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The Brain in Congenital Heart Disease across the Lifespan: The Cumulative Burden of Injury

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Abstract

The number of patients surviving with congenital heart disease (CHD) has soared over the last three decades. Adults constitute the fastest growing segment of the CHD population, now outnumbering children. Research to date on the heart-brain intersection in this population has largely been focused on neurodevelopmental outcomes in childhood and adolescence. Mutations in genes that are highly expressed in heart and brain may cause cerebral dysgenesis. Together with altered cerebral perfusion *in utero*, these factors are associated with abnormalities of brain structure and brain immaturity in a significant portion of neonates with critical CHD even before they undergo cardiac surgery. In infancy and childhood, the brain may be affected by risk factors related to heart disease itself or to its interventional treatments. As children with CHD become adults, they increasingly develop heart failure, atrial fibrillation, hypertension, diabetes and coronary disease. These acquired cardiovascular comorbidities can be expected to have effects similar to those in the general population on cerebral blood flow, brain volumes, and dementia. In both children and adults, cardiovascular disease may have adverse effects on achievement, executive function, memory, language, social interactions, and quality of life. In summary, against the backdrop of shifting demographics, risk factors for brain injury in the CHD population are cumulative and synergistic. As neurodevelopmental sequelae in children with CHD evolve to

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cognitive decline or dementia during adulthood, a growing population of CHD can be expected to require support services. We highlight evidence gaps and future research directions.

Keywords

congenital heart disease; neurovascular; neurocognitive

Journal Subject Terms

Cardiovascular Disease; Congenital Heart Disease; Vascular Disease

Introduction

With advances in diagnostic technologies, surgical management, and postoperative care, more than 90% of children with critical congenital heart disease (CHD) are expected to survive to adulthood in the current era. Congenital heart disease is now considered a lifelong condition. Figure 1 illustrates the prevalence of CHD in infants, children, adults and in geriatric subjects in the same population using the Quebec Congenital Heart Disease Database.¹⁻³ From 2000 to 2010, the prevalence of CHD rose by 11% in children compared to 57% in adults. Thus by 2010, two-thirds of the CHD population with severe and other forms of CHD were adults. We estimated that by 2010, 2.4 million people were living with CHD in the US: 1.4 million adults and 1 million children.

In children with CHD, this notable success has exposed a heightened risk of brain injury and developmental disorders or disabilities.⁴ Children with complex CHD have been recognized to have a distinct neurobehavioral signature, including mild reduction in cognitive performance, difficulties with social interaction, worse pragmatic language, inattention, impulsive behaviour, and impaired executive function.⁴ Despite a rich literature on neurodevelopment in children with CHD, few studies have addressed the translation of these findings to neurocognitive function in the adult congenital heart disease population. Evidence in the general adult population suggests that chronic cardiovascular disease (CVD) leads to cerebrovascular injury and dementia.⁵⁻⁷ The aging of the CHD population provides the impetus for this review on the continuum of neurocognitive injury across the lifespan.

A paradigm shift is needed to account for these emerging observations. In Figure 2, we propose a model that sequentially links CHD-related cardiovascular disease across the lifespan to abnormalities in the perinatal, childhood and adult brain. As life expectancy continues to increase, the window of opportunity for repeated injury continues to lengthen. Thus in a lifespan model, neurodevelopmental sequelae in children with CHD evolve during adulthood to cognitive decline or dementia. This review will synthesize and integrate data on the brain structure and function, including neurocognitive and psychosocial sequelae, in congenital heart patients from fetal life to adulthood.

Risk Factors for Adverse Neurologic and Developmental Outcomes in Children

Risk factors for adverse neurocognitive outcomes are multifactorial, interrelated, cumulative, and likely synergistic over time. Neurodevelopmental (ND) and behavioural morbidity in children can derive from genetic & epigenetic factors, patient factors other than genetic disorders (e.g., low birth weight or gestational age), aberrant fetal cerebral perfusion and oxygenation, sequelae of heart disease itself (severe cyanosis, cardiac arrests), and its medical and surgical management (e.g., perioperative hypoxic ischemic injury, stroke, factors associated with prolonged postoperative course). Twenty years ago, the impact of circulatory arrest in infants with CHD undergoing cardiac surgery ushered in an era of clinical trials to assess the effects of intraoperative conduct on neurologic and developmental outcomes (Figure 3).⁸ Recent data suggest that patient and preoperative risk factors, such as low birth weight or gestational age and social class, as well as cumulative postoperative morbidity, contribute a greater proportion of variability in outcomes after infant heart surgery than intraoperative support techniques.⁹

Genetic disorders are present in about one-third of individuals with congenital heart disease. These include chromosomal disorders (e.g., Trisomy 21), microdeletions (e.g., 22q11 microdeletion), or mutations (e.g., Noonan syndrome). However, known risk factors only explain approximately 30% of observed variation in ND outcome after cardiac surgery in infancy,^{10–12} suggesting that as yet unknown genetic and epigenetic factors may play an important role. Microdeletions causing CHDs may be associated with specific patterns of neurodevelopmental morbidity. For example, adults with 22q11 deletion have specific deficits in visual-spatial skills, executive functions (problem solving, organization, planning), abstract social thinking, and attentiveness.¹³ Pathogenic copy number variants, i.e., regions of DNA gains or losses, were reported to be present in 13.9% of infants with single ventricle heart disease, compared to 4.4% of controls, and were associated with inferior neurocognitive and somatic growth.¹⁴ Epigenetic factors, the study of protein changes that affect gene regulation without altering core DNA sequence, may also have a role in determining neurocognitive outcome.^{15, 16} Finally, genetic polymorphisms affecting host susceptibility and resiliency, such as the apolipoprotein E genotype, may affect the response of the brain to stresses associated with CHD, including cardiopulmonary bypass and perioperative events.¹⁷ With a burgeoning population of CHD survivors reaching reproductive age, research on the genetic underpinnings of neurodevelopmental disorders assumes increasing importance.

The Fetal and Perinatal Brain: Injury and Dysmaturation

In response to hypoxia-ischemia, the developing brain acquires characteristic patterns of injury that reflect the “selective vulnerability” of specific cell populations that are maturing at the time of the injury.¹⁸ For example, during the early third trimester of gestation, early lineage oligodendrocytes predominate in the brain’s white matter and are vulnerable to insults to which mature myelinating oligodendrocytes are resilient. Given this, neonates born

preterm most commonly acquire white matter injury, while term neonates respond to hypoxia-ischemia with a preponderance of injury to grey matter or neuronal structures.¹⁸

Recent experimental and clinical data in preterm neonates indicate that the primary issue in white matter injury is cellular maturation arrest rather than cell loss. As such, the primary mechanism of myelination failure in the preterm neonate is a failure of oligodendrocyte progenitor cells to differentiate into myelin forming oligodendrocytes (i.e. dysmaturation) rather than a predominance of necrotic lesions.^{19, 20} In preterm neonates, white matter dysmaturation is related to modifiable aspects of clinical illness including postnatal infections and procedural pain.^{21, 22} Of particular clinical relevance are the observations that brain dysmaturation is an important antecedent of adverse developmental outcomes.^{20, 22, 23}

Contrary to what is expected in *term* neonates, white matter injury is the characteristic pattern in neonates with CHD, and resembles that characteristic of preterm newborns.^{22, 24, 25} Other focal injuries such as stroke and microhemorrhage are also prevalent. Stroke is also increasingly recognized before and after surgery for CHD, and related in some studies to therapeutic catheterization procedures or regional cerebral perfusion bypass strategies.²⁴ Subtle hemorrhagic brain injury is also commonly seen on MRI after open heart surgery in infancy; these microhemorrhages have been associated with longer total support time and greater number of cardiac catheterizations, and also with worse developmental outcome.^{11, 26} Importantly, the range of neurodevelopmental sequelae in children with CHD are not fully explained by these focal brain injuries identified before and after cardiac surgery.²⁴ Therefore, the patterns of brain injury seen on diagnostic imaging of neonates with CHD are only the “tip of the iceberg”.

As in the preterm neonate, brain vulnerability in newborns with CHD is primarily a problem of dysmaturation. Converging evidence supports that newborns with CHD have diffuse impairments in the progression and rate of early brain maturation.^{24, 27–30} Compared to normal term newborns, those with CHD have an immature pattern of brain microstructure and metabolism,²⁷ less mature morphologic scoring,²⁸ and smaller brain volumes.³⁰ These findings likely explain why they are more vulnerable to white matter injury than the conventional “term” patterns of injury. Impaired brain maturation is also an important substrate for postnatal injury, and those with pre-operative brain injury have less robust brain maturation from the pre- to the post-operative scan.^{24, 31, 32} Consistent with observations in the preterm neonate, neurodevelopmental outcomes at 2 years of age in children born with severe CHD were more strongly related to brain maturity than to brain injury.³³ As in the preterm neonate, these data highlight the potential for promoting optimal brain development to improve functional outcomes in neonates with CHD.

Brain maturation slows in fetuses with CHD during the 3rd trimester of pregnancy, when the main brain development events include axon path finding, synapse formation, and refining cortical networks.^{25, 30} Over this period of dramatic increases in neuronal connectivity and activity, blood flow to the fetal brain is approximately one quarter of the combined ventricular output,³⁴ and fetal cerebral oxygen consumption is almost half of all fetal oxygen consumption.^{34, 35} In fetuses with CHD studied with phase contrast MRI and T2 mapping based MR oximetry, disrupted streaming of oxygenated blood from the placenta to the brain,

and reduced umbilical blood flow and placental oxygen exchange are observed.³⁶ Compared with normal controls, those with some forms of critical CHD have a 10% reduction in the oxygen saturation of blood in the ascending aorta; without a compensatory increase in cerebral blood flow or oxygen extraction, there is an associated one standard deviation reduction in fetal brain volume.³⁶ These *in utero* cardiovascular disturbances are especially relevant to the issues of brain dysmaturation outlined above given recent observations linking oligodendrocyte precursor cells to postnatal white matter angiogenesis and the early events of myelination through hypoxia-inducible factor.³⁷ Why the fetus with CHD does not compensate for *in utero* hypoxia with “brain sparing” physiology remains a critical question for future research.

Brain maturation, including the refinement of brain networks and myelination, continues through childhood, providing a significant window for recovery and highlighting the need for a life-span approach to optimizing the outcome trajectory for patients with CHD.³⁸ Fetal interventions to optimize cerebral oxygen delivery at the earliest phase of the lifespan are now on the horizon with the ultimate goal of preventing the onset of brain dysmaturation. As in the preterm neonate, abnormalities in brain maturation evident as early as the third trimester persist through childhood in those with CHD and predict adverse functional outcomes.^{29, 39, 40} Thus, a lifespan approach to improving neurocognitive outcomes in children with CHD must begin *in utero*.

The Brain in Children and Adolescents (Figures 3 and 4)

By school age, children with critical CHD, on average, have lower scores on tests of intelligence and achievement, worse fine motor and gross motor function, and higher likelihood of learning disabilities, use of special services, and abnormalities of speech, language, and behaviour.^{4, 10} Adverse neurodevelopmental and behavioural outcomes are more likely after repair of complex cardiac lesions, with the greatest neurodevelopmental morbidity in children with single ventricle heart disease, such as hypoplastic left heart syndrome.⁴¹ As these children reach adulthood, ND disabilities can limit educational achievements, employability, insurability, and quality of life.⁴²

Brain imaging studies using magnetic resonance imaging (MRI) in school age children and adolescents with CHD suggest that altered white matter microstructure, and resulting differences in network processes (i.e., the connectome), may underlie their cognitive impairment.³² In addition to diffuse abnormalities (e.g., white matter abnormalities, abnormal T2 hyperintensities, ventriculomegaly), focal or multi-focal abnormalities can occur secondary to thromboembolic events.¹⁰ The highest incidence of focal infarction occurs in individuals with cyanotic congenital heart disease; indeed, strokes can be detected by brain MRI in nearly half of cyanotic adults.⁴³ Taken together, brain MRI studies in children and adolescents who underwent infant heart surgery highlight the challenges of discriminating neurocognitive deficits that result from genetic abnormalities, deficient cerebral substrate delivery in fetal life, and postnatal injury.

Neurodevelopmental disabilities can adversely affect learning and the attainment of academic, social, and vocational skills, with greater need for remedial services, including

tutoring and special education, as well as physical, occupational, and speech therapy.⁴ In the CHD population without genetic syndromes or catastrophic events, intelligence quotient is relatively well preserved but specific areas of weakness include motor skills, higher order language (the ability to make up a coherent story when presented with pictures), visual spatial skills, and vigilance and sustained attention. Impairment in visual-spatial ability and planning are well illustrated by the difficulties that school age children and adolescents have shown in completing the Rey Osterreith complex figure, a complicated line drawing which a child is asked to copy (recognition) and then draw from memory (recall).⁴⁴ This task, which involves perception of shapes within shapes, requires integration of many different areas of the brain. In a population of complex CHD, attention deficit and hyperactivity disorder was reported to be 3–4 times higher than in the general population.⁴⁵ Indeed, the “lifetime prevalence” of ADHD in adolescents with d-TGA was 19%.¹⁰ Impairments in executive functions are a typical feature of the neurobehavioral signature of CHD patients and are associated with behavioural dysregulation and attention problems, lower working memory, and problems with organization and planning abilities.^{46, 47} Taken together, these findings explain the high rate of remedial services needed in the critical CHD population. Nearly half of 5–10 year old children in a mixed population of critical CHD were receiving remedial services.⁴⁵ By adolescence, 65% of patients with simple d-transposition of the great arteries (d-TGA)¹⁰ and 82% with tetralogy of Fallot¹¹ had received remedial academic or behavioural services, such as tutoring, early intervention, occupational therapy, or special education.

In the social and emotional sphere, children and adolescents with CHD often have deficits in social cognition, i.e., the ability to process social information, especially its encoding, storage, retrieval, and interpretation of social situations and relationships.^{44, 48} Decreased social cognition results in difficulty in “reading” other people, inferring their internal states, and interpreting their actions appropriately. Studies on psychiatric disorders in youth with CHD are limited. In structured psychiatric interviews, adolescents with d-TGA, compared to an optimal control group without known risk factors for brain disorders, had worse clinician-rated global psychosocial functioning, as well as more self-, parent- and clinician-rated symptoms of depression, anxiety, and disruptive behaviours.⁴⁹ Worse global psychosocial function was associated with lower cognitive function and greater parent stress.

Executive functions include higher-order neurocognitive abilities that facilitate the coordination and organization of actions towards a goal, allowing the individual to adapt to new or complex situations.⁵⁰ Mediated by the maturation of prefrontal structures, as well as fronto-parietal and sub-cortical networks,^{51, 52} executive functions depend upon the integrity of white matter pathways that may be disrupted by dysmaturation or postnatal hemodynamic stress. Executive dysfunction in adolescents with critical CHD is associated with worse psychosocial health status and quality of life,⁵³ suggesting that executive impairments are associated with reduced functioning in everyday life. It is likely that executive dysfunction impairs the ability of patients to adhere to medical recommendations and follow-up.⁵⁴

Health-related quality of life (HRQOL) is a multidimensional concept which is all the more complex in pediatric populations where patient, family and sibling experience are interrelated making measurement challenging. HRQOL contains elements of both

psychosocial and physical health status. Using the Pediatric Cardiac Quality of Life Inventory Testing Study and its corollary studies HRQOL in children, adolescents and their parent-proxy reporters was assessed.^{55, 56} In 1,605 patient-parent pairs in the US⁵⁵ and 771 patient-parent pairs in the United Kingdom,⁵⁶ findings related to impaired HRQOL were consistent. Lower patient- and parent-reported HRQOL scores resulted in greater health care utilization, including a greater number of cardiac surgeries, hospital admissions, and provider visits over a 12-month period. Lower HRQOL scores were also associated with decreased competency (Achenbach Youth Self-Report and Child Behaviour Checklist Total Competency score); impaired self-perception (Global Self-Worth and Self Perception Profile for Children and Adolescents); and increased behavioural and emotional problems (Achenbach Internalizing Problems Summary Scale score and DSM-IV Oriented Scale scores for affective, anxiety, somatic and attention deficit disorders).⁵⁵ In these populations of patients with pediatric heart disease, the majority of whom had CHD, HRQOL scores remained abnormal across all age categories and respondent types.

Compliance with surveillance recommendations can be impacted by disability in neurodevelopment, in social and emotional domains, in executive function and HRQOL. Patients with CHD are lost to follow-up during the transition to adult healthcare,⁵⁷ mediated at least in part by diminished working memory and self-organization. Resulting lapses in care affect health care utilization with resulting economic impact. Two thirds of CHD patients fall out of care by the time they reach age 18 with more than half falling out of care during transition years.^{58, 59} Whereas between the ages of 12 and 30 most emergency room visit rates decrease, CHD patients have higher admission rates via the emergency room.⁶⁰ Moreover, lapses in care are associated with inappropriate medication regimens and higher rates of urgent cardiac interventions.⁶¹ In a cross-sectional multicenter study that examined reasons for lapses in care in over 900 young adult CHD patients found that powerful predictors of care gaps included misinformation related to the perception of the need for care.⁶² This is likely multifactorial related both to the patient's capacity and willingness to receive information and health care providers' ability to deliver it. Improved compliance with follow-up requires improved processes of care delivery particularly during transition of care where gaps are common.^{58, 59, 63} There is a growing literature on the benefits of health information technology platforms to improve access to multiple elements of care both in the elderly with chronic disease and in youth with life-long conditions.⁶⁴ A systematic review of 17 internet-delivered health behaviour change interventions for adolescents or young adults revealed the importance of tailored communication including reminders and incentives.⁶⁵ These findings underscore the need for targeted interventions leveraging on-line tools to improve care pathways. These strategies seem particularly important in the CHD population, with its high prevalence of executive dysfunction.

Manifestations of Neurodevelopmental Abnormalities in Adults with CHD

Adults with CHD have an increased risk of anxiety, depression, pragmatic language impairment and social cognition issues, worse educational attainment, and underemployment, and delayed progression into independent adulthood.⁶⁶⁻⁶⁹ The prevalence of comorbid psychiatric disorders is 3 to 4 times higher among adults with neurocognitive impairment than in the general population.^{66, 67} These may result in parental

overprotection and impact self-management.^{66, 67, 70} Attention deficit, executive dysfunction, mood, language and social cognition issues may manifest themselves as inappropriate behaviour and may limit the ability to form healthy family, work/peer, and romantic relationships. The overall QOL for adults with CHD is reduced compared with the general population.⁷¹

There are few quantitative analyses measuring the impact of pediatric and adolescent ND and psychosocial impairments on adults with CHD. In non-CHD populations who have been tracked from childhood through adolescence to adulthood, some relevant data exist on patients with childhood attention deficit disorder (ADHD) and hyperactivity disorder, a common disorder in CHD patients. Adults with ADHD, compared to non-ADHD subjects from the same birth cohort, were found to have higher standardized mortality rate ratios.⁷² A longitudinal study comprised of 551 subjects with ADHD followed for up to 35 years were found to be at higher risk for impaired mental health, work performance and financial stress scores compared to demographic controls.⁷³ These observations provide the rationale for the growing recognition that wide-ranging neurodevelopmental and psychosocial dysfunction is expected to have significant implications for life success and societal costs as the CHD population continues to grow. In the Dutch CONCOR Study, with almost 1,500 patients at an average age of 39 years, only about two-thirds of patients were employed for more than 12 hours a week. Compared to controls, patients under 40 years of age had significantly lower education, more unemployment and fewer relationships.⁷⁴

The Aging Brain: Adding Insult to Injury (Figures 5 and 6)

The dynamic nature of cardiovascular morbidity in CHD underscores the challenge of investigating the intersection between heart and brain health in this population. We put forth the concept that impaired neurocognitive development becomes neurocognitive decline in adults with CHD. There is limited research on the long-term impact of CHD on cognitive functioning, structural or functional imaging outcomes, or dementia risk across the lifespan. In the absence of such evidence, we theorize potential connections between CHD and abnormal brain aging based on associations reported in the general population. As described above, brain lesions in infants with CHD are dynamic and associated with widespread impairments in brain maturation that persist, at least, through adolescence. Importantly, the cellular pathways most vulnerable to dysmaturation, are the same pathways that will maintain the brain's vulnerability to insult including hypoxia-ischemia and inflammation.²⁰ This negative synergy is evident as early as the neonatal period where infants with greater "dysmaturation" are most vulnerable to acquiring brain injuries such as white matter injury.²⁴ This negative synergy has been conceptualized as "tertiary brain damage", in that these brain changes predispose a patient to further injury, or prevent brain repair after an initial insult.⁷⁵ Inflammation and epigenetic modifications may be key mediators of tertiary brain damage.⁷⁵ Our hypothesis is congruent with increasing evidence in the general population that brain injury from cardiovascular disease precedes clinically evident cognitive decline and increases the risk of Alzheimer's dementia in the elderly as we review below. Individuals with CHD lesions are expected to develop adult causes of neurocognitive decline earlier in life than the general population because the brain is "primed" for vulnerability to early onset of adult cardiovascular risk factors for brain injury that accompany common

forms of critical CHD. In sub-groups of CHD populations, early onset of adult cardiovascular risk factors for brain injury include intraatrial reentrant tachycardia and atrial fibrillation (e.g., in atrial switch procedures or Fontan operations), hypertension (e.g., in coarctation of the aorta), disordered glucose metabolism (e.g., in Fontan procedures and in obesity in adult CHD patients), and coronary artery disease (e.g., in arterial switch operations, Ross procedures and congenital coronary anomalies). This earlier acquisition of brain injury related to adult onset cardiovascular risk factors will be additive with neurocognitive sequelae of brain dysmaturation and acquired injury through childhood and adulthood. We have recently shown the additive burden of heart failure in CHD patients as powerful predictor of stroke.⁷⁶ Thus, multiple common forms of prevalent cardiovascular disease known to affect older adults, including heart failure with low cardiac output, atrial fibrillation, cardiac arrest, coronary disease and acquired comorbidities in CHD, have been related to abnormal cognitive function and clinical dementia in elders without CHD are reviewed below.

Heart failure and low cardiac output have been increasingly recognized as a complication of CHD.⁷⁷ The chronic mismatch between ventricular preload and afterload resulting from abnormalities of cardiac anatomy in CHD patients result in sub-clinical heart failure.⁷⁸ Progressive heart failure accounts for approximately one third of deaths in CHD patients.⁷⁹ In non-CHD older adults, heart failure has been linked to impairment in global cognition, language, attention, executive functioning, and episodic memory,⁸⁰ as well as structural imaging changes seen with magnetic resonance imaging.⁸¹ Epidemiological data suggest that heart failure is associated with an increased risk of dementia of the Alzheimer's type over a 9-year follow-up period.⁸² The well-established association between heart failure and corresponding reductions in cerebral blood flow⁸³ is likely due to poor left ventricular ejection fraction and reduced cardiac output.⁸⁴ In older patients lower cardiac output was associated with worse executive functioning skills⁸⁵ and increased white matter hyperintensities seen on brain magnetic resonance imaging.⁸⁶ Epidemiological data from the Framingham Heart Study showed that, among more than 1000 adults age 40–89 years, lower ejection fraction was associated with worse visuospatial episodic memory and object recognition performances, even when excluding participants with prevalent cardiovascular disease.⁸⁷ Data from the same epidemiological cohort suggested that, among 1504 adults age 34–84 years, lower cardiac output was associated with smaller total brain volume, even after adjustment for vascular risk factors.⁵ More recently, a correlation between reduced cardiac output and smaller brain volume has been independently replicated in an Icelandic cohort of older adults.⁸⁸ Moreover, among adults age 60 and older in the Framingham Offspring Study, lower cardiac output was associated with a two-fold increase in dementia over a median follow-up period of nearly 8 years.⁷ Similar associations have been reported in an independent cohort of older adults in whom lower cardiac output was associated not only with a greater risk of dementia but also with its precursor, mild cognitive impairment.⁸⁸

Atrial fibrillation is perhaps one of the best examples of the abnormal offsetting of biological and pathological cardiac age in CHD populations. The lifetime risk of atrial fibrillation in a 20 year old with CHD is equivalent to that of a 55 year old without CHD, with more than 50% of patients with severe CHD developing atrial arrhythmias by age 65 years.⁸⁹ The presence of atrial fibrillation is associated with abnormal brain aging. Data

from the population-based Rotterdam Study of adults aged 55 to 106 years suggest that atrial fibrillation confers an increased risk for cognitive impairment and incident dementia (OR=2.3) compared to peers without atrial fibrillation.⁹⁰ Meta-analyses of data comprising more than 46,000 participants suggest that individuals with atrial fibrillation have a two-fold higher risk of dementia that further increases in the presence of recent stroke.⁹¹

Traditional vascular risk factors including high blood pressure, diabetes and coronary disease further exacerbate the growing burden of systemic complications as individuals with CHD age. In a population-based ACHD cohort consisting of 3,239 patients surviving to age 65 and followed for up to 15 years, predictors of mortality included dementia, diabetes and myocardial infarction.² Although risk factors are in part driven by age, and hypertension may occur in the context of specific CHD disorders such as coarctation of the aorta,⁹² atherosclerotic disease is observed in younger cohorts with CHD. Billet et al.⁹³ found that adults with ACHD were more likely to have hypertension, stroke, and chronic kidney disease (a coronary artery disease risk equivalent) than age-matched controls without ACHD. Moons et al. reported that at least 80% of adults with ACHD had at least one coronary artery disease risk factor, with the rates of hypertension and obesity being higher than in the general population.⁷⁰ The mean age in both of these studies was only 26 to 28 years, suggesting that ACHD patients may not only harbour risk factors for many years but may also have a higher risk burden over their lifetime.

Hypertension and diabetes have both been linked to abnormal brain health. Hypertension alters the cerebral vasculature, predisposing to infarction of both gray and white matter.⁹⁴ Even in the absence of hypertension, subclinical elevations in blood pressure are related to worse cognitive function. A recent meta-analysis of up to 4000 participants free of clinical dementia or stroke yielded evidence that elevated systolic blood pressure was associated with impairment of global cognition and episodic memory even after adjustment for vascular comorbidities.⁹⁵ Diabetes has been linked to an increased risk of clinical dementia possibly mediated by impaired insulin signalling in the brain and inflammatory or oxidative processes.^{96, 97.}

Coronary disease may occur in the context of specific CHD lesions. Of 400 patients who had undergone the arterial switch operation for d-transposition of the great arteries and were followed for an average of 25 years from birth, 5% had obstructive coronary disease.⁹⁸ In patients with coarctation of the aorta, coronary disease was found to be independently associated with poor risk factor control.⁹² Coronary artery disease, especially atherosclerosis, has been linked to abnormal brain aging in multiple studies. In men participating in the Honolulu-Asia Aging Study, coronary heart disease was associated with an increased risk for vascular dementia (OR=2.5).⁹⁹ Cross-sectional population-based data from more than 2000 Rotterdam Study participants suggested that atherosclerosis was associated with dementia (OR=1.3 to 1.9), including both Alzheimer's disease (OR=1.3 to 1.8) and vascular dementia (OR=1.9 to 3.2).¹⁰⁰ Longitudinal follow-up over 9 years for this population-based cohort suggested an increase in the risk of dementia.¹⁰¹ Associations between vascular risk factors and compromises in cognitive health appear to begin as early as mid-life or earlier.¹⁰² Blood pressure elevations appear to exert effects on late-life cognitive health and dementia risk beginning as early as mid-life.¹⁰³ Mid-life diabetes (vs.

no diabetes) is associated with greater cognitive decline over a 20 year follow-up period, and individuals with poorly controlled diabetes have worse cognitive decline than individuals with well-controlled diabetes.¹⁰⁴ Recent data suggest the exposure window may be even earlier than mid-life. Longitudinal exposure to higher systolic and diastolic blood pressures and higher fasting blood glucose starting in early-life corresponded to worse episodic memory, information processing speed, and executive function performances approximately 25 years later in mid-life.¹⁰² In light of post-mortem evidence that the pathogenesis of Alzheimer's disease begins decades before clinical symptoms manifest in late-life, it is plausible that vascular risk exposure may affect brain health much earlier than previously appreciated.⁶

Competing Gradients of Neurological Injury (Figure 6)

We began with Figure 1 to demonstrate how cumulative cardiovascular injury in CHD impacts the brain sequentially across the age continuum. In Figure 6, we illustrate two gradients of neurovascular injury.¹⁰⁵ As the cardiovascular disease burden shifts from factors associated with CHD to acquired cardiovascular disease, the decreasing gradient of neurodevelopmental abnormalities is replaced by an increasing gradient of neurovascular disease. This figure highlights the concept that there comes a point when the brain is no longer developing and thus the gradient of abnormal neurocognitive development wanes to be replaced by the increasing burden of neurological injury or even decline. Together these gradients magnify the potential for expression of neurological injury in the CHD patient across the lifespan. Thus, abnormal neurodevelopment in infants, children, and adolescents may become neurocognitive decline as patients with CHD age. We have already shown that young patients with CHD have aging hearts.⁸⁹ The question now is do these same patients have brains that show evidence of premature aging.

Conclusions

Dramatic advances have occurred in the survival of patients with CHD. At the present time, 9 in 10 children survive until adulthood, a minimum of 1 in 150 Americans has a congenital heart defect, and today there are more adults than children with CHD. In this first review of the relationship between heart health and brain health in CHD patients across the lifespan, we illustrate the link between cardiovascular and neurovascular diseases as patients age. In the absence of data on the impact of cardiovascular disease on neurovascular disease in CHD populations, we show the importance of acquired cardiovascular complications in CHD patients on cerebral blood flow, brain volumes and dementia. We put forth the idea that impaired neurocognitive development becomes neurocognitive decline in adults with CHD. We provide two conceptual models: the first illustrating the cumulative burden of cardiovascular injury expected to impact the brain in CHD populations and the second illustrating how neurovascular disease is expected to replace neurodevelopmental disabilities as patients age and CHD persists across the lifespan. This review has for the first time synthesized and integrated existing data on the brain structure and function, including neurocognitive and psychosocial sequelae, in CHD patients from fetal life to adulthood.

Future directions

This synthesis of available evidence has highlighted substantial knowledge gaps. Table 1 summarizes translational research objectives that are likely to result in patient and family-centered outcomes. In lifelong conditions such as CHD, the ‘nature’ vs ‘nurture’ dialogue is becoming increasingly important. It is believed that a ‘nurturing’ model of resilience and mitigation for neurodevelopmental and neurovascular risk factors is becoming increasingly important to optimize cognitive health and psychosocial functioning. Research using longitudinal cohorts is needed to measure serial outcomes from fetal life and early infancy to adulthood. In young patients who are stable, cardiac dysfunction even when clinically silent should be minimized. In older CHD adults, we need to understand if acquired cardiovascular risk factors are effect modifiers of brain injury. Although we have proposed a link between neurodevelopmental disabilities in children and neurocognitive decline in adults, the differences need to be characterized, explored and leveraged for meaningful intervention and prevention. Avoidable pathways of injury and modifiable risk factors across the lifespan need to be identified. Successfully identifying these pathways will require consideration of the wide range of hemodynamic disturbances in various congenital lesions and their differing risks for brain damage, from stroke or white matter injury.^{27, 106} A better understanding of the lesion-specific alterations in fetal hemodynamics, and their impact on the brain, should open the window to new opportunities to promote optimal brain development from the earliest days.³⁶ Moreover, a life-span perspective on neurocognitive function in patients with CHD is warranted to plan resource allocation and document the potential benefits of early intervention and prevention. Children are the adults of our future. Reducing the cumulative burden of brain injury and cognitive morbidity should be a priority for clinical care and research in the aging CHD population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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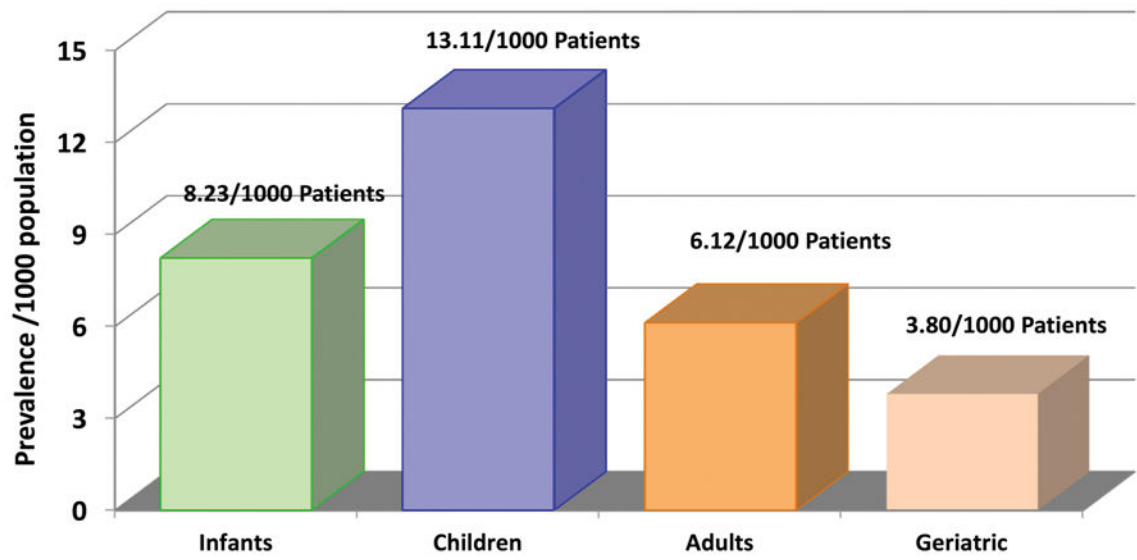


Figure 1. Prevalence of congenital heart disease across the lifespan.³ Reprinted with permission from Mazor Dray E, Marelli AJ. Adult Congenital Heart Disease: Scope of the Problem. *Cardiol Clin.* 2015;33(4):503–512.

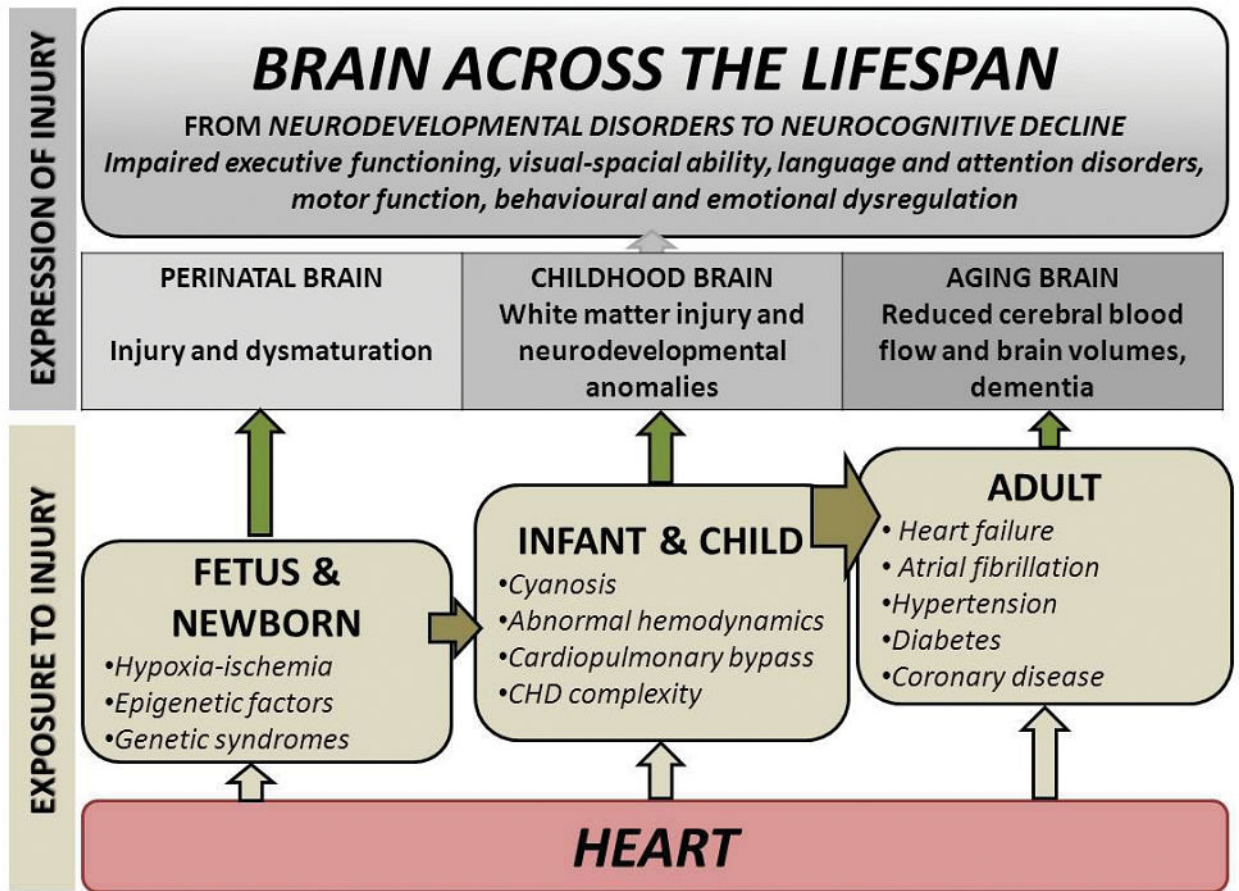


Figure 2.
 Neurocognitive impairment across the lifespan.

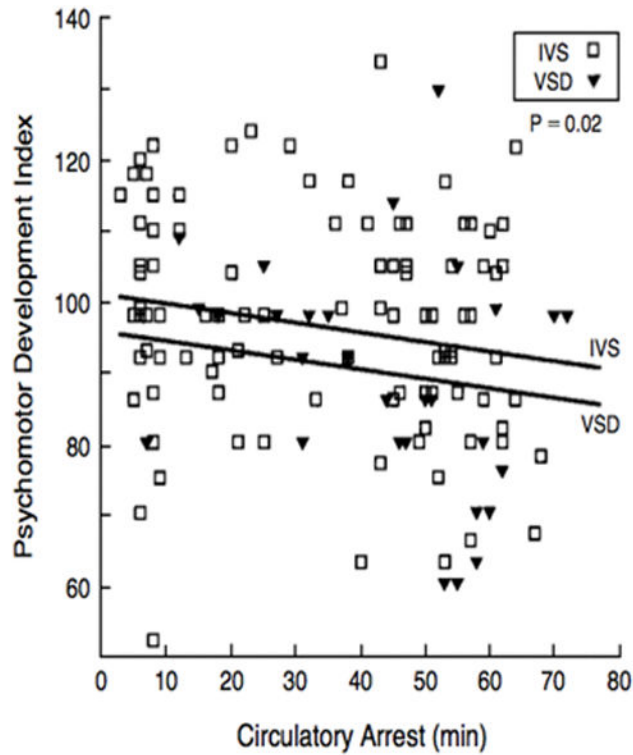


Figure 3.

Illustration of the inverse relation between circulatory arrest and psychomotor development index in infants at one-year post the neonatal arterial switch operation for complete transposition of the great arteries.⁸ Reprinted with permission from Bellinger DC, Jonas RA, Rappaport LA, Wypij D, Wernovsky G, Kuban KC, Barnes PD, Holmes GL, Hickey PR, Strand RD, Walsh AZ, Helmers SL, Constantinou JE, Carrazana EJ, Mayer JE, Hanley FL, Castaneda AR, Ware JH, Newburger JW. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *The New England Journal of Medicine*. 1995;332:549–555.

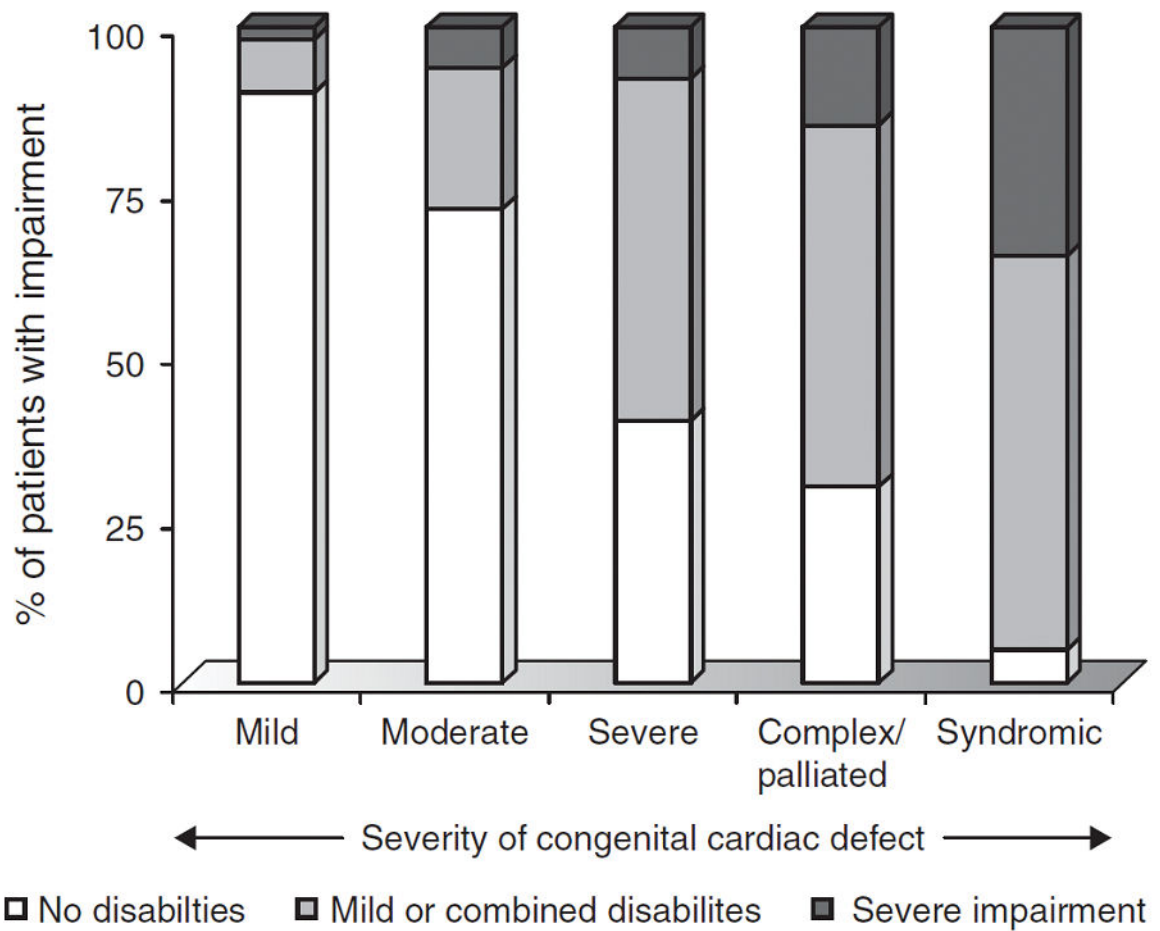
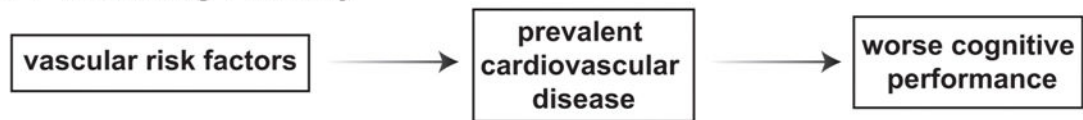
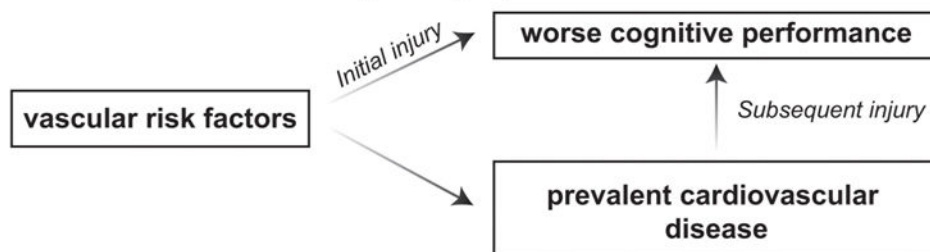
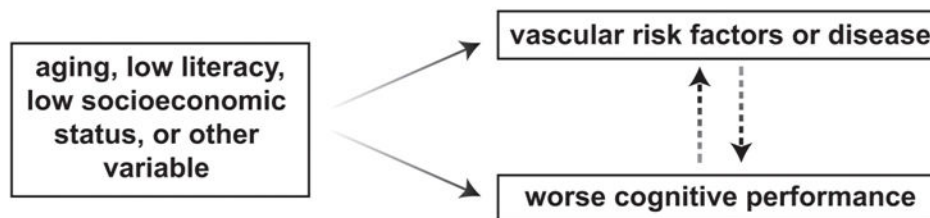


Figure 4. Gradient between congenital heart disease severity and prevalence of neurodevelopmental impairment.⁴ Reprinted with permission from Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. *Cardiol Young* 2006; 16 (Suppl 1): 92–104.

A Mediating Pathway**B Successive Pathway of Injury****C Epiphenomenon or Confound****Figure 5.**

Vascular risk factors and midlife cognition.⁶ Reprinted with permission from Jefferson AL. Vascular risk factors and midlife cognition: Rethinking the exposure window. *Circulation*. 2014;129:1548–1550

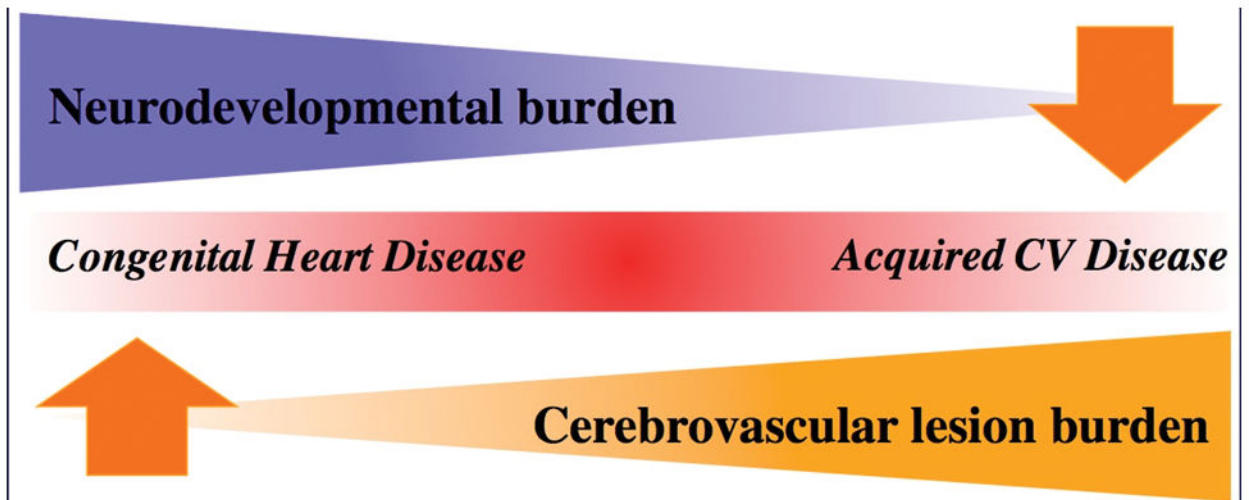


Figure 6.

Unifying hypothesis for the continuum of neurocognitive disease in the lifespan of congenital heart disease patients.¹⁰⁵ Inspired from Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: How to move forward? *Neurology*. 2009;72:368–374.

Table 1

Future directions for translational research resulting in improved patient and family centered outcomes.

Understanding of the relative importance of the risk factors for neurocognitive disability in CHD	
•	Genetic and epigenetic abnormalities
•	Fetal cerebral hemodynamics
•	Cardiac sequelae of congenital lesions including heart failure, arrhythmia, and valve disease
•	Complications of interventions to treat heart disease
•	Cardiovascular risk factors in the aging CHD populations
Interventions to promote brain health:	
•	Cerebral oxygen and substrate delivery
•	Cerebral emboli and microemboli
•	Perioperative methods of monitoring brain health
•	Risk factor modification for adult cardiovascular and associated neurovascular disease
Improvement of patient-centered and societal outcomes by:	
•	Educating patients, their families, and school systems about neurodevelopmental disabilities in children and adolescents with CHD
•	Providing neurobehavioral interventions to improve outcomes in children and adolescents to improve educational attainment, vocational skills, social cognition, and employment
•	Reduce adverse effects of CHD on mental health, including behavioural dysregulation, anxiety and depression

CHD= congenital heart disease

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