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AHA SCIENTIFIC STATEMENT

# Neurodevelopmental Outcomes for Individuals With Congenital Heart Disease: Updates in Neuroprotection, Risk-Stratification, Evaluation, and Management: A Scientific Statement From the American Heart Association

*Endorsed by the Cardiac Neurodevelopmental Outcome Collaborative*

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**ABSTRACT:** Over the past decade, new research has advanced scientific knowledge of neurodevelopmental trajectories, factors that increase neurodevelopmental risk, and neuroprotective strategies for individuals with congenital heart disease. In addition, best practices for evaluation and management of developmental delays and disorders in this high-risk patient population have been formulated based on literature review and expert consensus. This American Heart Association scientific statement serves as an update to the 2012 statement on the evaluation and management of neurodevelopmental outcomes in children with congenital heart disease. It includes revised risk categories for developmental delay or disorder and an updated list of factors that increase neurodevelopmental risk in individuals with congenital heart disease according to current evidence, including genetic predisposition, fetal and perinatal factors, surgical and perioperative factors, socioeconomic disadvantage, and parental psychological distress. It also includes an updated algorithm for referral, evaluation, and management of individuals at high risk. Risk stratification of individuals with congenital heart disease with the updated categories and risk factors will identify a large and growing population of survivors at high risk for developmental delay or disorder and associated impacts across the life span. Critical next steps must include efforts to prevent and mitigate developmental delays and disorders. The goal of this scientific statement is to inform health care professionals caring for patients with congenital heart disease and other key stakeholders about the current state of knowledge of neurodevelopmental outcomes for individuals with congenital heart disease and best practices for neuroprotection, risk stratification, evaluation, and management.

**Key Words:** AHA Scientific Statements ■ developmental disabilities ■ heart defects, congenital ■ neuroprotection ■ psychosocial functioning ■ risk assessment



In 2012, the American Heart Association published a scientific statement on the evaluation and management of neurodevelopmental outcomes in children with congenital heart disease.[1] This scientific statement contained the first-ever guidance for health care professionals aimed at optimizing neurodevelopmental outcomes for this large and growing high-risk patient population. The next decade saw a paradigm shift in the care of pediatric patients with congenital heart disease, with exponential growth in the number of cardiac neurodevelopmental clinical programs and in research and quality improvement science to close knowledge gaps and to improve clinical care.[2–11]



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Since publication of the original scientific statement, new research has improved our understanding of neurodevelopmental trajectories across the life span[12–16] and factors that increase neurodevelopmental risk, including genetic predisposition,[17] fetal and perinatal factors,[18–20] surgical and perioperative factors,[5,21] socioeconomic disadvantage,[22] and parental psychological distress.[15,23] In addition, research has identified promising neuroprotective strategies with potential to prevent brain injury and modify trajectories,[7,24] as well as interventions that may begin to address neurodevelopmental and neuropsychological issues that occur throughout the life span.[10]

This scientific statement serves as an update to the 2012 scientific statement and reflects the dramatic expansion of knowledge over the past decade. The goal of this updated scientific statement is to inform health care professionals caring for patients with congenital heart disease and other key stakeholders about the current state of knowledge of neurodevelopmental outcomes for individuals with congenital heart disease and best practices for neuroprotection, risk stratification, evaluation, and management. It includes revised risk categories for developmental delay or disorder and an updated list of factors that increase neurodevelopmental risk. It also includes an updated algorithm for referral, evaluation, and management of individuals at high risk. An executive summary of key updates is listed in Table 1.

## TERMINOLOGY AND SCOPE

Congenital heart disease represents a broad spectrum of conditions, from simple defects that may resolve without intervention to complex lesions requiring multiple cardiac surgeries and catheter-based interventions during infancy and throughout the life span. In this scientific statement, the term "complex congenital heart disease" is used to denote defects that necessitate cardiac surgery within the first year of life for survival. The full spectrum of congenital heart disease was considered when identifying risk categories for developmental delay or disorder and factors that increase neurodevelopmental risk. It should be noted, however, that neurodevelopmental research has focused on individuals with complex congenital heart

**Table 1. Executive Summary of Key Updates**

| Section | Updates |
|---|---|
| Extent of the Problem | Updated information about survival rates and size of the affected population |
| | Updated information about change in neurodevelopmental outcomes over time |
| | Updated information about neurodevelopmental trajectories and impacts across the life span |
| Risk Categories for Developmental Delay or Disorder in Individuals With Congenital Heart Disease | Risk categories are now assigned sequentially from Risk Category 1 to 2 to 3 |
| | Updated information that further supports Risk Categories 1 and 2 |
| | Substantially revised Risk Category 3, requiring sequential clinical criteria assessment, including the need for intervention or hospitalization secondary to congenital heart disease and 1 or more factors that increase neurodevelopmental risk |
| | Removed Risk Category 4 (other conditions determined at the discretion of the medical home providers) |
| | Clarified that risk categories are intended to identify those individuals for whom congenital heart disease may have significantly contributed to their risk of developmental delay or disorder |
| Factors That Increase Neurodevelopmental Risk in Individuals With Congenital Heart Disease | Added new risk factors based on new knowledge (eg, fetal and perinatal factors, social and family factors, factors related to growth and development) |
| | Updated information about genetic predisposition and surgical and perioperative factors that support prior impressions |
| | Clarified that risk factors increase neurodevelopmental risk in individuals with congenital heart disease (ie, not only those in Risk Category 3) |
| | Added a new section on emerging risk factors |
| How to Protect Those at Risk for Developmental Delay or Disorder | Added a new section on promising neuroprotective strategies |
| Risk Stratification, Referral, and Evaluation | Updated the algorithm for risk stratification of individuals with congenital heart disease into high or low risk for developmental delay or disorder |
| | Updated the algorithm for referral, evaluation, and management of individuals at high risk |
| | Provided new content on individualized and culturally sensitive approaches to evaluation |
| | Added current recommendations by the Cardiac Neurodevelopmental Outcome Collaborative for age-based evaluation |
| | Added a new section on evaluation in adulthood |
| | Added a new section on evaluation through telehealth |
| | Added current recommendations by the American Academy of Pediatrics for developmental surveillance and screening |
| Management of Developmental Delay or Disorder in Individuals with Congenital Heart Disease | Updated information about management of developmental delay or disorder in infants, children, and adolescents |
| | Added a new section on management of neuropsychological deficits in adults |

disease; therefore, less is known about the outcomes of individuals with milder forms of congenital heart disease.

The term "neurodevelopmental" is used to denote the acquisition, development, and execution of cognitive, academic, motor, language, neuropsychological, adaptive, social-emotional, behavioral, and psychiatric functioning during the developmental period. This scientific statement predominantly uses the term "neuropsychological" when describing outcomes in adults.

This scientific statement also uses terminology in accordance with the 2020 American Academy of Pediatrics clinical report on developmental surveillance and screening.[25] "Developmental delay" denotes that a child is not developing or achieving skills according to the expected time frames. In contrast, "developmental disorder" refers to a mental or physical impairment or combination of mental and physical impairments that result in substantial functional limitations in major life activities. Surveillance, screening, and evaluation are defined as follows: (1) "Surveillance" is the process of recognizing individuals who may be at risk for developmental delay or disorder; (2) "screening" is the use of standardized tools to identify and refine that recognized risk; and (3) "evaluation" is a process to identify specific developmental delays or disorders.

Neurodevelopmental outcomes are intertwined with psychological and psychosocial outcomes.[26] For example, difficulties regulating emotions and behaviors are associated with anxiety, depression, and behavior problems, and deficits in attention and executive function are core features of attention-deficit/hyperactivity disorder (ADHD). This scientific statement incorporates, but does not comprehensively review, psychological and psychosocial outcomes because they are the focus of a recent statement.[26]

# EXTENT OF THE PROBLEM

## A Large and Growing Population With Developmental Delays and Disorders

Congenital heart disease is the most common birth defect, with an estimated prevalence of 9 per 1000 live births worldwide.[27] Approximately 25% of cases require surgical or catheter-based intervention during infancy.[28] Congenital heart disease affects all racial, ethnic, and socioeconomic groups, although its incidence varies according to sociodemographic characteristics.[29]

As a result of advancements in medical and surgical care over the past several decades, >90% of individuals with congenital heart disease in developed countries now survive to adulthood.[30] It was estimated that ≈2.4 million people were living with congenital heart disease in the United States as of 2010,[31] and this number has continued to grow. Unfortunately, neurodevelopmental outcomes have not meaningfully improved concomitantly with survival.[6] In a large study of children who underwent infant cardiac surgery from 1996 to 2009, later year of birth did not predict better neurodevelopmental outcomes after adjustment for center and type of congenital heart disease, but later year of birth was associated with an increased proportion of high-risk infants (complexity of congenital heart disease and prevalence of genetic/extracardiac anomalies).[6] There was a modest improvement in neurodevelopmental outcomes over time after adjustment for innate patient risk factors (eg, birth weight, genetic/extracardiac anomalies). However, increased survival among high-risk patients has resulted in a growing population with developmental delays and disorders and a greater need for societal resources over time.[6]

## Neurodevelopmental Trajectories and Impacts Across the Life Span

Although not every individual with congenital heart disease will have a developmental delay or disorder, neurodevelopmental deficits rank among the most enduring and impactful complications faced by individuals with complex congenital heart disease. Impairments in motor, language, and cognitive skills are evident as early as infancy,[6,14] often alongside atypical autonomic and state regulation and difficulties with feeding and sleep.[32] Neurodevelopmental trajectories for individuals with congenital heart disease and associated impacts across the life span are briefly presented here. Although the information in this section is organized by neurodevelopmental domain, it is important to note that these domains are not entirely distinct, with overlaps and associations between neurodevelopmental domains.

### *Intellectual Functioning*

Throughout childhood and adolescence, general cognitive ability (ie, IQ; mean, 100±15) is lower on average among individuals with congenital heart disease, even in those without an underlying genetic syndrome.[33] However, the average magnitude of IQ deficits varies by disease severity, ranging from 1 to 2 standard score points for individuals with atrial and ventricular septal defects to 12 standard score points for those with hypoplastic left heart syndrome (HLHS).[33] These differences in IQ are expected to persist into adulthood, with associated impacts on educational attainment and employment.[34]

### *Academic Achievement*

Children with complex congenital heart disease experience a nearly 25% higher risk of substandard academic outcomes and are 50% more likely to require special educational services compared with children without congenital heart disease.[35,36] Greater risk for deficits in literacy and numeracy skills persists throughout adolescence and young adulthood.[37] Adults with congenital heart disease have lower average educational attainment, which, in conjunction with neuropsychological deficits,

may have downstream consequences on employment and economic self-sufficiency.[38]

### Motor Skills

Motor impairments are common in infants, children, and adolescents with complex congenital heart disease.[39] However, severe motor impairments are more prevalent in younger children,[39] and motor development is a domain in which early delays are commonly detected,[14] likely related to altered fetal brain development, white matter injury (WMI), hospitalizations, and postoperative restrictions.[24]

### Speech-Language Skills

Children with complex congenital heart disease are at increased risk for deficits in speech and language development, including receptive and expressive language skills, speech sound production, and social communication.[40,41] Young children with complex congenital heart disease have demonstrated worse speech and language performance relative to their cognitive functioning, with a greater level of deficit in expressive than receptive language by 24 months.[40] This pattern of greater deficit in expressive compared with receptive language persists throughout school age, although older age predicts better language scores.[41]

### Neuropsychological Outcomes

Across studies, the neuropsychological domains of attention, executive function, processing speed, memory, language/verbal, and visual-spatial processing/visual-motor integration are areas of vulnerability for children and adolescents with complex congenital heart disease.[33,37] Emerging investigations of adult congenital heart disease (ACHD) outcomes have demonstrated similar concerns.[34] Neuropsychological profiles can vary and do not reliably conform to a singular pathognomonic neurobehavioral signature. Deficits in attention and executive function skills (eg, working memory, planning, problem-solving) are particularly common in individuals with complex congenital heart disease,[37,42] with a 4 and 2 times greater risk of impairment on standardized parent and teacher ratings, respectively.[42] In a population-based study, dementia risk was greater among adults with congenital heart disease compared with those without, with hazard ratios of 1.5 for adults with mild to moderate congenital heart disease and 2.0 for adults with severe congenital heart disease.[43] Risk for early-onset dementia (ie, <65 years of age) was particularly high in adults with any form of congenital heart disease compared with those without, with a hazard ratio of 2.6.

### Adaptive Functioning

Persistent adaptive skills deficits have been documented as early as 18 to 24 months of age in children who have undergone the Norwood/stage 1 or arterial switch operation.[44] Moreover, the SVR trial (Single Ventricle Reconstruction) showed that nearly 29% of 6-year-old children with single-ventricle heart disease (SVHD) scored within the at-risk or impaired ranges on an adaptive skills measure.[13] Data on adaptive functioning in adolescents with congenital heart disease are scant, although a recent study found deficits across a range of practical, conceptual, and social adaptive skills in a clinic-referred sample of adolescents with complex congenital heart disease, with particular weaknesses noted in functional academics, self-direction, social, and home living skills.[45]

### Social-Emotional and Behavioral Functioning

A systematic review and meta-analysis reported that 25% of children and adolescents with complex congenital heart disease exhibit internalizing (eg, anxiety, depression) or externalizing (eg, aggression, hyperactivity) behavior problems.[46] Children and adolescents with complex congenital heart disease also scored worse than controls or normative data on measures of social cognition,[46] which may contribute to the lower rates of marriage or significant relationships in adults with congenital heart disease.[34] Relative risk of autism spectrum disorder also appears to be higher in individuals with congenital heart disease. One population-based study found that children with congenital heart disease were approximately twice as likely to develop autism spectrum disorder than children without congenital heart disease.[47]

### Psychiatric Outcomes

Children and adolescents with congenital heart disease are at increased risk for anxiety, depression, and ADHD. Children 4 to 9 years of age with mild to severe forms of congenital heart disease were found to have ≈5 to 7 times higher odds of diagnosis or treatment for anxiety and depression compared with children without congenital heart disease.[48] In the Boston Circulatory Arrest Study (BCAS), adolescents with transposition of the great arteries (TGA) had a significantly higher lifetime prevalence of ADHD compared with adolescents without congenital heart disease (19% versus 7%).[15] Research also suggests a higher prevalence of psychiatric concerns in individuals with ACHD compared with the general population, with current or lifetime prevalence rates of mood or anxiety disorders approaching 50%.[26]

### Health-Related Quality of Life

Health-related quality of life (HRQOL) refers to the influence of an illness, medical therapy, or health services policy on the ability to function in and derive personal satisfaction from physical, psychological, and social life contexts.[49,50] In a systematic review focused on HRQOL in children and adolescents with complex congenital heart disease, self-reported physical health, psychosocial health, social functioning, and school functioning were worse compared with healthy children in multiple studies.[51] Similarly, a meta-analysis of HRQOL in children, adolescents, and adults with Fontan circulation found

lower scores on all HRQOL domains compared with healthy referents or normative samples, with the largest difference in physical functioning.[52] In 2420 patient-parent pairs from 10 hospitals across the United States and United Kingdom, lower patient- and parent-reported HRQOL was associated with higher disease severity and increased medical care use, poorer patient self-perception and competency, and increased patient behavioral and emotional problems.[53,54]

## RISK CATEGORIES FOR DEVELOPMENTAL DELAY OR DISORDER IN INDIVIDUALS WITH CONGENITAL HEART DISEASE

To aid in risk stratification of this large and growing patient population, this scientific statement proposes 3 categories of individuals with congenital heart disease at high risk for developmental delay or disorder according to current scientific evidence (Figure 1). Risk Categories 1 and 2 are unchanged from the 2012 scientific statement because current evidence continues to support their importance, but they have been reworded for clarity. Risk Category 3 has been changed from the 2012 scientific statement and now includes individuals who do not meet criteria for Risk Categories 1 or 2 but had an intervention or hospitalization secondary to congenital heart disease in infancy, childhood, or adolescence and have 1 or more factors known to increase neurodevelopmental risk. Factors that increase neurodevelopmental risk have been updated on the basis of current evidence and are described in the next section. Although the presence of 1 or more of these factors is required to meet criteria for Risk Category 3, these factors also increase neurodevelopmental risk for individuals in Risk Categories 1 and 2 (Figure 1).

The risk categories proposed in this statement are intended to identify those individuals for whom congenital heart disease may have significantly contributed to their risk of developmental delay or disorder. There are likely to be individuals with mild forms of congenital heart disease not requiring an intervention or hospitalization

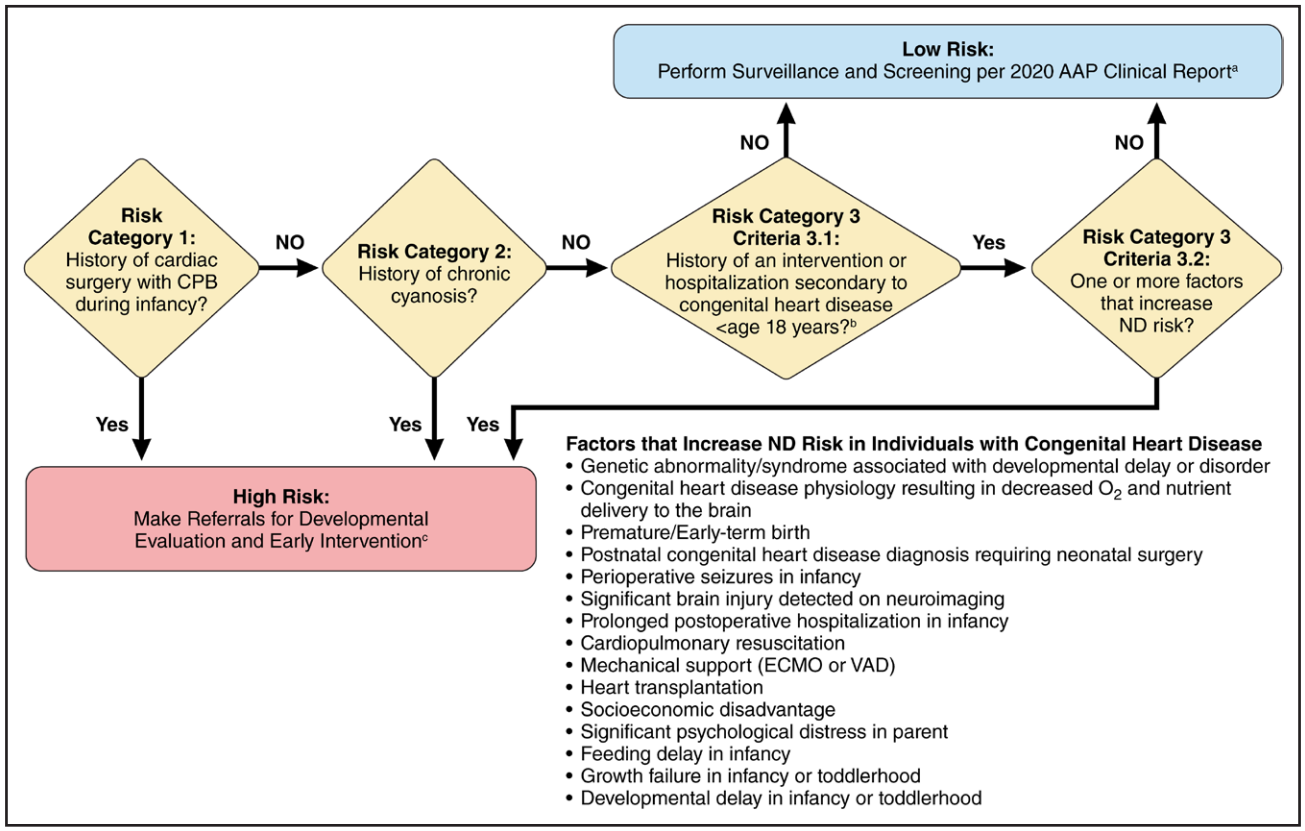


**Figure 1. Risk categories for developmental delay or disorder in individuals with congenital heart disease.**
AAP indicates American Academy of Pediatrics; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; ND, neurodevelopmental; and VAD, ventricular assist device. [a]Per the AAP clinical report on developmental surveillance and screening for the general pediatric population.[25] Clinical recommendations for co-occurring conditions (eg, premature birth, genetic syndromes) may also apply. Health care professionals can use their discretion when risk stratifying individuals with congenital heart disease who do not meet criteria for the risk categories proposed in this scientific statement but may require developmental evaluation. [b]Not including patent ductus arteriosus ligation or patent ductus arteriosus closure through intervention because of the lack of evidence that this intervention increases risk of developmental delay or disorder beyond the risk associated with premature birth. [c]Infants and toddlers who meet high-risk criteria should be referred directly to early intervention in addition to developmental evaluation to ensure that they receive intervention as soon as possible.

during infancy, childhood, or adolescence (eg, bicuspid aortic valve, small atrial or ventricular septal defect) who are at risk for developmental delay or disorder attributable to comorbidities or factors unrelated to their congenital heart disease. Although the identification of neurodevelopmental risk for these individuals is important, this is considered outside the scope of this scientific statement. Health care professionals can use their discretion when risk stratifying individuals with congenital heart disease who do not meet criteria for the risk categories proposed in this scientific statement but may require developmental evaluation.

## Risk Category 1: Individuals Who Had Cardiac Surgery With Cardiopulmonary Bypass During Infancy

The use of cardiopulmonary bypass (CPB) to repair congenital heart disease results in a hyperinflammatory response, an increased risk of microscopic and macroscopic emboli to the brain, and hypoperfusion resulting in global ischemia/reperfusion injury.[21] Several CPB variables affect perfusion of the developing neonatal and infant brain, including use and duration of deep hypothermic circulatory arrest (DHCA), total CPB time, cooling duration and degree, and regional cerebral perfusion.[24] The impact of DHCA on neurodevelopmental outcomes is nonlinear, without adverse effect in the era of the BCAS until its duration exceeded 41 minutes.[55] Moreover, the "safe" duration of DHCA is likely dependent on other factors such as patient age and other perfusion variables.[56] Research on the impact of hemodilution strategies during hypothermic CPB on neurodevelopmental outcomes suggests that lower hematocrit is nonlinearly associated with lower motor scores, with a plateau effect above 24%.[57] Although the hope was that use of regional (antegrade) cerebral perfusion would mitigate the adverse effects of DHCA, benefits were not demonstrated in numerous studies.[24,58,59] The type of intraoperative management strategy, although important, contributes less variance to neurodevelopmental outcomes than patient-specific and preoperative factors, perioperative hemodynamic instability, and postoperative morbidities.[5,21]

## Risk Category 2: Individuals With Chronic Cyanosis Who Did Not Have Cardiac Surgery With CPB During Infancy

Individuals with a history of chronic cyanosis who did not have cardiac surgery with CPB during infancy (eg, tetralogy of Fallot with major aortopulmonary collateral arteries, Ebstein anomaly) avoid some of the inherent risks associated with infant open heart surgery. However, these individuals are still at increased risk for developmental delay or disorder because of chronic hypoxemia caused by their underlying congenital heart disease. A systematic review evaluating the effect of chronic or intermittent hypoxia on cognition in childhood found adverse impacts of hypoxia on development, behavior, and academic achievement, including in patients with congenital heart disease.[60] In children with profound cyanosis from TGA with intact ventricular septum who underwent a Mustard procedure between 6 months to 6 years of age, older age at repair was associated with lower IQ, with greatest impact on perceptual motor function.[61] The impact of chronic hypoxemia on neurodevelopmental outcomes is likely multifactorial, including direct effects of hypoxia on brain structure and microstructure,[62] as well as medical, social, and environmental factors associated with prolonged severe cyanosis.

## Risk Category 3: Individuals With Increased Neurodevelopmental Risk Who Did Not Have Infant Cardiac Surgery With CPB and Were Not Chronically Cyanotic

Individuals who require an intervention or hospitalization secondary to congenital heart disease during infancy, childhood, or adolescence and do not meet criteria for Risk Categories 1 or 2 may still be at increased risk for developmental delay or disorder on the basis of their genetic, medical, surgical, perioperative, and social histories. Many factors that increase neurodevelopmental risk (Figure 1) have a heightened prevalence within the congenital heart disease population because of high rates of genetic syndromes,[17] growth abnormalities,[63] feeding issues,[64] medical and surgical complications,[21] and parental psychological distress.[23]

Individuals with mild forms of congenital heart disease not requiring an intervention or hospitalization during infancy, childhood, or adolescence are not included within Risk Category 3 because this category is intended to identify those individuals for whom congenital heart disease may have significantly contributed to their risk of developmental delay or disorder. In addition, infants with patent ductus arteriosus ligation or patent ductus arteriosus closure through intervention are not included because of the lack of evidence that this intervention increases risk of developmental delay or disorder beyond the risk associated with premature birth. It should be noted, however, that some of these individuals will be at risk for developmental delay or disorder attributable to comorbidities or factors unrelated to their congenital heart disease. For these individuals, risk criteria specific to the comorbidity or other factor can be applied (eg, children born preterm[65] and children with Down syndrome,[66] 22q11.2 deletion syndrome,[67] Williams syndrome,[68] or Turner syndrome[69]).

## FACTORS THAT INCREASE NEURODEVELOPMENTAL RISK IN INDIVIDUALS WITH CONGENITAL HEART DISEASE

Over the past decade, research has greatly improved our understanding of factors that increase neurodevelopmental risk in individuals with congenital heart disease. Neurodevelopmental risk factors may be categorized into genetic, fetal and perinatal, surgical and perioperative, social and family, and early growth and development factors. These neurodevelopmental risk factors are associated with abnormal brain development, brain injury, or contextual and physiological risk, which can result in adverse neurodevelopmental, psychosocial, and physical outcomes and ultimately poorer HRQOL (Figure 2).[7,17–24] Specific criteria for each neurodevelopmental risk factor based on current literature are listed in Table 2. Some identified risk factors may apply only to those with complex congenital heart disease, which is the patient population that has been the focus of most cardiac neurodevelopmental research to date. However, many neurodevelopmental risk factors (eg, genetic, social, family, and growth factors) likely also affect individuals with milder forms of congenital heart disease. Current knowledge of factors that increase neurodevelopmental risk in individuals with congenital heart disease is reviewed here. Evidence from studies outside of the congenital heart disease literature is included when findings are likely relevant for individuals with congenital heart disease (eg, socioeconomic disadvantage, parental psychological distress).

Neurodevelopmental risk factors likely differ in their level of neurodevelopmental impact and may be cumulative or synergistic. Current knowledge of these relationships is limited, and the evidence to date does not yet support triaging high-risk patients on the basis of the relative importance of individual risk factors or cumulative risk. However, research is urgently needed to evaluate the relative impact of neurodevelopmental risk factors and how these risk factors interact given the limited neurodevelopmental resources to serve this large and growing patient population.

### Genetic Factors

#### *Genetic Abnormality or Syndrome Associated With Developmental Delay or Disorder*

New genomic technologies have dramatically expanded our understanding of the genetic basis of congenital heart disease. Approximately 20% to 30% of congenital heart disease cases are caused by known genetic variants, including aneuploidies, pathogenic copy number variants, and single-gene disorders.[17] Genetic variants in fundamental biological pathways may alter fetal development not only of the heart but also of the brain and other organs.[17,70] Shared genetic contributions to cardiac and brain development are evident from a study that identified de novo mutations in 28% of children who had congenital heart disease along with neurodevelopmental

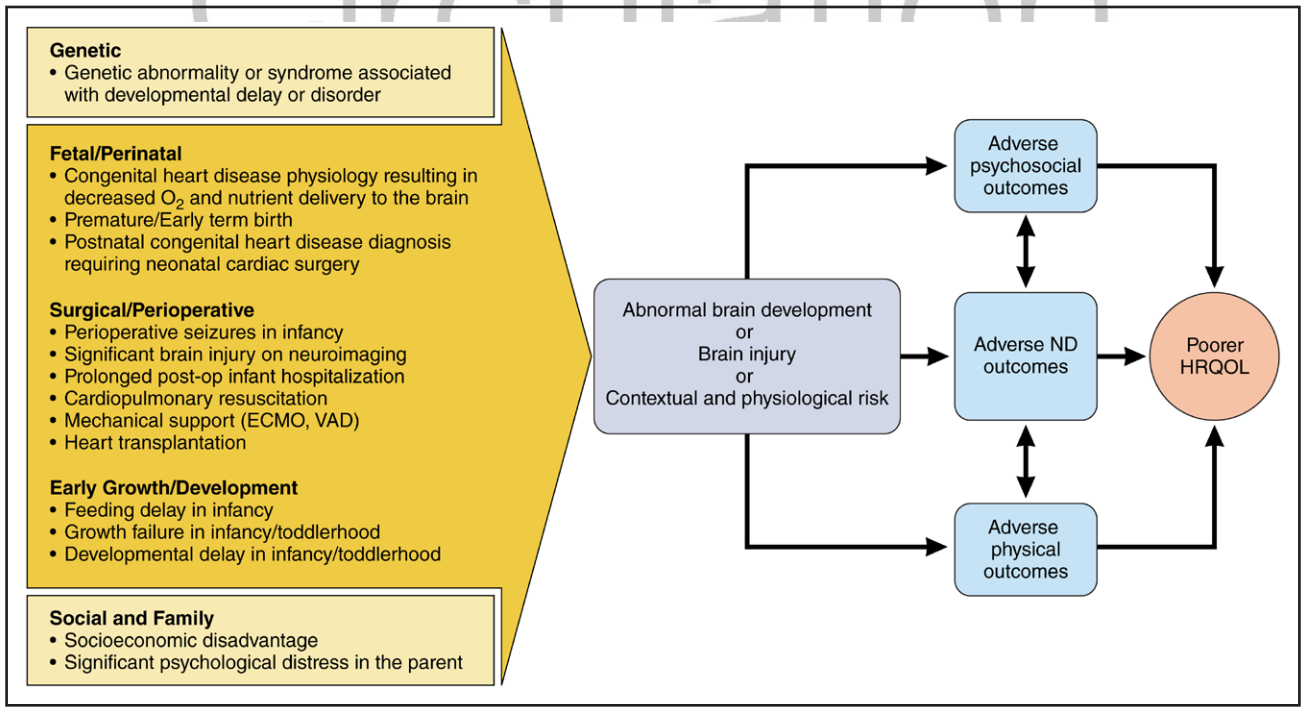


**Figure 2. Factors that increase neurodevelopmental risk in individuals with congenital heart disease.**
ECMO indicates extracorporeal membrane oxygenation; HRQOL, health-related quality of life; ND, neurodevelopmental; and VAD, ventricular assist device.

**Table 2. Factors That Increase Neurodevelopmental Risk in Individuals With Congenital Heart Disease**

| Domain | Risk factor | Criteria |
|---|---|---|
| Genetic | Genetic abnormality or syndrome associated with developmental delay or disorder | Genetic abnormality or syndrome AND<br>Abnormality/syndrome known to be associated with developmental delay or disorder* |
| Fetal and perinatal | Congenital heart disease physiology resulting in decreased oxygen and nutrient delivery to the brain | For example, TGA, SVHD |
| | Premature/early-term birth | Born before 37 wk of gestation OR<br>TGA or SVHD <39 wk of gestation |
| | Postnatal diagnosis of congenital heart disease requiring neonatal cardiac surgery | Postnatal congenital heart disease diagnosis AND<br>History of neonatal cardiac surgery |
| Surgical and perioperative | Perioperative seizures in infancy | Clinical seizure OR<br>Seizure noted on EEG |
| | Significant brain injury detected on neuroimaging | Brain MRI/CT or head ultrasound with significant brain injury noted |
| | Prolonged postoperative hospitalization in infancy | Postoperative hospitalization >14 d in infancy |
| | Cardiopulmonary resuscitation | History of cardiopulmonary resuscitation |
| | Mechanical support | History of ECMO support OR<br>History of VAD support |
| | Heart transplantation | History of heart transplantation |
| Social and family | Socioeconomic disadvantage | Household poverty OR<br>Neighborhood poverty (poverty rate ≥30% within the census track) OR<br>Maternal education less than high school diploma/GED |
| | Significant psychological distress in the parent | Parental diagnosis of anxiety, depression, or posttraumatic stress disorder OR<br>Clinically significant symptoms of parental anxiety, depression, posttraumatic stress, or parenting stress on a standardized measure |
| Growth and development | Feeding delay in infancy | Need for supplemental tube feeding outside the hospital |
| | Growth failure in infancy or toddlerhood | Small for gestational age (birth weight <10th percentile for gestational age) OR<br>Weight-for-age *Z* score ≤-2 (at time of surgery) OR<br>Length-for-age *Z* score ≤-2 (infancy or toddlerhood) OR<br>Head circumference-for-age *Z* score ≤-2 (birth, infancy, or toddlerhood) |
| | Developmental delay in infancy or toddlerhood | Developmental delay identified in infancy or toddlerhood |

CT indicates computed tomography; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram; GED, general educational development; MRI, magnetic resonance imaging; SVHD, single-ventricle heart disease; TGA, transposition of the great arteries; and VAD, ventricular assist device.

*See the work by Pierpont et al[17] for neurodevelopmental and psychiatric features of genetic abnormalities and syndromes associated with congenital heart disease.





disabilities and extracardiac anomalies but only 3% of those with isolated congenital heart disease.[70] Moreover, compared with the general population, individuals with congenital heart disease are more likely to have protein-truncating and deleterious missense de novo variants in genes affecting the connectome.[71] Even simple forms of congenital heart disease may be associated with genetic syndromes that affect neurodevelopment. Among children with valvar pulmonary stenosis, 14% have Noonan syndrome or a related disorder.[72] These data suggest that developmental delays and disorders in individuals with congenital heart disease are attributable, in part, to genetic variants common to cardiac and brain development. The neurodevelopmental and psychiatric features of genetic abnormalities and syndromes known to be associated with congenital heart disease are described in a 2018 scientific statement.[17] New genes associated with congenital heart disease continue to be discovered and will enhance our understanding of the associations between genetic abnormalities, congenital heart disease, and neurodevelopmental outcomes.

## Fetal and Perinatal Factors

### *Congenital Heart Disease Physiology Resulting in Decreased Oxygen and Nutrient Delivery to the Brain*

Fetuses with certain forms of complex congenital heart disease have abnormal brain development beginning in the third trimester. Fetuses and newborns with TGA and SVHD appear to be at highest risk, with smaller brain volumes, less organized white matter tracts, and abnormal brain metabolism,[73,74] all of which can contribute to impaired neurodevelopmental outcomes.[19] Multimodal fetal imaging techniques have demonstrated how altered cardiovascular physiology can lead to flow and

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oxygenation disturbances affecting in utero brain development. By combining fetal brain magnetic resonance imaging (MRI) and cardiovascular MRI, a study found a strong correlation between fetal cerebral oxygen consumption and brain size in fetuses with complex congenital heart disease.[75]

### *Premature/Early-Term Birth*

Although advancements in surgical techniques have allowed surgeons to perform congenital heart surgery in smaller and more premature infants with decreased mortality, there has been a concomitant increase in major neonatal morbidities such as intraventricular hemorrhage, periventricular leukomalacia, and other medical complications.[76] It is well known that premature birth poses a risk for neurodevelopmental abnormalities.[65] In individuals with certain forms of complex congenital heart disease (eg, TGA, SVHD), even early-term birth (ie, 37–38 weeks of gestation) is associated with worse neurodevelopmental outcomes compared with full-term birth.[18,77]

### *Postnatal Diagnosis of Congenital Heart Disease Requiring Neonatal Cardiac Surgery*

Prenatal detection of complex congenital heart disease allows timely initiation of prostaglandins and decreases risk for hemodynamic instability in the period before a neonatal cardiac operation.[78] Postnatal diagnosis of TGA and SVHD can be associated with greater risk for preoperative brain injury and less robust brain development in the neonatal period compared with prenatal detection.[20] In addition, postnatal diagnosis of TGA has been associated with worse neurodevelopmental outcomes in early childhood compared with prenatal diagnosis.[79]

## Surgical and Perioperative Factors

### *Perioperative Seizures in Infancy*

Seizures may be associated with adverse neurodevelopmental outcomes because they were caused by underlying brain damage, they caused brain damage, or both. Seizures occurred in 7.4% of neonates after cardiac surgery in a recent multicenter study, and most were detected only by continuous electroencephalographic monitoring.[80] Among bypass variables, longer DHCA is most highly associated with increased risk of seizures.[59,81] In the BCAS, postoperative seizures, detected clinically or by continuous electroencephalographic monitoring, were associated with worse neurodevelopmental outcomes at 16 years of age on tests of academic achievement, general memory, executive function, visual-spatial function, and social cognition.[82] The occurrence of perioperative seizures was also an independent risk factor for adverse adaptive behavior at 6 years of age in the SVR cohort.[59]

### *Significant Brain Injury Detected on Neuroimaging*

WMI occurs preoperatively in 20% of infants with complex congenital heart disease and is associated with brain immaturity.[83] New WMI after cardiac surgery has been found to occur in >40% of infants,[83] although recent data suggest that this rate is declining with improvements in postoperative management.[84] The greatest risk for WMI occurs among those with SVHD with arch obstruction.[83] Additional risk factors for postoperative WMI are longer duration of CPB, higher postoperative lactate level, and preoperative WMI and brain immaturity.[83] Moderate to severe degrees of WMI are independently associated with cognitive and motor outcomes in childhood.[85,86] Children and adolescents with Fontan circulation were found to have reduced subcortical and cortical volumes and cortical thicknesses, across all brain lobes, compared with healthy control subjects.[87] By adolescence, disruption of white matter pathways is associated with worse cognitive functioning in patients with TGA.[88,89] Moreover, studies of the connectome in adolescents with TGA reveal that differences in neurodevelopmental outcomes, including ADHD and executive function, are associated with global differences in white matter network topology.[90,91]

Global hypoxic-ischemic brain injury may occur as a result of cardiac arrest or a period of extremely low oxygen delivery to the brain and is associated with worse neurodevelopmental outcomes.[92–94] Cerebral microembolic and macroembolic events are also common in the complex congenital heart disease population. Microhemorrhages were detected in 21% and 54% of adolescents with TGA and Fontan circulation, respectively, but were not associated with neurodevelopmental outcomes.[82,95] The prevalence of stroke on brain MRI in neonates with complex congenital heart disease is 5% to 11% preoperatively and 4% to 21% postoperatively.[83,84] Furthermore, evidence of stroke on brain MRI was noted among 13% of adolescents with Fontan circulation; concerningly, 40% of these had been silent.[95]

### *Prolonged Postoperative Hospitalization in Infancy*

Longer hospital length of stay after infant heart surgery is found to increase neurodevelopmental risk in virtually all studies including this variable.[5,24,96] The mechanisms by which longer hospital length of stay is associated with worse neurodevelopmental outcomes are likely multifactorial and interactive. Risk factors such as unanticipated complications; acute or chronic hypotension; acute or chronic hypoxia; persistent inflammation; altered hormonal milieu; noxious stimulation from bright lights, noise, and pain; lack of positive stimulation; maternal separation; oral feeding disruptions; and exposure to plasticizers have all been posited to play a role.[5,97,98] Infants and particularly neonates are especially susceptible to environmental toxicities because of brain immaturity.

### *Cardiopulmonary Resuscitation*

Cardiac arrest requiring resuscitation occurs in ≈7 per 1000 hospitalizations of children with cardiovascular disease, >10-fold higher than the rate in hospitalizations of

children without cardiovascular disease.[92] Outcomes after cardiac arrest in children with congenital heart disease are affected by whether the arrest is witnessed, its cause, the quality of resuscitation, and the time to return of circulation, either through return of spontaneous circulation or by the use of extracorporeal membrane oxygenation (ECMO).[92] Hypoxic-ischemic brain injury from cerebral hypoperfusion is associated with oxidative stress, reperfusion injury, and ongoing neuronal cellular necrosis and apoptosis that can continue for weeks after cardiac arrest. In children who had cardiac arrest requiring chest compressions for at least 2 minutes and remained dependent on mechanical ventilation after the return of circulation, survival with favorable 12-month adaptive functioning (ie, standard score ≥70) occurred in only 37% with in-hospital arrest and 16% with out-of-hospital arrest.[93,94] Moreover, brain death or withdrawal of support for poor neurological prognosis were leading causes of death after in-hospital or out-of-hospital cardiac arrest.[93,94]

### *Mechanical Support (ECMO or Ventricular Assist Device)*

Patients supported by ECMO are at high risk for stroke and hypoxic-ischemic injury.[99] Stroke may be secondary to thromboembolic events related to circuit issues or ineffective anticoagulation. Hypoxic-ischemic injury may occur before ECMO, secondary to cardiac arrest or severe hypotension, or during ECMO secondary to hypotension from circuit issues. Children supported by ECMO for cardiac indications at <3 years of age frequently scored ≥1 SD below the normative mean in gross motor (61%), language (43%), and cognitive (29%) domains.[100] Risk factors included older age at first cannulation and a greater number of cardiac catheterizations and operations.[100] In addition, ≈10% of children supported by ventricular assist devices (VADs) were found to experience strokes, many within the first 30 days after VAD implantation.[101] Recent reductions in stroke incidence and rates of bleeding and thrombosis in patients supported with ECMO or VAD have been attributed to the use of bivalirudin, a direct thrombin inhibitor, and to improvements in bedside VAD management.[102]

### *Heart Transplantation*

Studies on neurodevelopmental outcomes after heart transplantation have indicated developmental test scores in the range of 1 to 2 SD below the normative mean[103] and verbal and nonverbal IQ scores that are approximately 1 SD below the normative mean.[104,105] Compared with children with cardiomyopathy, those whose transplantation was performed for congenital heart disease scored worse on tests of cognitive functioning and expressive language.[104] In adolescents who underwent heart transplantation in infancy, transplant recipients demonstrated substantial impairments in cognitive functioning, receptive and expressive language, visual motor integration, fine motor, and executive function, raising concerns about their ability to reach independence by adulthood.[105]

## Social and Family Factors

### *Socioeconomic Disadvantage*

Socioeconomic disadvantage exerts a powerful influence on neurodevelopment, with evidence supporting relationships between child poverty and brain structure and function.[106,107] Children living in poverty are at heightened risk for developmental delays, academic difficulties, and emotional and behavioral problems.[108,109] A systematic review found that poverty and lower maternal educational attainment were associated with worse neurodevelopmental outcomes in children with congenital heart disease.[22] In the SVR trial, lower maternal education and neighborhood socioeconomic status (census-based score including income, education, and occupation) were associated with greater delays in communication and problem-solving skills for children with congenital heart disease at 3 years of age, with progressive delays in problem-solving and fine motor skills between 3 and 5 years of age.[109] A study of children with tetralogy of Fallot found that neighborhood-level factors related to poverty were associated with greater odds of abnormal neurodevelopment.[108]

### *Significant Psychological Distress in the Parent*

A systematic review found that >80% of parents of children with complex congenital heart disease had clinically significant symptoms of trauma, 25% to 50% had symptoms of depression or anxiety, and 30% to 80% experienced severe psychological distress.[23] These problems typically begin early, with high rates of parental anxiety, depression, and posttraumatic stress after fetal cardiac diagnosis and during the infant hospitalization.[23,110] Studies have shown an impact of maternal stress during pregnancy on the developing fetal brain through epigenetic mechanisms involving the placenta.[111] In the congenital heart disease population, increased maternal stress and anxiety during pregnancy were found to be associated with smaller fetal hippocampal and cerebellar volumes.[110] In the BCAS, parenting stress when the child was 8 years old predicted lifetime risk of an ADHD diagnosis and global psychosocial functioning at 16 years of age and was a stronger predictor of psychosocial outcomes than illness severity or other medical characteristics.[15] Parental posttraumatic stress was also associated with adolescent global psychosocial functioning.[15] Although most congenital heart disease research on neurodevelopmental outcomes has focused on the impact of maternal mental health, research in the general population suggests that paternal mental health may also affect neurodevelopmental outcomes.[112]

## Factors Related to Growth and Development

### *Feeding Delay in Infancy*

Infants with complex congenital heart disease often require supplemental tube feedings because of inattention, swallowing dysfunction, or other medical complications.[64]

Coordinated oral feeding of suck-swallow-breathe patterns is a complex cognitive and motor process, requiring attention and maintenance of an awake, alert state.[64] The need for supplemental tube feedings during infancy, which may indicate underlying cognitive or motor delays, is associated with worse neurodevelopmental outcomes in individuals with congenital heart disease.[12,14,113,114]

### Growth Failure in Infancy or Toddlerhood

Growth failure is common in infants and young children with congenital heart disease.[63] A recent systematic review examining the impact of growth on neurodevelopmental outcomes in infants with congenital heart disease reported that poor growth in utero, as measured by weight and head circumference at birth, has been associated with worse neurodevelopmental outcomes, and being small for gestational age predicted lower IQ and communication skills.[63] Lower weight at the time of infant cardiac surgery has also been associated with worse developmental test scores.[63] In addition, poorer linear growth and smaller head circumference in infancy and toddlerhood have been associated with worse neurodevelopment outcomes for children with congenital heart disease.[12,113–115] Although clear cutoffs for weight-for-age *Z* scores, length-for-age *Z* scores, or head circumference-for-age *Z* scores have not yet been determined for poor neurodevelopmental outcomes, a history of growth failure in infancy or toddlerhood is associated with worse neurodevelopmental outcomes for individuals with congenital heart disease.

### Developmental Delay in Infancy or Toddlerhood

A history of developmental delay in infants and young children with congenital heart disease increases long-term neurodevelopmental risk.[12,47,116] Among children in the SVR trial, worse developmental test scores at 14 months of age were significantly associated with worse parent-reported development at 3 years of age.[12] Similarly, among children in the BCAS, developmental test scores at 1 year of age were significantly associated with IQ and academic achievement scores at 8 years of age.[116] However, a developmental delay or disorder can emerge at later ages even among individuals with normal development during infancy or toddlerhood.[12,116] In the BCAS, more than half of the children with low scores at 8 years of age exhibited normal development at 1 year of age.[116]

## Emerging Factors

Established risk factors for neurodevelopmental impairment explain only approximately one-third of the variance in outcomes for individuals with congenital heart disease.[6] Emerging risk factors have been identified through preliminary research. Further investigation is needed to determine the clinical significance of these and other potential risk factors, to enhance predictive models for neurodevelopmental outcomes, and to uncover new opportunities for neuroprotection. Preliminary evidence for the role of emerging factors in brain development and neurodevelopmental outcomes for individuals with congenital heart disease is presented below.

### Effect of Altered Cardiovascular Physiology on In Utero Brain Blood Flow And Development

Multimodal fetal imaging techniques demonstrate how altered cardiovascular physiology can lead to brain blood flow disturbances, affecting in-utero brain development. Fetal transcranial Doppler can assess cerebral vascular resistance in the middle cerebral artery. Fetuses with HLHS have a lower resistance within the middle cerebral artery.[117] This likely reflects a response to overcome an overall decrease in oxygen and nutrient delivery (eg, glucose) to the fetal brain.[117] This concept has been directly explored with the use of novel fetal cardiac MRI techniques. One MRI study in fetuses with congenital heart disease found that reductions in umbilical vein oxygen content were associated with a mean reduction in ascending aortic saturation of 10%, whereas cerebral blood flow and cerebral oxygen extraction were no different from those of controls.[75] This accounted for a mean 15% reduction in cerebral oxygen delivery and a 32% reduction in cerebral oxygen consumption in fetuses. Cerebral oxygen consumption was directly correlated with fetal brain volume. Future research is needed to determine how these early alterations in cardiovascular physiology affect long-term neurodevelopmental outcomes.

### Abnormal Placental Development

The placenta appears to be an important organ in mediating environmental factors for the developing fetus. Several studies have observed abnormal placental development and function in fetuses with congenital heart disease, including thrombosis, infarction, immature villi, and abnormal placental perfusion.[118] It is unclear whether placental abnormalities precede the development of congenital heart disease, placental pathology develops secondary to abnormal cardiovascular physiology, or common risk factors contribute to both the development of congenital heart disease and an abnormal placenta. Shared genetic pathways in placental, cardiac, and brain development involving angiogenesis are hypothesized to play a role in the pathology observed in fetuses with congenital heart disease.[119] Placental dysfunction may contribute to decreased fetal cerebral oxygen delivery, resulting in poor brain growth, brain abnormalities, and impaired neurodevelopment.[118] However, more research is needed to evaluate this theory.

### Prolonged or Repeated Anesthetic Exposure

Animal studies have shown detrimental effects of prolonged anesthetic exposure on the developing brain. In particular, prolonged exposure to volatile anesthetic agents is associated with diffuse WMI in preclinical models.[120] Mammalian models suggest that an array of

analgesics and sedatives, including opioids and benzodiazepines, may adversely affect the creation of neurons and synapses, as well as production of myelin by brain oligodendrocytes.[121] In human infants, repeated anesthetic exposure may be neurotoxic and cause brain injury.[122] Volatile anesthetic use during neonatal cardiac surgery has been associated with lower developmental test scores at 12 months of age.[123] Larger and more comprehensive prospective studies are needed to elucidate the effects of prolonged and frequent exposure to anesthetic, opioid, and sedative agents and their interactions with patient-specific and perioperative risk factors.

### *Exposure to Neurotoxic Chemicals*

Recent studies suggest that cardiac surgery results in significant exposure to neurotoxic chemicals from medical devices, tubing, and blood bags.[98] Greater toxicant exposures during infancy, as measured by urine and blood biomarkers of chemicals, particularly phthalates, are associated with worse language and motor scores in toddlers with congenital heart disease.[124] Exposure to industrial solvents such as cyclohexanone negatively influenced neurodevelopmental performance at 12 months of age.[125] More research is needed to determine the breadth and depth of environmental toxicant exposure for infants and children with congenital heart disease and its independent effect on neurodevelopment.

### *Multiple Interventions and Complications in Childhood*

Much of the literature on the impact of multiple interventions and complications in childhood focuses on SVHD, including a study demonstrating that increased reinterventions were associated with worse neurodevelopmental outcomes before the Fontan procedure.[126] In the SVR trial, greater course complexity and morbidity were associated with worse scores on measures of behavioral symptoms and HRQOL at 6 years of age.[59] By adolescence, more operations and operative complications were independently associated with worse neurodevelopmental outcomes in a Fontan cohort study.[95] More research is needed to determine the impact of multiple interventions and complications in children with other forms of congenital heart disease.

## HOW TO PROTECT THOSE AT RISK FOR DEVELOPMENTAL DELAY OR DISORDER

Over the past decade, research has identified promising neuroprotective strategies with potential to prevent or mitigate brain injury and to modify neurodevelopmental trajectories. Although these neuroprotective strategies have not been shown in clinical trials to consistently prevent brain injury or to improve longer-term neurodevelopmental outcomes, observational studies suggest that they may prevent or mitigate initial brain injury or early neurodevelopmental deficits. Current knowledge of neuroprotection for individuals with congenital heart disease is reviewed in the next section.

### Fetal and Perinatal Neuroprotection

#### *Prenatal Detection of Congenital Heart Disease*

Neuroprotection begins with prenatal detection of congenital heart disease, particularly for those with ductdependent lesions requiring a neonatal intervention.[78] Although prenatal detection rates have improved over time, a substantial percentage of patients continue to be diagnosed with congenital heart disease after birth.[127] Research demonstrates that patients with lower socioeconomic status have lower rates of prenatal detection of congenital heart disease, possibly related to inadequate access to subspecialist care.[127] Efforts to increase education about congenital heart disease detection and to improve linkages between primary and subspecialist care in communities with lower socioeconomic status may decrease these disparities.[127]

#### *Timing of Delivery and Delivery Room Practices*

Planning for a full-term delivery is key in minimizing additive effects of prematurity on brain development and brain injury. Most fetuses with congenital heart disease can be delivered full-term by spontaneous vaginal delivery or induction of labor, with cesarean delivery being reserved for obstetrical indications.[78] However, alterations to typical delivery planning may be necessary (eg, early-term delivery at 37–38 weeks, scheduled cesarean delivery) within the context of a heart defect requiring immediate intervention (eg, HLHS with intact/restrictive atrial septum, TGA with intact atrial septum).[128] Delivery room practices may include access to immediate intervention for types of congenital heart disease prone to hemodynamic instability shortly after birth.[78]

### Surgical and Perioperative Neuroprotection

#### *Timing of Cardiac Surgery*

Timing of cardiac surgery in a neonate with complex cyanotic heart disease must balance the recovery of vital organ injury secondary to preoperative hemodynamic compromise with a shorter duration of time to surgery to minimize preoperative risk factors for brain injury, including hemodynamic instability and worsening cerebral oxygenation.[129] In neonates with TGA, longer time to arterial switch operation increased risk for WMI on preoperative MRI.[130] Similarly, neonates with TGA who had an arterial switch operation at >2 weeks of age were found to have impaired brain growth and worse language development than those who underwent surgery at a younger age.[131] In neonates with HLHS, older age at Norwood/stage 1 procedure was associated with a greater incidence of new postoperative WMI.[132] Studies applying noninvasive

optical techniques in preoperative newborns with TGA and HLHS show a temporal trend toward lower cerebral oxygen saturation and higher oxygen extraction.[129] Unmeasured factors that delay surgery may cause confounding by indication, thereby limiting causal inference. However, current data suggest that in a stable neonate, earlier surgery may carry benefit for brain health.

### *Good Technical Operation*

Published studies suggest that neurodevelopment is best optimized by an operation that is expeditious and technically satisfactory (ie, leaves the child with an excellent hemodynamic result).[21] Longer total support time was found to be associated with worse neurodevelopmental outcomes,[21] although this can be a surrogate for more complex anatomy and greater difficulty of surgery. Children with major residual lesions have also been shown to have adverse cognitive and motor outcomes at 16 months of age.[133]

### *Minimizing Deleterious Effects of CPB*

CPB has multiple deleterious effects, including gaseous and thrombotic emboli, hemolysis, hemorrhage, and inflammation. Oxygen delivery can be compromised by excessive hemodilution, rapid cooling, alkaline pH, and inadequate flow rate.[134] It is important for the surgical, anesthesia, and perfusion team to have a good understanding of the interaction of these factors to optimize cerebral protection, particularly if the team plans to use DHCA.[56] Methods of selective perfusion of the brain, often with minimal hypothermia, are widely used as an alternative to DHCA, although details of technique such as flow rate and cannulation vary widely, and superior outcomes have not been demonstrated.[58]

### *Monitoring of Cerebral Perfusion and Oxygen Delivery*

Patients with congenital heart disease are at risk of inadequate oxygen delivery to the brain during surgery and perioperatively. Individuals with a single ventricle and systemic outflow obstruction with a shunt or ductal-dependent circulation, as well as those with a heavy collateral burden, are particularly at risk as a result of steal from the cerebral/systemic to the pulmonary circulation.[135] Thus, it may be beneficial to avoid a significant reduction in the pulmonary-to-systemic resistance ratio (eg, through hyperventilation or 100% oxygen administration). Cerebral near-infrared spectroscopy may be useful to monitor oxygen delivery to the brain, particularly in neonates and infants, although its reliability in predicting and preventing brain injury remains controversial.[136] Furthermore, there is concern that it may be less reliable in people with darker skin.[137]

## In-Hospital Neuroprotection

### *Family-Centered Developmental Care*

On the basis of neuroprotective benefits demonstrated in the premature infant population, family-centered developmental care has been suggested as a key approach to providing neuroprotection to hospitalized infants with congenital heart disease.[97] Developmental care encompasses interventions in the hospital setting designed to individualize care and to minimize stress to maximize neurological development. Elements of developmental care include control of external stimuli (vestibular, auditory, visual, tactile), regulatory infant support, clustering of care activities, positioning support, cue-based feeding, and nonpharmacological comfort measures. Infant behavioral cues inform the response needed to meet the infant's unique neurodevelopmental needs as the infant interacts with their environment.[97] Developmental care interventions have been well studied in premature infants, demonstrating benefits in early psychomotor and cognitive development.[138] Developmental care interventions have not yet been thoroughly investigated in infants with congenital heart disease, although studies on specific developmental care practices such as skin-to-skin care and massage have demonstrated safety and feasibility for infants with congenital heart disease.[139,140]

### *Supporting Parents in the Role of Primary Caregiver*

Family-centered developmental care recognizes parents as primary caregivers and supports parental participation in care, information sharing, shared decision-making, and collaboration between families and health care professionals.[97] It emphasizes authentic partnership with parents to enact their parental role, including those for whom English is not the primary language or who may be unable to attend bedside rounds because of familial, financial, or other reasons. Preliminary research in congenital heart disease suggests that interventions focused on supporting parental partnership in care in the hospital setting or building parental coping skills can increase participation in care,[141] reduce maternal anxiety,[140,142] and improve infant neurodevelopment.[143]

### *Habilitative Services*

The inpatient care setting provides important opportunities for infants and children to receive timely, intensive therapies, including physical, occupational, and speech-language therapies. National neonatal and perinatal associations endorse the integration of physical and occupational therapists and speech-language pathologists for the provision of neuroprotective services to infants admitted to neonatal intensive care units,[144] including those that provide care to infants with congenital heart disease. Inpatient habilitative services improve neurobehavioral organization and motor and cognitive development in hospitalized neonates born preterm and may have similar benefits for infants with congenital heart disease.[145,146] Speech-language pathologists can provide strategies to support safe oral feeding and to mitigate oral aversion, including oral sensory motor stimulation, which has been

shown to support independent oral feeding in premature infants.[147] Practice recommendations for critically ill children include early mobility and rehabilitative strategies to support passive range of motion, positioning, readiness for mobility, assisted transfers, and ambulation.[148]

## Supporting Transition From Hospital to Home

### *Early Discharge Planning and Assessment of Postdischarge Needs*

Patients with congenital heart disease often require medications, feeding tubes, nutritional support, and follow-up services and appointments after hospital discharge.[149] Discharge planning can begin early in the hospitalization and includes family education and ongoing assessment of postdischarge needs such as equipment, resources, and referrals to early intervention (EI) and neurodevelopmental services. In-hospital developmental screening can also be used to identify neurodevelopmental vulnerabilities, which can inform discharge planning and family education. Developmental screening by trained health care professionals using validated instruments has been applied successfully for infants with congenital heart disease before hospital discharge.[32,150]

### *Care Coordination*

Care coordination, which provides supports across the continuum of care to ensure that the patient receives necessary services, can promote effective transitions from hospital to home for patients with congenital heart disease.[151] Children with special health care needs who receive care coordination experience improved outcomes such as less health care use, reduced family financial burden and time spent coordinating care, and increased family functioning and satisfaction.[152] Research indicates that children with congenital heart disease receive fewer neurodevelopmental services than other children with similar neurodevelopmental risks,[153] and only half of those with SVHD receive EI after discharge.[154] The integration of care coordination for children with congenital heart disease may begin to address these disparities across the continuum of care.

## RISK STRATIFICATION, REFERRAL, AND EVALUATION

Risk stratification of individuals with congenital heart disease into high or low risk for developmental delay or disorder is shown in Figure 1. The algorithm for referral, evaluation, and management of individuals at high risk is shown in Figure 3.

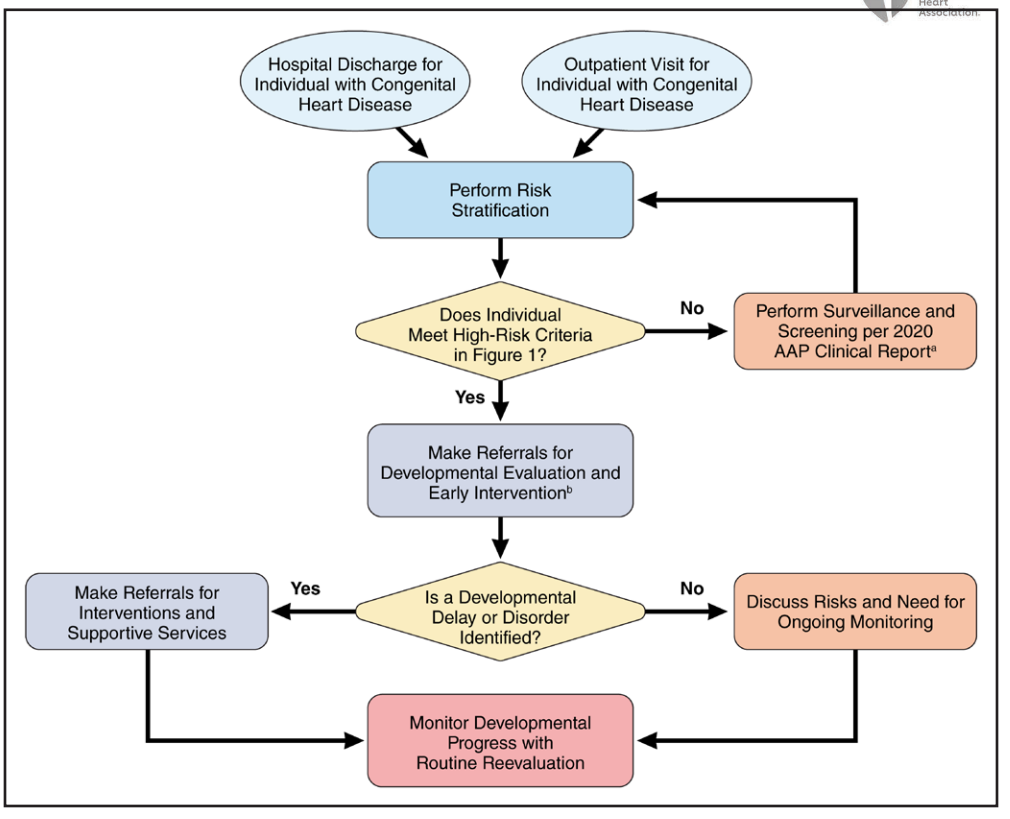


**Figure 3. Algorithm for referral, evaluation, and management for individuals at high risk.**
AAP indicates American Academy of Pediatrics. [a]Per the AAP clinical report on developmental surveillance and screening for the general pediatric population.[25] Developmental evaluation may be warranted when surveillance or screening identifies a developmental concern. Clinical recommendations for co-occurring conditions (eg, premature birth, genetic syndromes) may also apply. [b]Infants and toddlers who meet high-risk criteria should be referred directly to early intervention in addition to developmental evaluation to ensure that they receive intervention as soon as possible.

## Risk Stratification

Risk stratification should occur before hospital discharge and periodically throughout childhood and adolescence through the patient's coordinated system of care. Individuals initially at low risk may later move to high risk according to their medical, surgical, or social history. Of note, accurate risk stratification requires identification of factors that increase neurodevelopmental risk, including social and family factors that have not been consistently assessed within pediatric health care despite their demonstrated impact on child outcomes.

## Referral of Individuals at High Risk for Developmental Delay or Disorder

Individuals at high risk should be referred for developmental evaluation. Infants and toddlers at high risk should also be referred directly to EI. Timely referral ensures that infants and toddlers who are eligible for EI receive intervention as soon as possible. Referral for medical evaluation may also be warranted for specific concerns (eg, genetic evaluation for suspected genetic abnormality or syndrome[17]; physical/occupational therapy and neurological evaluation for neuromotor concerns[3,155]; audiological evaluation for potential hearing loss[156]; pulmonary evaluation for sleep issues[157]; speech-language pathology, gastroenterology, and otolaryngology evaluation for feeding difficulties[64,158]).

## Evaluation of Individuals at High Risk for Developmental Delay or Disorder

### *Individualized and Culturally Sensitive Approaches to Evaluation*

Evaluation conducted by a qualified professional is considered the gold standard for gauging the neurodevelopmental and neuropsychological status of an individual with congenital heart disease. The administration of standardized tests and questionnaires enables comparison with same-age peers and identification of specific strengths and deficits. The Cardiac Neurodevelopmental Outcome Collaborative has published recommended age-based standardized test batteries for individuals with congenital heart disease.[3,4] Their goal was to identify standardized tests that assess domains known to be affected in individuals with congenital heart disease to ensure comprehensive evaluation and to reduce unnecessary variation in test selection across patients and sites. Domains for age-based evaluation are displayed in Table 3.

Individuals with congenital heart disease are a heterogeneous group with varied comorbid conditions, sociodemographic factors, and developmental trajectories. It may be necessary to depart from the recommended test battery or to modify testing conditions for patients unable to comply with standardized testing procedures, including those with substantial cognitive delays, sensory or motor impairments, or language barriers, or when the referral question requires a departure from the recommended battery. Professionals conducting and interpreting these evaluations must also possess cultural humility in assessing diverse populations and understand the potential impact of culture and language on performance

**Table 3. Domains for Age-Based Developmental Evaluation**

| Age | Domain* |
|---|---|
| Birth–5 y | Developmental history (milestones, feeding, sleep, therapies) |
| | Growth |
| | Cognitive |
| | Speech-language (receptive, expressive, sound production, social-pragmatic) |
| | Motor (fine, gross) |
| | School readiness |
| | Attention |
| | Executive functions |
| | Emotional and behavioral functioning |
| | Social skills |
| | Adaptive skills |
| School age and adolescence | Developmental and school history |
| | Intelligence |
| | Academic achievement |
| | Attention |
| | Executive functions |
| | Memory |
| | Speech-language |
| | Visual-spatial processing |
| | Motor |
| | Emotional and behavioral functioning |
| | Social skills |
| | Adaptive skills |
| Adulthood | Work, school, social, and developmental history |
| | Intelligence |
| | Attention |
| | Executive functions |
| | Memory |
| | Speech-language |
| | Visual-spatial processing |
| | Motor |
| | Emotional and behavioral functioning |
| | Social skills |
| | Adaptive skills |

*Medical evaluation may also be warranted for specific concerns (eg, genetic evaluation for suspected genetic abnormality or syndrome; neurological, physical therapy, and occupational therapy evaluation for neuromotor concerns; audiological evaluation for potential hearing loss; pulmonary evaluation for sleep issues; gastroenterology, otolaryngology, and speech-language pathology evaluation for feeding impairment).

when selecting norms and interpreting results.[159] Given long-standing racial disparities in standardized test performance, testing methods and practices that reduce bias and inequity in assessment and decision-making must be identified and implemented.[159]

Although many cardiac centers provide developmental evaluation for individuals with congenital heart disease,[2] the cardiac center may not be easily accessible for all families, including those who live far from their center or experience other barriers to care.[160] These services may also be provided within primary care, through school, or in the community to meet the neurodevelopmental needs of individuals with congenital heart disease. Communication and collaboration across the system of care[151] are crucial to ensure that individuals with congenital heart disease are receiving appropriate neurodevelopmental services (Figure 4).

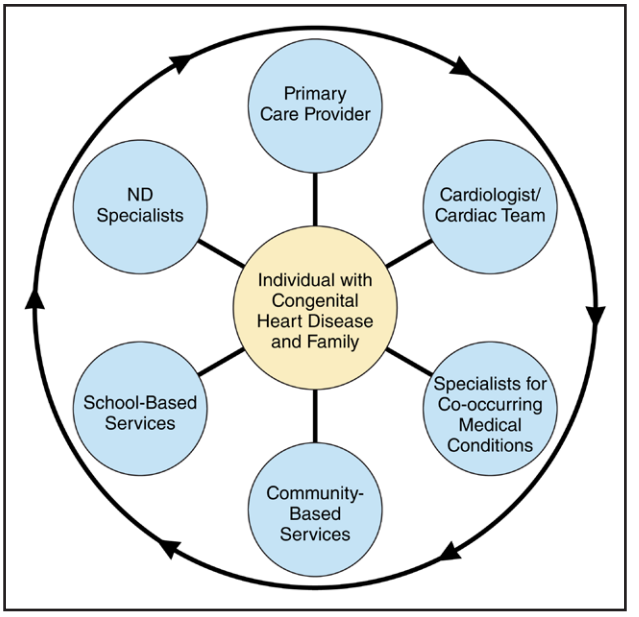


**Figure 4. Family-centered, comprehensive, and coordinated system of care for individuals with congenital heart disease.**
ND indicates neurodevelopmental.

### Age-Based Evaluations: Birth to 5 Years of Age

The Cardiac Neurodevelopmental Outcome Collaborative recommends that young children with congenital heart disease at high risk for developmental delay or disorder participate in developmental evaluation at key developmental stages: infancy (≈6 months), toddlerhood (≈18 months), preschool (≈3 years), and before the transition to formal schooling (≈5 years).[3] Standardized testing assesses cognitive, language, and motor development at each developmental stage, as well as school readiness before kindergarten entry. Standardized parent questionnaires assess other domains known to be impaired in young children with congenital heart disease, including adaptive skills, emerging executive functions, and social, emotional, and behavioral functioning (Table 3).

### Age-Based Evaluations: School Age and Adolescence

The Cardiac Neurodevelopmental Outcome Collaborative recommends that school-aged children and adolescents with congenital heart disease at high risk for developmental delay or disorder participate in neurodevelopmental evaluation at key transition points: third to fourth grade transition, middle school entry, high school entry, and transition to adulthood.[4] These evaluations include standardized tests and questionnaires assessing domains important for school-aged and adolescent functioning, including intellectual functioning, academic achievement, attention, executive functions, memory, visual-spatial processing, adaptive skills, and social, emotional, and behavioral functioning (Table 3). As developmental expectations change over time, weaknesses in higher-order skills may emerge even in the absence of early delays or after early delays resolve, warranting repeated developmental evaluation throughout school age and adolescence.[4]

### Age-Based Evaluations: Adulthood

Individuals with developmental delay or disorder are likely to have neuropsychological deficits in adulthood that may require evaluation[16] (Table 3). Formal evaluation can assist with supporting independence, including preparing adults for higher education and vocational selection. In addition, there are growing concerns about possible neurodegenerative processes that may start in middle adulthood, including dementia.[43] As adults with congenital heart disease age, it is important to consider the cumulative risk of diagnosis, repeated interventions, and changes due to aging that may further exacerbate neuropsychological issues.[16]

### Evaluations Through Telehealth

Telehealth has increasingly been used in the neurodevelopmental and psychosocial care of individuals with congenital heart disease. Early in the COVID-19 pandemic, 80% of cardiac neurodevelopmental clinical programs reported using telehealth for evaluation or intervention, with one-third administering standardized tests to school-aged or adolescent patients through telehealth.[161] No programs reported administering standardized tests to infants or young children through telehealth, and some tests recommended by the Cardiac Neurodevelopmental Outcome Collaborative for this age range cannot be administered virtually. A recent article identified opportunities for integrating telehealth within developmental evaluation and alternative tests that can be administered through telehealth.[162] Use of telehealth may increase access for patients who would not otherwise receive evaluation because of distance, transportation barriers, or scheduling constraints, including families for whom English is not their first language.[163]

## Surveillance and Screening of Individuals at Low Risk for Developmental Delay or Disorder

Children at low risk should receive routine developmental surveillance and screening per the 2020 American Academy of Pediatrics clinical report.[25] Although this report focuses on children up to 5 years of age, the authors acknowledge that surveillance and screening beyond 5 years of age may be needed. American Academy of Pediatrics recommendations for screening for anxiety, depression, and suicide risk also apply to individuals with congenital heart disease.[164,165] In addition, some individuals stratified as low risk will experience developmental delay or disorder attributable to comorbidities or factors unrelated to their congenital heart disease. In these cases, clinical recommendations specific to the comorbidity or other factor can be followed.[65–69]

# MANAGEMENT OF DEVELOPMENTAL DELAY OR DISORDER IN INDIVIDUALS WITH CONGENITAL HEART DISEASE

## Educating Families About Current Status and Ongoing Risks

Evaluation may result in the identification of a developmental delay or disorder. Information about the delay or disorder, including description, expected outcomes, recommendations for intervention, and relevant resources, should be discussed with the family. When evaluation identifies a potential medical issue (eg, neuromotor impairment, hearing loss), referral for additional medical evaluation may be warranted. Developmental evaluation may also identify at-risk symptoms or behaviors warranting close monitoring. All individuals determined to be high risk by risk stratification should be referred for routine reevaluation at the next developmental stage or transition point,[3,4] or sooner if needed. The rationale for planned reevaluation should be discussed with the family so that they are prepared to return at the recommended time.

## Management of Developmental Delay or Disorder in Infants and Young Children

Failure to address a developmental delay or disorder may contribute to future delays and disorders. Using a "wait and see" approach can result in lost opportunities for intervention during critical windows for development.[3]

### *Infant and Toddler Early Intervention*

The Individuals With Disabilities Education Act authorizes federal funding to states to support EI services for infants and toddlers from birth to 3 years of age.[166] An Individualized Family Service Plan documenting goals and services is developed with family input for infants and toddlers deemed eligible for EI. Participation in EI is associated with positive outcomes in cognition, language, academics, and behavior for infants and toddlers with developmental delays or disorders in the general population and other high-risk groups (eg, infants born premature, children with autism spectrum disorder[146,166]). Infants and toddlers at high risk for developmental delay or disorder should be referred to EI, as well as those who are at low risk when there are concerns about development.

### *Preschool Educational Services*

The Individuals With Disabilities Education Act also authorizes federal funding to states to support special education services starting at 3 years of age. Children can be referred to their public school district for evaluation of eligibility for special education preschool services. For those deemed eligible, an Individualized Education Program documenting goals and services is developed with family input. Parents can also share testing reports from evaluations conducted outside the school setting to support the development of Individualized Education Program goals. Participation in high-quality preschool services before kindergarten is associated with improved learning and behavioral outcomes.[167] Participation in preschool, including Head Start for those who qualify, can be encouraged for all children with congenital heart disease.

### *Clinic-Based Neurodevelopmental Services*

EI or special education preschool services can be supplemented with clinic-based neurodevelopmental services (eg, developmental pediatrics, physical therapy, speech-language therapy). Evaluation by outpatient therapists can determine individual child needs, which can then be used to support the design and implementation of treatment goals. Outpatient therapies may also be considered for children demonstrating mild delays, who score below the threshold to meet eligibility for EI or special education preschool services. However, there may be financial considerations (eg, limited health insurance coverage, copayments) or long wait times affecting the accessibility of clinic-based neurodevelopmental services.

### *Family-Based Interventions*

Family-based interventions have potential for supporting the development of young children with congenital heart disease, particularly given the high rates of parental psychological distress[23] and associations between parental mental health and neurodevelopmental outcomes. One family-based intervention tested in 4- to 5-year-old children with congenital heart disease demonstrated improvements in maternal mental health and family functioning.[168] Although no differences were found between the intervention and control groups on measures of child behavior, children receiving intervention were perceived as sick less often by their mother and missed fewer school days. Other family-based interventions in congenital heart disease have focused on procedural preparation before a cardiac procedure and demonstrated improvements

in child adjustment and school functioning, as well as caregiver competency and behavior.[169] There is a large body of literature on the positive impact of family-based interventions for parenting skills, family functioning, and child neurodevelopmental and behavioral outcomes[170] within the general population and other high-risk groups. More research is needed to evaluate family-based interventions for congenital heart disease.

## Management of Developmental Delay or Disorder in School-Aged Children and Adolescents

Although many individuals with congenital heart disease reach a point of relative medical stability by school age or adolescence, academic and psychosocial difficulties may become more pronounced. As expectations for independence in problem-solving and self-care increase over time, children and adolescents with congenital heart disease often find themselves less able to manage these expectations without increased support. Recognition and management of these issues are critical for supporting independence and the successful navigation of developmental challenges beyond early childhood.

### *School-Based Services*

Many children and adolescents require formal supports in school such as an Individualized Education Program for those requiring specialized modifications to the curriculum or a Section 504 Plan for those requiring accommodations to permit access to the general education curriculum (eg, extended time on tests). Accessing school-based supports can be challenging, particularly when families encounter educational systems that do not appreciate the academic and social implications of congenital heart disease. Hospital-based education liaison programs can be helpful[171] but are typically not reimbursed by health insurance. It is important to note that developmental evaluation may help in obtaining necessary educational services for children with congenital heart disease.[172]

### *Clinic-Based Interventions*

Clinic-based interventions are limited, and those tested to date have proved largely unsuccessful in ameliorating neurodevelopmental deficits in children and adolescents with congenital heart disease.[173] For both children and adolescents, exercise training has been shown to be beneficial, particularly for social and HRQOL outcomes.[174]

### *Psychological and Psychopharmacological Interventions*

Psychological interventions are often indicated for managing emotional and behavioral concerns. Because of the limited research on psychological interventions in children and adolescents with congenital heart disease, evidence for the benefits of psychotherapy in this specific patient population is lacking.[26,169] However, there is considerable support for the efficacy of psychological interventions in other healthy and chronic disease populations.[169] Psychological interventions are often most accessible and acceptable to patients and families when mental health professionals are integrated within the medical team.[26]

Psychopharmacological interventions for the treatment of psychiatric disorders can be applied safely in the congenital heart disease population, although special consideration must be given to various risk factors.[26] With high rates of ADHD, stimulant and nonstimulant medications are used often by children and adolescents with congenital heart disease. Although more research is needed, the current consensus is that these medications are generally safe to use in this population.[175,176]

## Management of Neuropsychological Deficits in Adults

### *Interventions to Promote Self-Management and Transition Skills*

Neuropsychological deficits can affect the ability to function independently and effectively transition to adult care.[177,178] In particular, deficits in executive function, including impaired working memory and problems with planning and organization, can result in difficulties adhering to treatment recommendations, including medications.[179–181] Transition education programming has been found to increase disease knowledge and self-management skills and to reduce the likelihood of a delay in ACHD care.[182] However, transition to independent adulthood and adult care may be prolonged for individuals with neuropsychological deficits who may benefit from support over the course of years to develop skills to promote treatment adherence and disease self-management, as well as compensatory strategies for navigating the complex medical system.[178] Transition may be particularly challenging for individuals from communities with limited resources,[183] including limited access to transition programming or ACHD specialists. Telehealth presents an opportunity to mitigate some of these disparities in access to care,[163] even among individuals for whom English is not the primary language, provided that health care professionals can maximize its utility and receive reimbursement across state lines for transition programming and ACHD appointments.

### *Clinic-Based Interventions*

Clinic-based interventions for patients with ACHD and neuropsychological deficits often aim to promote HRQOL and to improve control of vascular and stroke risk factors that could worsen neuropsychological deficits over time.[34] Beyond treating metabolic contributors to neuropsychological symptoms (eg, hypertension, hyperlipidemia/metabolic syndrome), medications should be reviewed to identify polypharmacy interactions or those that can interfere with neuropsychological





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functioning.[34] Patients should be counseled on tobacco/alcohol use and engagement in aerobic exercise.[34,177] For individuals with complex congenital heart disease and hematologic or neurological comorbidities, early involvement with neurologists and cardiologists specializing in coagulopathies and stroke may be beneficial for preventing future neurological insults that could further compound neuropsychological deficits.[184]

### *Psychological and Psychopharmacological Interventions*

Psychological interventions may be helpful for reducing concomitant symptoms of anxiety or mood disorders that could further exacerbate neuropsychological deficits.[177] Roughly 88% of adults who engaged with psychological services integrated within ACHD care reported reduced or absent psychological distress after treatment.[185] Medications such as cholinesterase inhibitors, selective serotonin reuptake inhibitors, and antipsychotics may aid with improving cognition or managing behavioral symptoms (eg, psychomotor retardation, agitation).[177]

### *Job Training, Vocational Rehabilitation, and Education*

Educational attainment and employment are lower in the ACHD population compared with the general population, and neuropsychological deficits are likely a significant contributor.[34,177] Accommodations can be helpful in the school setting, including extended time on tests and use of adaptive software or devices.[34] Adults with cognitive impairments may find assistance through job training or vocational programs that provide guidance on compensating for cognitive impairments in the workplace.[34] Targeted employment interventions to increase hiring for underrepresented groups may be used to reduce employment disparities.

## CONCLUSIONS AND FUTURE DIRECTIONS

New research over the past decade has informed updates to the categories of individuals at high risk for developmental delay or disorder and to factors that increase neurodevelopmental risk. Risk stratification of individuals with congenital heart disease using the updated categories and risk factors will identify a large and growing population of survivors at high risk for developmental delay or disorder and associated impacts across the life span. Although knowledge of neuroprotection, evaluation, and management of these issues has increased substantially, we continue to know more about the problems that individuals with congenital heart disease face than effective strategies to prevent or mitigate those problems. Critical next steps must include efforts to prevent or mitigate developmental delays and disorders. Neurodevelopmental outcomes for individuals with congenital heart disease have not improved meaningfully despite dramatic advancements in medical and surgical outcomes. This has important downstream impacts on academic achievement, employment, independent living, and HRQOL and places a high burden on individuals, families, communities, and society, particularly as this patient population grows and ages.

It is critically important that researchers, health care professionals, and other key stakeholders work to identify neuroprotective and intervention strategies that will prevent or mitigate developmental delay or disorder and ultimately improve HRQOL for individuals with congenital heart disease.[10,11] Patients and families from diverse backgrounds and health care professionals and leaders from diverse settings will need to be included as partners in this work to ensure that strategies can be implemented effectively across the entire population of individuals with congenital heart disease. Advocacy for the prevention and treatment of developmental delays and disorders and critical policy changes at the institutional, state, and federal levels are required to minimize barriers to accessing important neurodevelopmental services and to ensure sufficient funds for cardiac neurodevelopmental research. Neurodevelopmental research and clinical care must be prioritized over the next decade to improve the neurodevelopmental outcomes and HRQOL of individuals with congenital heart disease across the life span.



## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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