationship between psychosocial

and medical health (Kovacs & Bellinger, 2021), though few programs have been evaluated. Aerobic/physical activity programs have been shown to have positive effects on psychosocial outcomes, cognitive functioning, and quality of life based on self- and proxy-report (Dulfer et al., 2017). While some psychosocial intervention protocols have been described and determined feasible for adolescents and adults with CHD, there is limited evidence for the efficacy of these interventions (Tesson et al., 2019).

In addition to interventions that directly target psychosocial and cognitive health in adolescents and young adults, interventions to address loss to medical follow up have become more important. Namely, transition to continued specialized medical care is critical to reduce morbidity and mortality, and additional invasive interventions, which presumably would also improve psychological and neurocognitive outcomes over the remainder of the lifespan (Kollengode et al., 2018; Moceri et al., 2015; Nitta et al., 2021). There is also a more recent focus on developing interventions focused on preparing adolescents with CHD to enter adult care. One such nurse-led program has demonstrated efficacy in improving transition readiness (Mackie et al., 2018). Implementation of another CHD Transition Clinic intervention, including focused teaching, completing of self-assessment questionnaires, and tracking through a clinical registry, resulted in improved follow-up rates and self-ratings of transition readiness (Gaydos et al., 2020). Additional clinical trials geared towards improving independence and mental health over the course of the transition to adulthood are underway (Saarijärvi et al., 2021).

Despite the rapidly increasing population of older adults with CHD, the topic of monitoring and intervention in this group remains understudied and in its early phases (Keir et al., 2019). From a practical standpoint, few centers offer neurodevelopmental monitoring past adolescence and young adulthood; indeed, most centers still focus care on early childhood (T. A. Miller et al., 2020). While expansion of neurodevelopmental care into adulthood presents logistical challenges and would require collaboration across specialties, this should be viewed as a critical opportunity to improve long term care and outcomes.

## Dilemmas and Future Directions

In individuals with CHD, alterations to the trajectory of brain development begin in utero, evolve over time, and are compounded by additional injury. These interact with a multitude of medical and demographic factors and lead to a heterogeneous array of adverse neurodevelopmental outcomes. Improved understanding of brain development in the context of these factors provides us with a conceptual framework for the development of targeted interventions that might improve neurodevelopmental trajectories and outcomes.

Despite the promising interventions described above, there are several gaps in our understanding of neurodevelopment in CHD that limit our progress. Firstly, the majority of research on neurodevelopment in CHD is cross-sectional, with fewer longitudinal studies in limited cohorts (for a review, see Sanz et al., 2021). As a result, we have a poor understanding of the relationship between early neurological and neurodevelopmental findings and later outcomes at school age, adolescence, and young adulthood. It is likely that many of the impacts of these early alterations to fetal and brain development manifest

in later development, though these connections have not yet been clearly characterized. We also have limited data regarding the *efficacy* of earlier interventions on subsequent neurodevelopmental trajectories and outcomes. Additionally, the heterogeneity of this patient population presents a significant research challenge. These factors highlight the need for larger, collaborative clinical data registries that will allow for more complex analyses of factors that contribute to neurodevelopmental trajectories across the lifespan. Fortunately, these collaborative efforts are underway, with the Cardiac Neurodevelopmental Outcome Collaborative and Cardiac Networks United leading effort to establish longitudinal, multisite registries to answer these questions (Gaies et al., 2019; Marino et al., 2020).

Additionally, social determinants of health have consistently been a significant contributor to both medical and neurodevelopmental outcomes in CHD (Lopez et al., 2022). These social determinants of health impact even the earliest stages of care, with lower rates of prenatal diagnosis (Krishnan et al., 2021) and poorer surgical outcomes (Gallegos et al., 2022) in specific demographic groups. Emerging research also strongly suggests that socioeconomic factors are important, primary drivers of neurodevelopmental outcomes in CHD (Bucholz et al., 2020; Favilla et al., 2021), and that the impacts of socioeconomic factors not only persist, but become more pronounced over the course of a child's development (Bucholz et al., 2021). Our understanding of racial and socioeconomic contributors to neurodevelopmental outcomes is inadequate and needs to become a focus of continued research. Important barriers to address include improved inclusion of diverse populations in research, development of improved culturally and linguistically appropriate measurement tools for neurodevelopmental and psychological outcomes in diverse populations, and improved representation of diverse populations in our clinical and research teams (Sanz et al., 2021). Though addressing these barriers will improve our *understanding* of the issue, we also need clear, actionable changes to our care pathways and specific interventions to address these inequities in neurodevelopmental and health outcomes. Examples of this may include interventions to improve access to neurodevelopmental evaluations, which may improve access to needed therapies or early intervention services that are currently underutilized in CHD (Mussatto et al., 2018; Brosig Soto et al., 2011). Other possible interventions include supporting parents in providing a more stimulating home environment to promote cognitive development (Bonthrone et al., 2021).

Along these lines, we suspect that addressing disparities in *access* to clinical care, specifically equitable participation in formal neurodevelopmental follow-up programs, is critical. This is needed to provide earlier identification and clear documentation of neurodevelopmental problems, which is often required in order to access needed therapies and services in the community. Despite this, there are likely financial barriers (e.g., insurance coverage), language barriers, and cultural barriers that reduce access to needed care and thus create disparities in neurodevelopmental trajectories. Breaking down these barriers to care across the lifespan will also be critical to improving outcomes for *all* individuals with CHD.

In sum, we are now developing a better understanding of neurological and neurodevelopmental trajectories in individuals with CHD. This understanding should now begin to serve the development and evaluation of specific intervention strategies to improve

the trajectory, with targets for intervention across the lifespan, beginning in fetal life and continuing through adulthood. The development of large-scale registries and collaborations will be necessary to better understand the long-term consequences of these interventions. Finally, improved inclusion of diverse populations in our clinical and research efforts will be critical to begin to weave in an understanding of the impacts of social determinants of health.

## Funding Sources:

National Institutes of Health grant R01HL139712 (N.I.) National Institutes of Health grant R01HL146670 (N.I.) National Institutes of Health grant R21NS127051 (N.I.) National Institutes of Health grant R33HL146394 (N.I.) Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Medical Research Program under Award No. W81XWH2010199 (N.I.)

## References

Als H, Duffy FH, Mcanulty GB, Rivkin MJ, Vajapeyam S, Mulkern RV, Warfield SK, Huppi PS, Butler SC, Conneman N, Fischer C, & Eichenwald EC (2004). Early Experience Alters Brain Function and Structure. Pediatrics, 113(4), 846–857. 10.1542/peds.113.4.846 [PubMed: 15060237]

Andropoulos DB, Ahmad HB, Haq T, Brady K, Stayer SA, Meador MR, Hunter JV, Rivera C, Voigt RG, Turcich M, He CQ, Shekerdemian LS, Dickerson HA, Fraser CD, Dean McKenzie E, Heinle JS, & Blaine Easley R (2014). The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: A retrospective cohort study. Paediatric Anaesthesia, 24(3), 266–274. 10.1111/pan.12350 [PubMed: 24467569]

Andropoulos DB, Easley RB, Brady K, Mckenzie ED, Heinle JS, Dickerson HA, Shekerdemian L, Meador M, Eisenman C, Hunter JV, Turcich M, Voigt RG, & Fraser CD (2012). Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation. The Annals of Thoracic Surgery, 94(4), 1250–1256. 10.1016/j.athoracsur.2012.04.050 [PubMed: 22748448]

Andropoulos DB, Hunter JV, Nelson DP, Stayer S, Stark AR, McKenzie ED, Heinle JS, Graves DE, & Fraser CD (2010). Brain immaturity is associated with MRI brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. Journal of Thoracic Cardiovascular Surgery, 139(3), 543–556. [PubMed: 19909994]

Bale TL (2015). Epigenetic and transgenerational reprogramming of brain development. Nature Reviews. Neuroscience, 16(6), 332–344. 10.1038/nrn3818 [PubMed: 25921815]

Barbu D, Mert I, Kruger M, & Bahado-Singh RO (2009). Evidence of fetal central nervous system injury in isolated congenital heart defects: Microcephaly at birth. American Journal of Obstetrics and Gynecology, 201(1), 43.e1–7. 10.1016/j.ajog.2009.03.029

Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, Finucane K, Brizard C, Dance B, & Shekerdemian LS (2013). New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. Circulation, 127(9), 971–979. 10.1161/CIRCULATIONAHA.112.001089 [PubMed: 23371931]

Bellinger DC, & Newburger J (2010). Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease. Progress in Pediatric Cardiology, 29(2), 87–92.

Bellinger DC, Newburger JW, Wypij D, Kuban KCK, duPlessis AJ, & Rappaport LA (2009). Behaviour at eight years in children with surgically corrected transposition: The Boston Circulatory Arrest Trial. Cardiology in the Young, 19, 86–97. [PubMed: 19079812]

Birca A, Vakorin VA, Porayette P, Madathil S, Chau V, Seed M, Doesburg SM, Blaser S, Nita DA, Sharma R, Duerden EG, Hickey EJ, Miller SP, & Hahn CD (2016). Interplay of brain structure and function in neonatal congenital heart disease. Annals of Clinical and Translational Neurology, 3(9), 708–722. 10.1002/acn3.336 [PubMed: 27648460]

Block AJ, Mcquillen PS, Chau V, Glass H, Poskitt KJ, Barkovich AJ, Esch M, Soulikias W, Azakie A, Campbell A, & Miller SP (2010). Clinically silent preoperative brain injuries do not worsen with

surgery in neonates with congenital heart disease. The Journal of Thoracic and Cardiovascular Surgery, 140(3), 550–557. 10.1016/j.jtcvs.2010.03.035 [PubMed: 20434174]

Bonthrone AF, Chew A, Kelly CJ, Almedom L, Simpson J, Victor S, Edwards AD, Rutherford MA, Nosarti C, & Counsell SJ (2021). Cognitive function in toddlers with congenital heart disease: The impact of a stimulating home environment. Infancy, 26(1), 184–199. 10.1111/infa.12376 [PubMed: 33210418]

Boskovski MT, Homsy J, Nathan M, Sleeper LA, Morton S, Manheimer KB, Tai A, Gorham J, Lewis M, Swartz M, Alfieris GM, Bacha EA, Karimi M, Meyer D, Nguyen K, Bernstein D, Romano-Adesman A, Porter GA, Goldmuntz E, … Seidman CE (2020). De Novo Damaging Variants, Clinical Phenotypes, and Post-Operative Outcomes in Congenital Heart Disease. Circulation. Genomic and Precision Medicine, 13(4), e002836. 10.1161/CIRCGEN.119.002836 [PubMed: 32812804]

Brosig CL, Mussatto KA, Kuhn EM, & Tweddell JS (2007). Neurodevelopmental outcome in preschool survivors of complex congenital heart disease: Implications for clinical practice. Journal of Pediatric Health Care, 21(1), 3–12. [PubMed: 17198894]

Brossard-Racine M, du Plessis A, Vezina G, Robertson R, Donofrio M, Tworetzky W, & Limperopoulos C (2016). Brain Injury in Neonates with Complex Congenital Heart Disease: What Is the Predictive Value of MRI in the Fetal Period? AJNR Am J Neuroradiol, 37(7), 1338–1346. 10.3174/ajnr.A4716 [PubMed: 26988809]

Bucholz EM, Sleeper LA, Goldberg CS, Pasquali SK, Anderson BR, Gaynor JW, Cnota JF, & Newburger JW (2020). Socioeconomic Status and Long-term Outcomes in Single Ventricle Heart Disease. Pediatrics, 146(4), e20201240. 10.1542/peds.2020-1240 [PubMed: 32973120]

Bucholz EM, Sleeper LA, Sananes R, Brosig CL, Goldberg CS, Pasquali SK, & Newburger JW (2021). Trajectories in Neurodevelopmental, Health-Related Quality of Life, and Functional Status Outcomes by Socioeconomic Status and Maternal Education in Children with Single Ventricle Heart Disease. The Journal of Pediatrics, 229, 289–293.e3. 10.1016/j.jpeds.2020.09.066 [PubMed: 33031800]

Butler SC, Huyler K, Kaza A, & Rachwal C (2017). Filling a significant gap in the cardiac ICU: Implementation of individualised developmental care. Cardiology in the Young, 27(9), 1797–1806. 10.1017/S1047951117001469 [PubMed: 28780917]

Butler SC, Sadhwani A, Stopp C, Singer J, Wypij D, Dunbar-Masterson C, Ware J, & Newburger JW (2019). Neurodevelopmental assessment of infants with congenital heart disease in the early postoperative period. Congenital Heart Disease, 14(2), 236–245. 10.1111/chd.12686 [PubMed: 30324749]

Calderon J, & Bellinger DC (2015). Executive function deficits in congenital heart disease: Why is intervention important? Cardiology in the Young, 25(7), 1238–1246. 10.1017/S1047951115001134 [PubMed: 26082199]

Calderon J, Wypij D, Rofeberg V, Stopp C, Roseman A, Albers D, Newburger JW, & Bellinger DC (2020). Randomized Controlled Trial of Working Memory Intervention in Congenital Heart Disease. The Journal of Pediatrics, 227, 191–198.e3. 10.1016/j.jpeds.2020.08.038 [PubMed: 32827526]

Campbell K, Malik L, Jones C, Ou Z, Presson A, Miller TA, Winter S, & Glotzbach K (2022). Abnormal infant neurobehavior and later neurodevelopmental delays in children with critical CHD. Cardiology in the Young, 1–10. 10.1017/S1047951122002013

Case-Smith J (2013). Systematic review of interventions to promote social-emotional development in young children with or at risk for disability. The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association, 67(4), 395–404. 10.5014/ajot.2013.004713 [PubMed: 23791314]

Cassidy AR, Butler SC, Briend J, Calderon J, Casey F, Crosby LE, Fogel J, Gauthier N, Raimondi C, Marino BS, Sood E, & Butcher JL (2021). Neurodevelopmental and psychosocial interventions for individuals with CHD: A research agenda and recommendations from the Cardiac Neurodevelopmental Outcome Collaborative. Cardiology in the Young, 31(6), 888–899. 10.1017/S1047951121002158 [PubMed: 34082844]

Cassidy AR, Ilardi D, Bowen SR, Hampton LE, Heinrich KP, Loman MM, Sanz JH, & Wolfe KR (2017). Congenital heart disease: A primer for the pediatric neuropsychologist.

Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence, 1–44. 10.1080/09297049.2017.1373758

Cassidy AR, White MT, DeMaso DR, Newburger JW, & Bellinger DC (2015). Executive Function in Children and Adolescents with Critical Cyonotic Congenital Heart Disease. Journal of the International Neuropsychological Society, 20, 34–49.

Claessens NHP, Algra SO, Ouwehand TL, Jansen NJG, Schappin R, Haas F, Eijsermans MJC, de Vries LS, Benders M, & Utrecht CHDLSG (2018). Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. Dev Med Child Neurol, 60(10), 1052–1058. 10.1111/dmcn.13747 [PubMed: 29572821]

Claessens NHP, Jansen NJG, Breur JMPJ, Algra SO, Stegeman R, Alderliesten T, van Loon K, de Vries LS, Haas F, Benders MJNL, & Lemmers PMA (2019). Postoperative cerebral oxygenation was not associated with new brain injury in infants with congenital heart disease. The Journal of Thoracic and Cardiovascular Surgery, 158(3), 867–877.e1. 10.1016/j.jtcvs.2019.02.106 [PubMed: 30982585]

Claessens NHP, Khalili N, Isgum I, Ter Heide H, Steenhuis TJ, Turk E, Jansen NJG, De Vries LS, Breur JMPJ, De Heus R, & Benders MJNL (2019). Brain and CSF Volumes in Fetuses and Neonates with Antenatal Diagnosis of Critical Congenital Heart Disease: A Longitudinal MRI Study. American Journal of Neuroradiology, 40(5), 885–891. 10.3174/ajnr.a6021 [PubMed: 30923087]

Clancy RR, McGaurn SA, Goin JE, Hirtz DG, Norwood WI, Gaynor JW, Jacobs ML, Wernovsky G, Mahle WT, Murphy JD, Nicolson SC, Steven JM, & Spray TL (2001). Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. Pediatrics, 108, 61–70. [PubMed: 11433055]

Clancy T, Jordan B, de Weerth C, & Muscara F (2020). Early Emotional, Behavioural and Social Development of Infants and Young Children with Congenital Heart Disease: A Systematic Review. Journal of Clinical Psychology in Medical Settings, 27(4), 686–703. 10.1007/s10880-019-09651-1 [PubMed: 31506852]

Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, Robertson RL, Evans AC, Newburger JW, & Limperopoulos C (2013). Delayed cortical development in fetuses with complex congenital heart disease. Cerebral Cortex (New York, N.Y.: 1991), 23(12), 2932–2943. 10.1093/cercor/bhs281 [PubMed: 22977063]

Dent CL, Spaeth JP, Jones BV, Schwartz SM, Glauser TA, Hallinan B, Pearl JM, Khoury PR, & Kurth CD (2005). Brain magnetic resonance imaging abnormalities after the Norwood procedure using regional cerebral perfusion. The Journal of Thoracic and Cardiovascular Surgery, 130(6), 1523–1530. 10.1016/j.jtcvs.2005.07.051 [PubMed: 16307993]

Desai H, Jones CE, Fogel JL, Negrin KA, Slater NL, Morris K, Doody LR, Engstler K, Torzone A, Smith J, & Butler SC (2023). Assessment and management of feeding difficulties for infants with complex CHD. Cardiology in the Young, 33(1), 1–10. 10.1017/S1047951122004024

Diamond A, & Ling DS (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. Developmental Cognitive Neuroscience, 18, 34–48. 10.1016/j.dcn.2015.11.005 [PubMed: 26749076]

Dimitropoulos A, McQuillen PS, Sethi V, Moosa A, Chau V, Xu D, Brant R, Azakie A, Campbell A, Barkovich AJ, Poskitt KJ, & Miller SP (2013). Brain injury and development in newborns with critical congenital heart disease. Neurology, 81(3), 241–248. 10.1212/WNL.0b013e31829bfdcf [PubMed: 23771484]

Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, Cetta F, Falkensammer CB, Huhta JC, & Kleinman CS (2003). Autoregulation of cerebral blood flow in fetuses with congenital heart disease: The brain sparing effect. Pediatric Cardiology, 24(5), 436–443. 10.1007/s00246-002-0404-0 [PubMed: 14627309]

Donofrio MT, Duplessis AJ, & Limperopoulos C (2011). Impact of congenital heart disease on fetal brain development and injury. Curr Opin Pediatr, 23(5), 502–511. 10.1097/MOP.0b013e32834aa583 [PubMed: 21881507]

Donofrio MT, & Massaro AN (2010). Impact of congenital heart disease on brain development and neurodevelopmental outcome. Int J Pediatr, 2010. 10.1155/2010/359390

Dulfer K, Helbing WA, & Utens EMWJ (2017). The Influence of Exercise Training on Quality of Life and Psychosocial Functioning in Children with Congenital Heart Disease:A Review of Intervention Studies. Sports (Basel, Switzerland), 5(1), E13. 10.3390/sports5010013

Edwards LA, Lara DA, Sanz Cortes M, Hunter JV, Andreas S, Nguyen MJ, Schoppe LJ, Zhang J, Smith EM, Maskatia SA, Sexson-Tejtel SK, Lopez KN, Lawrence EJ, Wang Y, Challman M, Ayres NA, Altman CA, Aagaard K, Becker JA, & Morris SA (2019). Chronic Maternal Hyperoxygenation and Effect on Cerebral and Placental Vasoregulation and Neurodevelopment in Fetuses with Left Heart Hypoplasia. Fetal Diagnosis and Therapy, 46(1), 45–57. 10.1159/000489123 [PubMed: 30223262]

El-Farrash RA, Shinkar DM, Ragab DA, Salem RM, Saad WE, Farag AS, Salama DH, & Sakr MF (2020). Longer duration of kangaroo care improves neurobehavioral performance and feeding in preterm infants: A randomized controlled trial. Pediatric Research, 87(4), Article 4. 10.1038/s41390-019-0558-6

Favilla E, Faerber JA, Hampton LE, Tam V, DeCost G, Ravishankar C, Gaynor JW, Burnham A, Licht DJ, & Mercer-Rosa L (2021). Early Evaluation and the Effect of Socioeconomic Factors on Neurodevelopment in Infants with Tetralogy of Fallot. Pediatric Cardiology, 42(3), 643–653. 10.1007/s00246-020-02525-6 [PubMed: 33533966]

Gaies M, Anderson J, Kipps A, Lorts A, Madsen N, Marino BS, Costello J, Brown D, Jacobs J, Kasnic D, Lihn S, Lannon C, Margolis P, Pearson GD, Kaltman J, Charpie JR, Redington AN, Pasquali SK, & Cardiac Networks United Executive Committee and Advisory Board. (2019). Cardiac Networks United: An integrated paediatric and congenital cardiovascular research and improvement network. Cardiology in the Young, 29(2), 111–118. [PubMed: 30567622]

Gakenheimer-Smith L, Glotzbach K, Ou Z, Presson AP, Puchalski M, Jones C, Lambert L, Delgado-Corcoran C, Eckhauser A, & Miller T (2019). The Impact of Neurobehavior on Feeding Outcomes in Neonates with Congenital Heart Disease. The Journal of Pediatrics, 214, 71–78.e2. 10.1016/j.jpeds.2019.06.047 [PubMed: 31402138]

Gallegos FN, Woo JL, Anderson BR, & Lopez KN (2022). Disparities in surgical outcomes of neonates with congenital heart disease across regions, centers, and populations. Seminars in Perinatology, 151581. 10.1016/j.semperi.2022.151581 [PubMed: 35396037]

Galli KK, Zimmerman RA, Jarvik GP, Wernovsky G, Kuypers MK, Clancy RR, Montenegro LM, Mahle WT, Newman MF, Saunders AM, Nicolson SC, Spray TL, & Gaynor JW (2004). Periventricular leukomalacia is common after neonatal cardiac surgery. The Journal of Thoracic and Cardiovascular Surgery, 127(3), 692–704. 10.1016/j.jtcvs.2003.09.053 [PubMed: 15001897]

Gaydos SS, Chowdhury SM, Judd RN, & McHugh KE (2020). A transition clinic intervention to improve follow-up rates in adolescents and young adults with congenital heart disease. Cardiology in the Young, 30(5), 633–640. 10.1017/S1047951120000682 [PubMed: 32279695]

Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, Goldberg CS, Hövels-Gürich H, Ichida F, Jacobs JP, Justo R, Latal B, Li JS, Mahle WT, McQuillen PS, … International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. (2015). Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics, 135(5), 816–825. 10.1542/peds.2014-3825 [PubMed: 25917996]

Gaynor JW, Wernovsky G, Jarvik GP, Bernbaum J, Gerdes M, Zackai E, Nord AS, Clancy RR, Nicolson SC, & Spray TL (2007). Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg, 133, 1344–1353, 1353 e1–3. 10.1016/j.jtcvs.2006.10.087 [PubMed: 17467455]

Griffin KJ, Elkin TD, & Smith CJ (2003). Academic outcomes in children with congenital heart disease. Clinical Pediatrics, 42(5), 401–409. 10.1177/000992280304200503 [PubMed: 12862342]

Gunn JK, Beca J, Hunt RW, Olischar M, & Shekerdemian LS (2012). Perioperative amplitude-integrated EEG and neurodevelopment in infants with congenital heart disease. Intensive Care Medicine, 38(9), 1539–1547. 10.1007/s00134-012-2608-y [PubMed: 22653373]

Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, Giardini A, Aleman A, Gelb BD, Mac Neal M, Porter GA, Kim R, Brueckner M, Lifton RP, Edman S, Woyciechowski S,

Mitchell LE, & Agopian AJ (2018). The Congenital Heart Disease Genetic Network Study: Cohort description. PLoS ONE, 13(1). 10.1371/journal.pone.0191319

Hoffman GM, Niebler RA, Scott JP, Bertrandt RA, Wakeham MK, Thompson NE, Ghanayem NS, Stuth EA, Mitchell ME, Woods RK, Hraska V, Mussatto KA, & Tweddell JS (2021). Interventions Associated With Treatment of Low Cardiac Output After Stage 1 Norwood Palliation. The Annals of Thoracic Surgery, 111(5), 1620–1627. 10.1016/j.athoracsur.2020.05.068 [PubMed: 32652068]

Hogan WJ, Moon-Grady AJ, Zhao Y, Cresalia NM, Nawaytou H, Quezada E, Brook M, McQuillen P, & Peyvandi S (2021). Fetal cerebrovascular response to maternal hyperoxygenation in congenital heart disease: Effect of cardiac physiology. Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology, 57(5), 769–775. 10.1002/uog.22024 [PubMed: 32202689]

Hogan WJ, Winter S, Pinto NM, Weng C, Sheng X, Conradt E, Wood J, Puchalski MD, Tani LY, & Miller TA (2018). Neurobehavioral evaluation of neonates with congenital heart disease: A cohort study. Developmental Medicine & Child Neurology, 60(12), 1225–1231. 10.1111/dmcn.13912 [PubMed: 29748956]

Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, DePalma SR, McKean D, Wakimoto H, Gorham J, Jin SC, Deanfield J, Giardini A, Porter GA, Kim R, Bilguvar K, Lopez F, Tikhonova I, Mane S, … Chung WK (2015). De novo mutations in Congenital Heart Disease with Neurodevelopmental and Other Birth Defects. Science (New York, N.Y.), 350(6265), 1262–1266. 10.1126/science.aac9396 [PubMed: 26785492]

Ilardi D, Ono KE, McCartney R, Book W, & Stringer AY (2017). Neurocognitive functioning in adults with congenital heart disease. Congenital Heart Disease, 12(2), 166–173. 10.1111/chd.12434 [PubMed: 27957813]

Ing C, Warner DO, Sun LS, Flick RP, Davidson AJ, Vutskits L, McCann ME, O'Leary J, Bellinger DC, Rauh V, Orser BA, Suresh S, & Andropoulos DB (2022). Anesthesia and Developing Brains: Unanswered Questions and Proposed Paths Forward. Anesthesiology, 136(3), 500–512. 10.1097/ALN.0000000000004116 [PubMed: 35015802]

Jin SC, Homsy J, Zaidi S, Lu Q, Morton S, DePalma SR, Zeng X, Qi H, Chang W, Sierant MC, Hung W-C, Haider S, Zhang J, Knight J, Bjornson RD, Castaldi C, Tikhonoa IR, Bilguvar K, Mane SM, … Brueckner M (2017). Contribution of rare inherited and de novo variants in 2,871 congenital heart disease probands. Nature Genetics, 49(11), 1593–1601. 10.1038/ng.3970 [PubMed: 28991257]

Kaltman JR, Di H, Tian Z, & Rychik J (2005). Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology, 25(1), 32–36. 10.1002/uog.1785 [PubMed: 15593334]

Keir M, Ebert P, Kovacs AH, Smith JMC, Kwan E, Field TS, Brossard-Racine M, & Marelli A (2019). Neurocognition in Adult Congenital Heart Disease: How to Monitor and Prevent Progressive Decline. The Canadian Journal of Cardiology, 35(12), 1675–1685. 10.1016/j.cjca.2019.06.020 [PubMed: 31570238]

Kelly CJ, Arulkumaran S, Tristão Pereira C, Cordero-Grande L, Hughes EJ, Teixeira RPAG, Steinweg JK, Victor S, Pushparajah K, Hajnal JV, Simpson J, Edwards AD, Rutherford MA, & Counsell SJ (2019). Neuroimaging findings in newborns with congenital heart disease prior to surgery: An observational study. Archives of Disease in Childhood, 104(11), 1042–1048. 10.1136/archdischild-2018-314822 [PubMed: 31243012]

Kollengode MS, Daniels CJ, & Zaidi AN (2018). Loss of follow-up in transition to adult CHD: A single-centre experience. Cardiology in the Young, 28(8), 1001–1008. 10.1017/S1047951118000690 [PubMed: 29966538]

Kovacs AH, & Bellinger DC (2021). Neurocognitive and psychosocial outcomes in adult congenital heart disease: A lifespan approach. Heart (British Cardiac Society), 107(2), 159–167. 10.1136/heartjnl-2016-310862 [PubMed: 32887738]

Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, Ong L, Colman J, Oechslin E, & Nolan RP (2009). Depression and anxiety in adult congenital heart disease: Predictors and prevalence. International Journal of Cardiology, 137(2), 158–164. 10.1016/j.ijcard.2008.06.042 [PubMed: 18707776]

Krishnan A, Jacobs MB, Morris SA, Peyvandi S, Bhat AH, Chelliah A, Chiu JS, Cuneo BF, Freire G, Hornberger LK, Howley L, Husain N, Ikemba C, Kavanaugh-McHugh A, Kutty S, Lee C, Lopez KN, McBrien A, Michelfelder EC, … Fetal Heart Society. (2021). Impact of Socioeconomic Status, Race and Ethnicity, and Geography on Prenatal Detection of Hypoplastic Left Heart Syndrome and Transposition of the Great Arteries. Circulation, 143(21), 2049–2060. 10.1161/CIRCULATIONAHA.120.053062 [PubMed: 33993718]

Laraja K, Sadhwani A, Tworetzky W, Marshall AC, Gauvreau K, Freud L, Hass C, Dunbar-Masterson C, Ware J, Lafranchi T, Wilkins-Haug L, & Newburger JW (2017). Neurodevelopmental Outcome in Children after Fetal Cardiac Intervention for Aortic Stenosis with Evolving Hypoplastic Left Heart Syndrome. The Journal of Pediatrics, 184, 130–136.e4. 10.1016/j.jpeds.2017.01.034 [PubMed: 28233547]

Latal B (2016). Neurodevelopmental Outcomes of the Child with Congenital Heart Disease. Clinics in Perinatology, 43(1), 173–185. 10.1016/j.clp.2015.11.012 [PubMed: 26876129]

Leon RL, Sharma K, Mir IN, Herrera CL, Brown SL, Spong CY, & Chalak LF (2022). Placental vascular malperfusion lesions in fetal congenital heart disease. American Journal of Obstetrics and Gynecology, 227(4), 620.e1–620.e8. 10.1016/j.ajog.2022.05.038

Leonetti C, Back SA, Gallo V, & Ishibashi N (2019). Cortical Dysmaturation in Congenital Heart Disease. Trends in Neurosciences, 42(3), 192–204. 10.1016/j.tins.2018.12.003 [PubMed: 30616953]

Li X, Laplante DP, Paquin V, Lafortune S, Elgbeili G, & King S (2022). Effectiveness of cognitive behavioral therapy for perinatal maternal depression, anxiety and stress: A systematic review and meta-analysis of randomized controlled trials. Clinical Psychology Review, 92, 102129. 10.1016/j.cpr.2022.102129 [PubMed: 35123346]

Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, & Vossough A (2009). Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg, 137(3), 529–536; discussion 536–7. 10.1016/j.jtcvs.2008.10.025 [PubMed: 19258059]

Lim Jessie Mei, Porayette Prashob, Davide Marini, Vann Chau, Au-Young Stephanie H., Saini Amandeep, Ly Linh G., Blaser Susan, Shroff Manohar, Branson Helen M., Sananes Renee, Hickey Edward J., Gaynor J. William, Van Arsdell Glen, Miller Steven P., & Seed Mike. (2019). Associations Between Age at Arterial Switch Operation, Brain Growth, and Development in Infants With Transposition of the Great Arteries. Circulation, 139(24), 2728–2738. 10.1161/CIRCULATIONAHA.118.037495 [PubMed: 31132861]

Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, & Tchervenkov C (1999). Neurologic status of newborns with congenital heart defects before open heart surgery. Pediatrics, 103(2), 402–8. [PubMed: 9925832]

Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, & Tchervenkov C (2000). Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. J Pediatr, 137(5), 638–645. 10.1067/mpd.2000.109152 [PubMed: 11060529]

Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, & du Plessis AJ (2010). Brain volume and metabolism in fetuses with congenital heart disease: Evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation, 121, 26–33. 10.1161/CIRCULATIONAHA.109.865568 [PubMed: 20026783]

Lisanti AJ, Cribben J, Connock EM, Lessen R, & Medoff-Cooper B (2016). Developmental Care Rounds. Clinics in Perinatology, 43(1), 147–156. 10.1016/j.clp.2015.11.010 [PubMed: 26876127]

Lisanti AJ, Vittner D, Medoff-Cooper B, Fogel J, Wernovsky G, & Butler S (2019). Individualized Family-Centered Developmental Care. Journal of Cardiovascular Nursing, 34(1), 85–93. 10.1097/jcn.0000000000000546 [PubMed: 30303895]

Loblein HJ, Vukmirovich PJ, Donofrio MT, & Sanz JH (2022). Prevalence of Neurodevelopmental Disorders in a Clinically Referred Sample of Children with Congenital Heart Disease. Cardiology in the Young, In process.

Lopez KN, Baker-Smith C, Flores G, Gurvitz M, Karamlou T, Nunez Gallegos F, Pasquali S, Patel A, Peterson JK, Salemi JL, Yancy C, Peyvandi S, & American Heart Association Congenital Cardiac Defects Committee of the Council on Lifelong Congenital Heart Disease and Heart

Health in the Young; Council on Epidemiology and Prevention; and Council on Lifestyle and Cardiometabolic Health. (2022). Addressing Social Determinants of Health and Mitigating Health Disparities Across the Lifespan in Congenital Heart Disease: A Scientific Statement From the American Heart Association. Journal of the American Heart Association, 11(8), e025358. 10.1161/JAHA.122.025358 [PubMed: 35389228]

Lynch JM, Buckley EM, Schwab PJ, McCarthy AL, Winters ME, Busch DR, Xiao R, Goff DA, Nicolson SC, Montenegro LM, Fuller S, Gaynor JW, Spray TL, Yodh AG, Naim MY, & Licht DJ (2014). Time to surgery and preoperative cerebral hemodynamics predict postoperative white matter injury in neonates with hypoplastic left heart syndrome. J Thorac Cardiovasc Surg, 148(5), 2181–2188. 10.1016/j.jtcvs.2014.05.081 [PubMed: 25109755]

Lynch JM, Ko T, Busch DR, Newland JJ, Winters ME, Mensah-Brown K, Boorady TW, Xiao R, Nicolson SC, Montenegro LM, Gaynor JW, Spray TL, Yodh AG, Naim MY, & Licht DJ (2018). Preoperative cerebral hemodynamics from birth to surgery in neonates with critical congenital heart disease. J Thorac Cardiovasc Surg, 156(4), 1657–1664. 10.1016/j.jtcvs.2018.04.098 [PubMed: 29859676]

Mackie AS, Rempel GR, Kovacs AH, Kaufman M, Rankin KN, Jelen A, Yaskina M, Sananes R, Oechslin E, Dragieva D, Mustafa S, Williams E, Schuh M, Manlhiot C, Anthony SJ, Magill-Evans J, Nicholas D, & McCrindle BW (2018). Transition Intervention for Adolescents With Congenital Heart Disease. Journal of the American College of Cardiology, 71(16), 1768–1777. 10.1016/j.jacc.2018.02.043 [PubMed: 29673467]

Maeda T, Sarkislali K, Leonetti C, Kapani N, Dhari Z, Al Haj I, Ulrey R, Hanley PJ, Jonas RA, & Ishibashi N (2020). Impact of Mesenchymal Stromal Cell Delivery Through Cardiopulmonary Bypass on Postnatal Neurogenesis. The Annals of Thoracic Surgery, 109(4), 1274–1281. 10.1016/j.athoracsur.2019.08.036 [PubMed: 31563487]

Majnemer A (1998). Benefits of early intervention for children with developmental disabilities. Seminars in Pediatric Neurology, 5(1), 62–69. 10.1016/s1071-9091(98)80020-x [PubMed: 9548643]

Manzar S, Nair AK, Pai MG, & Al-Khusaiby SM (2005). Head size at birth in neonates with transposition of great arteries and hypoplastic left heart syndrome. Saudi Medical Journal, 26(3), 453–456. [PubMed: 15806218]

Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, & Kaouache M (2014). Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation, 130(9), 749–756. 10.1161/CIRCULATIONAHA.113.008396 [PubMed: 24944314]

Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr., Li J, Smith SE, Bellinger DC, Mahle WT, American Heart Association Congenital Heart Defects Committee, C. on C. D. in the Y. C. on C. N., & Stroke, C. (2012). Neurodevelopmental outcomes in children with congenital heart disease: Evaluation and management: A scientific statement from the American Heart Association. Circulation, 126(9), 1143–1172. 10.1161/CIR.0b013e318265ee8a [PubMed: 22851541]

Marino BS, Sood E, Cassidy AR, Miller TA, Sanz JH, Bellinger D, Newburger J, & Goldberg CS (2020). The origins and development of the cardiac neurodevelopment outcome collaborative: Creating innovative clinical, quality improvement, and research opportunities. Cardiology in the Young, 30(11), 1597–1602. 10.1017/S1047951120003510 [PubMed: 33269669]

McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, Grobler A, Stargatt R, Hunt RW, Sheppard SJ, Marmor J, Giribaldi G, Bellinger DC, Hartmann PL, Hardy P, Frawley G, Izzo F, von Ungern Sternberg BS, Lynn A, … GAS Consortium. (2019). Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): An international, multicentre, randomised, controlled equivalence trial. Lancet (London, England), 393(10172), 664–677. 10.1016/S0140-6736(18)32485-1 [PubMed: 30782342]

McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, Craig B, Stewart M, & Casey F (2010). A controlled trial of early interventions to promote maternal adjustment and development in infants born with severe congenital heart disease. Child: Care, Health and Development, 36(1), 110–117. [PubMed: 19961494]

McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland HC, Sands A, Craig BG, Stewart M, & Casey FA (2012). Randomized controlled trial of interventions to promote adjustment of children

with congenital heart disease entering school and their families. Journal of Pediatric Psychology, 37(10), 1089–1103. [PubMed: 22976507]

Mcquillen PS, Barkovich AJ, Hamrick SEG, Perez M, Ward P, Glidden DV, Azakie A, Karl T, & Miller SP (2007). Temporal and Anatomic Risk Profile of Brain Injury With Neonatal Repair of Congenital Heart Defects. Stroke, 38(2), 736–741. 10.1161/01.str.0000247941.41234.90 [PubMed: 17261728]

Mcquillen PS, Hamrick SEG, Perez MJ, Barkovich AJ, Glidden DV, Karl TR, Teitel D, & Miller SP (2006). Balloon Atrial Septostomy Is Associated With Preoperative Stroke in Neonates With Transposition of the Great Arteries. Circulation, 113(2), 280–285. 10.1161/circulationaha.105.566752 [PubMed: 16401771]

Mebius MJ, Oostdijk NJE, Kuik SJ, Bos AF, Berger RMF, Bilardo CM, Kooi EMW, & Ter Horst HJ (2018). Amplitude-integrated electroencephalography during the first 72 h after birth in neonates diagnosed prenatally with congenital heart disease. Pediatric Research, 83(4), 798–803. 10.1038/pr.2017.311 [PubMed: 29244798]

Medoff-Cooper B, Irving SY, Hanlon AL, Golfenshtein N, Radcliffe J, Stallings VA, Marino BS, & Ravishankar C (2016). The Association among Feeding Mode, Growth, and Developmental Outcomes in Infants with Complex Congenital Heart Disease at 6 and 12 Months of Age. The Journal of Pediatrics, 169, 154–159.e1. 10.1016/j.jpeds.2015.10.017 [PubMed: 26585995]

Melazzini L, Codari M, Vitali P, & Sardanelli F (2019). Brain vascular changes in adults with congenital heart disease: A systematic review. NeuroImage. Clinical, 23, 101873. 10.1016/j.nicl.2019.101873 [PubMed: 31158693]

Melby-Lervåg M, & Hulme C (2013). Is working memory training effective? A meta-analytic review. Developmental Psychology, 49(2), 270–291. 10.1037/a0028228 [PubMed: 22612437]

Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, & Vigneron DB (2007). Abnormal brain development in newborns with congenital heart disease. N Engl J Med, 357(19), 1928–1938. 10.1056/NEJMoa067393 [PubMed: 17989385]

Miller TA, Sadhwani A, Sanz J, Sood E, Ilardi D, Newburger JW, Goldberg CS, Wypij D, Gaynor JW, & Marino BS (2020). Variations in practice in cardiac neurodevelopmental follow-up programs. Cardiology in the Young, 30(11), 1603–1608. 10.1017/S1047951120003522 [PubMed: 33094709]

Moceri P, Goossens E, Hascoet S, Checler C, Bonello B, Ferrari E, Acar P, & Fraisse A (2015). From adolescents to adults with congenital heart disease: The role of transition. European Journal of Pediatrics, 174(7), 847–854. 10.1007/s00431-015-2557-x [PubMed: 25957970]

Morton PD, Ishibashi N, Jonas RA, & Gallo V (2015). Congenital cardiac anomalies and white matter injury. Trends in Neurosciences, 38(6), 353–363. 10.1016/j.tins.2015.04.001 [PubMed: 25939892]

Morton PD, Korotcova L, Lewis BK, Bhuvanendran S, Ramachandra SD, Zurakowski D, Zhang J, Mori S, Frank JA, Jonas RA, Gallo V, & Ishibashi N (2017). Abnormal neurogenesis and cortical growth in congenital heart disease. Science Translational Medicine, 9(374), eaah7029. 10.1126/scitranslmed.aah7029 [PubMed: 28123074]

Mulkey SB, Govindan R, Metzler M, Swisher CB, Hitchings L, Wang Y, Baker R, Larry Maxwell G, Krishnan A, & du Plessis AJ (2019). Heart rate variability is depressed in the early transitional period for newborns with complex congenital heart disease. Clin Auton Res. 10.1007/s10286-019-00616-w

Mulkey SB, Swearingen CJ, Melguizo MS, Schmitz ML, Ou X, Ramakrishnaiah RH, Glasier CM, Bradley Schaefer G, & Bhutta AT (2013). Multi-tiered analysis of brain injury in neonates with congenital heart disease. Pediatr Cardiol, 34(8), 1772–1784. 10.1007/s00246-013-0712-6 [PubMed: 23652966]

Mulkey SB, Yap VL, Bai S, Ramakrishnaiah RH, Glasier CM, Bornemeier RA, Schmitz ML, & Bhutta AT (2015). Amplitude-integrated EEG in newborns with critical congenital heart disease predicts preoperative brain magnetic resonance imaging findings. Pediatr Neurol, 52(6), 599–605. 10.1016/j.pediatrneurol.2015.02.026 [PubMed: 25838043]

Mussatto KA, Hollenbeck-Pringle D, Trachtenberg F, Sood E, Sananes R, Pike NA, Lambert LM, Mahle WT, Goldberg DJ, Goldberg CS, Dunbar-Masterson C, Otto M, Marino BS, Bartle BH,

Williams IA, Jacobs JP, Zyblewski SC, & Pemberton VL (2018). Utilisation of early intervention services in young children with hypoplastic left heart syndrome. Cardiology in the Young, 28(1), 126–133. 10.1017/S104795111700169X [PubMed: 28847329]

Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M, Mussatto KA, Williams IA, Gustafson KE, Mital S, Pike N, Sood E, Mahle WT, Cooper DS, Dunbar-Masterson C, Krawczeski CD, Lewis A, Menon SC, Pemberton VL, … Gaynor JW (2012). Early Developmental Outcome in Children With Hypoplastic Left Heart Syndrome and Related Anomalies: The Single Ventricle Reconstruction Trial. Circulation, 125, 2081–2091. 10.1161/CIRCULATIONAHA.111.064113 [PubMed: 22456475]

Nitta M, Ochiai R, Nakano S, Nakashima R, Matsumoto K, Sugano T, Ishigami T, Ishikawa T, Tamura K, Nakano Y, Watanabe S, Hokosaki T, Machida D, Masuda M, & Kimura K (2021). Characteristics of patients with adult congenital heart disease treated by non-specialized doctors: The potential loss of follow-up. Journal of Cardiology, 77(1), 17–22. 10.1016/j.jjcc.2020.06.018 [PubMed: 33317801]

Nores M, & Barnett WS (2010). Benefits of early childhood interventions across the world: (Under) Investing in the very young. Economics of Education Review, 29(2), 271–282. 10.1016/j.econedurev.2009.09.001

Nugent BM, & Bale TL (2015). The omniscient placenta: Metabolic and epigenetic regulation of fetal programming. Frontiers in Neuroendocrinology, 39, 28–37. 10.1016/j.yfrne.2015.09.001 [PubMed: 26368654]

Ortinau C, Beca J, Lambeth J, Ferdman B, Alexopoulos D, Shimony JS, Wallendorf M, Neil J, & Inder T (2012). Regional alterations in cerebral growth exist preoperatively in infants with congenital heart disease. J Thorac Cardiovasc Surg, 143(6), 1264–1270. 10.1016/j.jtcvs.2011.10.039 [PubMed: 22143100]

Ortinau CM, Mangin-Heimos K, Moen J, Alexopoulos D, Inder TE, Gholipour A, Shimony JS, Eghtesady P, Schlaggar BL, & Smyser CD (2018). Prenatal to postnatal trajectory of brain growth in complex congenital heart disease. NeuroImage : Clinical, 20, 913–922. 10.1016/j.nicl.2018.09.029 [PubMed: 30308377]

Peterson JK, & Evangelista LS (2017). Developmentally Supportive Care in Congenital Heart Disease: A Concept Analysis. Journal of Pediatric Nursing, 36, 241–247. 10.1016/j.pedn.2017.05.007 [PubMed: 28579078]

Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, Montenegro LM, Tabbutt S, Zimmerman RA, & Licht DJ (2009). Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy. Circulation, 119(5), 709–716. 10.1161/CIRCULATIONAHA.107.760819 [PubMed: 19171858]

Peyvandi S, Chau V, Guo T, Xu D, Glass HC, Synnes A, Poskitt K, Barkovich AJ, Miller SP, & McQuillen PS (2018). Neonatal Brain Injury and Timing of Neurodevelopmental Assessment in Patients With Congenital Heart Disease. J Am Coll Cardiol, 71(18), 1986–1996. [PubMed: 29724352]

Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ, Xu D, Barkovich AJ, Miller S, & McQuillen P (2016). Association of Prenatal Diagnosis of Critical Congenital Heart Disease With Postnatal Brain Development and the Risk of Brain Injury. JAMA Pediatr, 170(4), e154450. 10.1001/jamapediatrics.2015.4450 [PubMed: 26902528]

Peyvandi S, Kim H, Lau J, Barkovich AJ, Campbell A, Miller S, Xu D, & McQuillen P (2018). The association between cardiac physiology, acquired brain injury, and postnatal brain growth in critical congenital heart disease. The Journal of Thoracic and Cardiovascular Surgery, 155(1), 291–300.e3. 10.1016/j.jtcvs.2017.08.019 [PubMed: 28918207]

Peyvandi S, Latal B, Miller SP, & McQuillen PS (2019). The neonatal brain in critical congenital heart disease: Insights and future directions. NeuroImage, 185, 776–782. 10.1016/j.neuroimage.2018.05.045 [PubMed: 29787864]

Peyvandi S, Xu D, Wang Y, Hogan W, Moon-Grady A, Barkovich AJ, Glenn O, McQuillen P, & Liu J (2021). Fetal Cerebral Oxygenation Is Impaired in Congenital Heart Disease and Shows Variable Response to Maternal Hyperoxia. Journal of the American Heart Association, 10(1), e018777. 10.1161/JAHA.120.018777 [PubMed: 33345557]

Razzaghi H, Oster M, & Reefhuis J (2015). Long-term outcomes in children with congenital heart disease: National Health Interview Survey. The Journal of Pediatrics, 166(1), 119–124. 10.1016/j.jpeds.2014.09.006 [PubMed: 25304924]

Romanowicz J, Leonetti C, Dhari Z, Korotcova L, Ramachandra SD, Saric N, Morton PD, Bansal S, Cheema A, Gallo V, Jonas RA, & Ishibashi N (2019). Treatment With Tetrahydrobiopterin Improves White Matter Maturation in a Mouse Model for Prenatal Hypoxia in Congenital Heart Disease. Journal of the American Heart Association, 8(15), e012711. 10.1161/JAHA.119.012711 [PubMed: 31331224]

Rosenthal GL (1996). Patterns of Prenatal Growth among Infants with Cardiovascular Malformations: Possible Fetal Hemodynamic Effects. American Journal of Epidemiology, 143(5), 505–513. 10.1093/oxfordjournals.aje.a008771 [PubMed: 8610666]

Rudolph AM (2018). Circulatory changes during gestational development of the sheep and human fetus. Pediatric Research, 84(3), 348–351. 10.1038/s41390-018-0094-9 [PubMed: 30013152]

Ryan KR, Jones MB, Allen KY, Marino BS, Casey F, Wernovsky G, & Lisanti AJ (2019). Neurodevelopmental Outcomes Among Children With Congenital Heart Disease: At-Risk Populations and Modifiable Risk Factors. World Journal for Pediatric & Congenital Heart Surgery, 10(6), 750–758. 10.1177/2150135119878702 [PubMed: 31658880]

Rychik J, Donaghue DD, Levy S, Fajardo C, Combs J, Zhang X, Szwast A, & Diamond GS (2013). Maternal psychological stress after prenatal diagnosis of congenital heart disease. The Journal of Pediatrics, 162(2), 302–307.e1. 10.1016/j.jpeds.2012.07.023 [PubMed: 22974576]

Rychik J, Goff D, McKay E, Mott A, Tian Z, Licht D, & Gaynor J (2018). Characterization of the Placenta in the Newborn with Congenital Heart Disease: Distinctions Based on Type of Cardiac Malformation. Pediatric Cardiology, 39, 1–7. 10.1007/s00246-018-1876-x [PubMed: 29043396]

Saarijärvi M, Wallin L, Moons P, Gyllensten H, & Bratt E-L (2021). Mechanisms of impact and experiences of a person-centred transition programme for adolescents with CHD: The Stepstones project. BMC Health Services Research, 21(1), 573. 10.1186/s12913-021-06567-1 [PubMed: 34112174]

Sadhwani A, Wypij D, Rofeberg V, Gholipour A, Mittleman M, Rohde J, Velasco-Annis C, Calderon J, Friedman KG, Tworetzky W, Grant PE, Soul JS, Warfield SK, Newburger JW, Ortinau CM, & Rollins CK (2022). Fetal Brain Volume Predicts Neurodevelopment in Congenital Heart Disease. Circulation, 145(15), 1108–1119. 10.1161/CIRCULATIONAHA.121.056305 [PubMed: 35143287]

Sanz JH, Anixt J, Bear L, Basken A, Beca J, Marino BS, Mussatto KA, Nembhard WN, Sadhwani A, Sananes R, Shekerdemian LS, Sood E, Uzark K, Willen E, & Ilardi D (2021). Characterisation of neurodevelopmental and psychological outcomes in CHD: A research agenda and recommendations from the cardiac neurodevelopmental outcome collaborative. Cardiology in the Young, 31(6), 876–887. 10.1017/S1047951121002146 [PubMed: 34082845]

Sanz JH, Berl MM, Armour AC, Wang J, Cheng YI, & Donofrio MT (2017). Prevalence and pattern of executive dysfunction in school age children with congenital heart disease. Congenital Heart Disease, 12(2), 202–209. 10.1111/chd.12427 [PubMed: 27863079]

Sarajuuri A, Jokinen E, Mildh L, Tujulin AM, Mattila I, Valanne L, & Lonnqvist T (2012). Neurodevelopmental burden at age 5 years in patients with univentricular heart. Pediatrics, 130(6), e1636–46. 10.1542/peds.2012-0486 [PubMed: 23166336]

Sarić N, Hashimoto-Torii K, Jevtović-Todorović V, & Ishibashi N (2022). Nonapoptotic caspases in neural development and in anesthesia-induced neurotoxicity. Trends in Neurosciences, 45(6), 446–458. 10.1016/j.tins.2022.03.007 [PubMed: 35491256]

Scheinost D, Kwon SH, Lacadie C, Sze G, Sinha R, Constable RT, & Ment LR (2016). Prenatal stress alters amygdala functional connectivity in preterm neonates. NeuroImage : Clinical, 12, 381–388. 10.1016/j.nicl.2016.08.010 [PubMed: 27622134]

Scheinost D, Sinha R, Cross SN, Kwon SH, Sze G, Constable RT, & Ment LR (2017). Does prenatal stress alter the developing connectome? Pediatric Research, 81(1–2), 214–226. 10.1038/pr.2016.197 [PubMed: 27673421]

Schidlow DN, Freud L, Friedman K, & Tworetzky W (2017). Fetal interventions for structural heart disease. Echocardiography (Mount Kisco, N.Y.), 34(12), 1834–1841. 10.1111/echo.13667 [PubMed: 29287139]

Schlatterer SD, Govindan RB, Murnick J, Barnett SD, Lopez C, Donofrio MT, Mulkey SB, Limperopoulos C, & du Plessis AJ (2021). In infants with congenital heart disease autonomic dysfunction is associated with pre-operative brain injury. Pediatr Res. 10.1038/s41390-021-01931-7

Sethi V, Tabbutt S, Dimitropoulos A, Harris KC, Chau V, Poskitt K, Campbell A, Azakie A, Xu D, Barkovich AJ, Miller SP, & McQuillen PS (2013). Single-ventricle anatomy predicts delayed microstructural brain development. Pediatr Res, 73(5), 661–667. 10.1038/pr.2013.29 [PubMed: 23407116]

Shillingford AJ, Ittenbach RF, Marino BS, Rychik J, Clancy RR, Spray TL, Gaynor JW, & Wernovsky G (2007). Aortic morphometry and microcephaly in hypoplastic left heart syndrome. Cardiology in the Young, 17(2), 189–195. 10.1017/S1047951107000248 [PubMed: 17338838]

Sood E, Berends WM, Butcher JL, Lisanti AJ, Medoff-Cooper B, Singer J, Willen E, & Butler S (2016). Developmental Care in North American Pediatric Cardiac Intensive Care Units. Advances in Neonatal Care, 16(3), 211–219. 10.1097/anc.0000000000000264 [PubMed: 27140031]

Sood E, Gramszlo C, Perez Ramirez A, Braley K, Butler SC, Davis JA, Divanovic AA, Edwards LA, Kasparian N, Kelly SL, Neely T, Ortinau CM, Riegel E, Shillingford AJ, & Kazak AE (2022). Partnering With Stakeholders to Inform the Co-Design of a Psychosocial Intervention for Prenatally Diagnosed Congenital Heart Disease. Journal of Patient Experience, 9, 23743735221092490. 10.1177/23743735221092488

Soto CB, Olude O, Hoffmann RG, Bear L, Chin A, Dasgupta M, & Mussatto K (2011). Implementation of a routine developmental follow-up program for children with congenital heart disease: Early results. Congenital Heart Disease, 6(5), 451–460. 10.1111/j.1747-0803.2011.00546.x [PubMed: 21718458]

Spittle AJ, Orton J, Doyle LW, & Boyd R (2007). Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants. The Cochrane Database of Systematic Reviews, 2, CD005495. 10.1002/14651858.CD005495.pub2

Stegeman R, Sprong MCA, Breur J, Groenendaal F, de Vries LS, Haas F, van der Net J, Jansen NJG, Benders M, Claessens NHP, & Utrecht CHDLSG (2022). Early motor outcomes in infants with critical congenital heart disease are related to neonatal brain development and brain injury. Dev Med Child Neurol, 64(2), 192–199. 10.1111/dmcn.15024 [PubMed: 34416027]

Sun L, Macgowan CK, Sled JG, Yoo S-J, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, Hickey E, Miller S, & Seed M (2015). Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation, 131(15), 1313–1323. 10.1161/CIRCULATIONAHA.114.013051 [PubMed: 25762062]

Tesson S, Butow PN, Sholler GF, Sharpe L, Kovacs AH, & Kasparian NA (2019). Psychological interventions for people affected by childhood-onset heart disease: A systematic review. Health Psychology, 38(2), 151–161. 10.1037/hea0000704 [PubMed: 30652913]

Torowicz D, Lisanti AJ, Rim J-S, & Medoff-Cooper B (2012). A Developmental Care Framework for a Cardiac Intensive Care Unit A Paradigm Shift. Advances in Neonatal Care, 12(5S), S28–S32. 10.1097/ANC.0b013e318265aeef [PubMed: 22968003]

Tsao P-C, Lee Y-S, Jeng M-J, Hsu J-W, Huang K-L, Tsai S-J, Chen M-H, Soong W-J, & Kou YR (2017). Additive effect of congenital heart disease and early developmental disorders on attention-deficit/hyperactivity disorder and autism spectrum disorder: A nationwide population-based longitudinal study. European Child & Adolescent Psychiatry, 26(11), 1351–1359. 10.1007/s00787-017-0989-8 [PubMed: 28417257]

van der Mheen M, Meentken MG, van Beynum IM, van der Ende J, van Galen E, Zirar A, Aendekerk EWC, van den Adel TPL, Bogers AJJC, McCusker CG, Hillegers MHJ, Helbing WA, & Utens EMWJ (2019). CHIP-Family intervention to improve the psychosocial well-being of young children with congenital heart disease and their families: Results of a randomised controlled trial. Cardiology in the Young, 29(9), 1172–1182. 10.1017/S1047951119001732 [PubMed: 31378215]

Verrall CE, Blue GM, Loughran-Fowlds A, Kasparian N, Gecz J, Walker K, Dunwoodie SL, Cordina R, Sholler G, Badawi N, & Winlaw D (2019). “Big issues” in neurodevelopment for children and

adults with congenital heart disease. Open Heart, 6(2), e000998. 10.1136/openhrt-2018-000998 [PubMed: 31354955]

Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, Webb CL, American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee, & American Heart Association Council on Cardiovascular Nursing. (2008). Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]: A scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation, 117(18), 2407–2423. 10.1161/CIRCULATIONAHA.107.189473 [PubMed: 18427125]

Volpe JJ (2014). Encephalopathy of congenital heart disease—Destructive and developmental effects intertwined. Journal of Pediatrics, 164(5), 962–965. [PubMed: 24529617]

Ware J, Butcher JL, Latal B, Sadhwani A, Rollins CK, Brosig Soto CL, Butler SC, Eiler-Sims PB, Ullman Shade CV, & Wernovsky G (2020). Neurodevelopmental evaluation strategies for children with congenital heart disease aged birth through 5 years: Recommendations from the cardiac neurodevelopmental outcome collaborative. Cardiology in the Young, 30(11), 1609–1622. 10.1017/S1047951120003534 [PubMed: 33143781]

Wernovsky G (2006). Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiology in the Young, 16(S1), 92–104.

Wilson WM, Smith-Parrish M, Marino BS, & Kovacs AH (2015). Neurodevelopmental and psychosocial outcomes across the congenital heart disease lifespan. Progress in Pediatric Cardiology, 39(2, Part B), 113–118. 10.1016/j.ppedcard.2015.10.011

Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, Evans SW, Flinn SK, Froehlich T, Frost J, Holbrook JR, Lehmann CU, Lessin HR, Okechukwu K, Pierce KL, Winner JD, Zurhellen W, & SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER. (2019). Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics, 144(4), e20192528. 10.1542/peds.2019-2528 [PubMed: 31570648]

Wu Y, Kapse K, Jacobs M, Niforatos-Andescavage N, Donofrio MT, Krishnan A, Vezina G, Wessel D, du Plessis A, & Limperopoulos C (2020). Association of Maternal Psychological Distress With In Utero Brain Development in Fetuses With Congenital Heart Disease. JAMA Pediatrics, 174(3), e195316. 10.1001/jamapediatrics.2019.5316 [PubMed: 31930365]

You W, Andescavage NN, Kapse K, Donofrio MT, Jacobs M, & Limperopoulos C (2020). Hemodynamic Responses of the Placenta and Brain to Maternal Hyperoxia in Fetuses with Congenital Heart Disease by Using Blood Oxygen-Level Dependent MRI. Radiology, 294(1), 141–148. 10.1148/radiol.2019190751 [PubMed: 31687920]

Zaidi S, & Brueckner M (2017). Genetics and Genomics of Congenital Heart Disease. Circulation Research, 120(6), 923–940. 10.1161/CIRCRESAHA.116.309140 [PubMed: 28302740]

**Table 1:**

Risk Factors and Proposed Interventions for Brain Injury in Complex Congenital Heart Disease

| | Risk Factors | Supporting Studies | Interventions under Investigation |
|---|---|---|---|
| **Prenatal** | *Immature Brain Development* | Miller, S. P. *et al.*, 2007<br>Limperopulos, C et al, 2010<br>Andropoulos, D. B. *et al.* 2010<br>Beca, J. *et.al.* 2013<br>Dimitropoulos, A. *et al.* 2013<br>Brossard-Racine, M. *et al.* 2016<br>Claessens, N. H. P. *et al.* 2019 | *Maternal Hyperoxygenation tetrahydrobiopterin (BH4) Maternal Progesterone* |
| | *Cardiac Physiology (Single vs Two Ventricle)* | Limperopoulos, C. *et al.* 2000<br>McQuillen, P. *et.al.* 2007<br>Mulkey, S. B. *et al.* 2013<br>Beca, J. *et.al.* 2013<br>Peyvandi, S. *et al.* 2018 | |
| | *Timing of Diagnosis of Cardiac Disease*[*] | Peyvandi, S. *et al.* 2016 | *Decreased time to surgery/Delivery planning* |
| | *Placental Pathology* | Rychik et al., 2018<br>You et al., 2020<br>Leon et al., 2022 | |
| | *Maternal Stress* | Rychik et al., 2013<br>Wu et al., 2020 | *Psychological Intervention for Maternal Stress* |
| **Preoperative** | *Lower O2 Saturation* | Petit, C. J. *et al.* 2009<br>Block, A. J. *et al.* 2010<br>Dimitropoulos, A. *et al.* 2013 | *Allopurinol Precision monitoring/therapy to optimize blood pressure, oxygenation, and cerebral perfusion* |
| | *Hypotension* | Dimitropoulos, A. *et al.* 2013 | |
| | *Immature Autonomic Function* | Schlatterer, S.D. *et al.* 2021 | |
| | *Length of Time to Surgery* | Petit, C. J. *et al.* 2009<br>Lynch, J. M. *et al.* 2014 | *Decreased time to surgery* |
| | *Balloon Atrial Septostomy* | *Mcquillen, P. S. et al.* 2006<br>Block, A. J. *et al.* 2010<br>Dimitropoulos, A. *et al.* 2013<br>Kelly, C.J. *et al.* 2019 | |
| **Intraoperative** | *Prolonged Cardiopulmonary Bypass* | Beca, J. *et.al.* 2013 | *Non-neurotoxic/neuroprotective anesthesia Mesenchymal Stromal Cells Precision monitoring* |
| | *Prolonged Circulatory Arrest* | Beca, J. *et.al.* 2013 | |
| | *Anesthesia* | Andropoulos *et al.*, 2014 | |
| **Postoperative** | *Lower O2 saturation* | Galli, K. K. *et al.* 2004 | *Precision monitoring* |
| | *Lower Cerebral rSO2*[**] | Dent, C. L. *et al.*2005<br>Mcquillen, P. S. *et al.* 2007 | |
| | *Hypotension* | Galli, K. K. *et al.* 2004<br>Mcquillen, P. S. *et al.* 2007<br>Dimitropoulos, A. *et al.* 2013 | |
| **Outpatient** | *Developmental Cascades Increasing Environmental Demands/Expectations* | Sanz, J. *et al.*, 2021 | *Early Interventions (OT, Speech, PT) Parent-oriented Psychoeducation Neurocognitive Intervention Psychopharmacology Psychosocial Interventions* |
| | *Comorbid Medical/Genetic Conditions* | Marino, B. *et al.*, 2012<br>Latal, B. *et al.*, 2016<br>Wernovksy, G. *et al.* 2006 | |
| | *Vascular Processes During Aging Cardiovascular Events* | Keir, M. *et al.*, 2019<br>Melazzini, L. *et al.*, 2019 | *Psychosocial Interventions Transition Readiness Interventions Expansion of Neurodevelopmental Care* |

| | Risk Factors | Supporting Studies | Interventions under Investigation |
|---|---|---|---|
| | *Socio-Economic and Demographic Factors* | Bucholz *et al.*, 2021 | *Improving access/utilization of services Promoting a more stimulating home environment* |

*Peyvandi, S. et al. 2016 found infants prenatally diagnosed with CHD had less brain injury.(Peyvandi et al., 2016)

**Claessens, N.H.P *et al.* 2019 found lower cerebral rSO2 was NOT associated with brain injury.(Claessens, Jansen, et al., 2019)