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Double-Trouble: Atherosclerotic Risk Factors and Congenital Heart Disease

Justin P. Zachariah[1]

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Abstract

Purpose of Review Youth with congenital heart disease (CHD) are uniquely vulnerable to genetic and acquired atherosclerotic cardiovascular disease (ASCVD) risk factors. With the increasingly successful management of CHD, it is important to prevent or optimally managed risk factors with the goal of improving outcomes and longevity.

Recent Findings This review summarizes guidelines for the evaluation and management of obesity, dyslipidemia, and hypertension in youth (< 18 years of age), focusing on the special vulnerabilities associated with the type of repair and the presence of residual disease in those who undergo cardiac surgery.

Summary Clinicians must focus on targeting these highly prevalent ASCVD risk factors to protect CHD survivors from preventable ASCVD morbidity and mortality by applying lifestyle, pharmacologic, or surgical therapies as needed. Future work should examine interventions to identify and treat ASCVD risk factors in CHD patients. Given the increased prevalence of ASCVD risk factors in youth and the morbidity and premature mortality associated with CHD, it is important for clinicians to assess global risk factors in these patients frequently, encourage adherence to lifestyle changes, and recommend pharmacotherapy and surgical interventions when clinically indicated. Future efforts should identify barriers and opportunities for improving risk factor assessment and timely intervention as a routine part of clinical care.

Keywords Childhood obesity · Cholesterol · Congenital heart disease · Pediatric cardiology · Pediatric hypertension · Lipid disorders · Review

Introduction

ASCVD is a leading cause of death worldwide, with a prevalence of 48% in US adults [1••]. Risk factors such as age, sex, blood pressure (SBP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), cigarette smoking, and diabetes (both type 1 and type 2) contribute to atherosclerosis, the underlying cause of ASCVD, and predictable future adverse events and poor outcomes [1••, 2]. Fortunately, from ~ 1980 to 2015, ASCVD-attributable mortality decreased in the USA and other high- and middle-income countries [3]. According to data from the IMPACT mortality model, 44% of the observed decrease was due to primary prevention strategies including optimizing TC and SBP, smoking avoidance/cessation, and increasing physical inactivity, while secondary strategies accounted for 47%, the latter primarily driven by risk factor modification following an ASCVD-relayed event [3].

ASCVD begins in childhood and risk factors, present at an early age (1) track into adulthood and (2) predict subclinical atherosclerosis in youth and (3) ASCVD-related events later in life [4, 5, 6••]. Observational data have shown that early and effective interventions greatly reduce or prevent atherosclerosis [7•]. Meta-analyses confirm that individuals with fewer or less severe risk factors over their life span have less ASCVD risk, a finding which exceeds risk factor reduction initiated later in life, such as use of lipid-lowering medication [8]. This suggests that avoidance or optimum management of lifelong risk factors should be the primary goal of ASCVD prevention.

Cardiac malformations are the most common form of birth defects with a prevalence of ~ 0.8% [9]. The types of malformations vary and are influenced by in utero exposures and genetic factors, although the cause of many remain

✉ Justin P. Zachariah
justin.zachariah@bcm.edu

[1] Section of Pediatric Cardiology, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX 77030, USA

unknown. Extreme anatomic and physiologic variability leads to oxygen desaturation, failure to thrive, easy fatigue, tachypnea, and hypertension, with many children experiencing cardiorespiratory failure. Over the decades, survival has dramatically improved primarily due to more effective and timely medical and surgical interventions such that the number of adults with congenital heart disease (CHD) exceeds that of children [10]. However, the vast majority of interventions for CHD are palliative rather than curative, with patients continuing to need lifelong monitoring often due to the highly specific vulnerabilities of their heart, vessels, brain, and other organ systems [11]. The interaction of genetic and/or acquired risk factors over a lifetime in the setting of a vulnerable cardiovascular system results in CHD survivors being at high risk of morbidity and premature mortality, both of which can be greatly improved or are potentially avoidable. This review will briefly discuss ASCVD risk factors in childhood, including obesity, lipids, and hypertension, before focusing on the specific risks unique to youth with CHD.

Obesity

Epidemiology, Tracking, and Temporal Trends

With some notable exceptions, BMI [weight (kg)/height (m^2)] is strongly correlated with measurement of body fat and a commonly used tool in clinical practice to assess adiposity [12]. Obesity is defined as a body mass index (BMI) ≥ 95th percentile for age and sex and overweight BMI 85th–94th percentile. Severe obesity is considered present when the BMI is ≥ 35 or when the BMI exceeds 120% of the 95th percentile [13]. According to NHANES data, 33.4% of children are overweight, 17.2% obese, and 5.6% severely obese. While obesity amongst those with a higher socioeconomic status (SES) status has decreased, rates have increased in lower SES [14]. Racial-ethnic stratified data shows that obesity is more prevalent in Blacks and Hispanics compared to Whites and Asians. With respect to sex, obesity is slightly more prevalence amongst boys than girls; however, there is no difference in severe obesity [1••, 13]. Disturbingly, meta-analyses show that 50% of obese children will become obese adolescents and 80% of obese adolescents obese adults, making them 5 times more likely to become obese adults [15].

Children with excess body weight often have significant comorbidities including hypertension, dyslipidemia, insulin resistance, nonalcoholic fatty liver disease, sleep apnea, asthma, psychological/behavioral disorders, and musculoskeletal complications [16]. Excessive body weight is associated with changes in cardiac structure and function, arterial stiffness, structure and function, endothelial dysfunction, and accelerated vascular aging [17].

A systematic review showed children who were overweight and obese had an increased risk of ASCVD-related adverse outcomes [18]. A report of Native American youth found that the rate of premature deaths in the highest BMI quartile for age and sex was double that of the lowest BMI quartile [19]. Data from a Swedish cohort of children with obesity reported a 2–3 times increased risk of premature death [20].

Diagnosis and Management

Annual screening for overweight and obesity using a calculated BMI is recommended by most professional societies, USPSTF, and governmental entities [21, 22]. Inadequate diagnosis of obesity in the pediatric age group is often due to the perceived ineffectiveness of preventative counseling, concerns about low parental motivation, problems with billing/reimbursement, cultural variation in perception of body image, and concerns about the stigmatization associated with being overweight and obese at an early age [23–26].

With respect to treatment, the USPTF analyzed data from intensive weight loss programs that included at least 26 patient contact hours which resulted in weight loss [27]. Cornerstones of successful weight management include increasing intake of fruits and vegetables, reducing portion sizes, and avoiding calorie-dense foods like sugar-sweetened beverages (SSB) and ultra-processed foods. A randomized trial of healthy adults comparing calorie and macronutrient-matched "high processed" versus "unprocessed" foods concluded that an ultra-processed diet induced higher energy intake compared to an unprocessed diet, suggesting "ultra-processed" foods have a disproportionate effect on weight [28]. Sedentary activities (i.e., screen time) should be limited to < 2 h per day, and physical activity increased to 5 h of moderate-to-vigorous exercise per week [29]. Studies have shown improvements in hypertension and dyslipidemia with weight loss [29]. Unfortunately, "failure" in pediatric weight loss programs is common due to competing forces of intended weight loss versus growth-driven weight gain [30]. As weight decreases, resting energy expenditure also decreases, requiring proportionally more effort to achieve additional weight loss [31]. Public health policy changes may help achieve more "personal responsibility" in achieving and maintaining a healthy weight. Some experts believe that obesity is a natural consequence of a "toxic" food environment and have called for a collective action [32].

Pharmacotherapies for youth who are overweight or obese are rapidly emerging, including promising results from SGLT2 inhibitor clinical trials along with previously approved Orlistat [33, 34]. Data on the long-term use of weight loss drugs is in process. Bariatric surgery has become

more acceptable for select youth with severe obesity and comorbidities [35]. Bariatric surgery reduces BMI and improves dyslipidemia and hyperinsulinism. However, 15% of those who undergoes bariatric surgery needed one or more additional surgeries, and 33% suffered adverse effects [36]. Since bariatric surgery permanently alters enterohepatic and biliary circulation, the long-term effects need further study. In addition, over 20% who achieve weight loss after the initial bariatric surgical procedure regain their prior weight and experience a recurrence of comorbid conditions [35]. Thus, the appropriateness and availability of surgery will depend on totality of assessment and long-term follow-up data. Statements from the American Academy of Pediatrics note that the long-term safety and efficacy in youth of both medications and surgery remain unknown. Future studies will help future clinical decision-making.

Accumulating Lipids and Lipoproteins

Epidemiology

ASCVD is the consequence of fatty streaks and plaques accumulation within the vasculature [37, 38]. Recent metacohort observational data from children followed into adulthood shows lipid and lipoprotein levels predict future ASCVD-related events during adulthood [6••]. Multiple studies demonstrate children with dyslipidemia have adverse vascular health in young adulthood [5]. In particular, familial hypercholesterolemia (FH), caused by genetically elevated low-density lipoprotein cholesterol (LDL-C), firmly links the effects of lifelong elevations of LDL-C to premature ASCVD-related events. Registry and genetic metacohort data show that individuals with FH-associated genetic variants (APOB, LDLR, LDLRAP1, and PCSK9) have a multifold higher risk for ASCVD than their non-FH peers [1••, 39].

Despite the rise of obesity in the USA, lipid and lipoprotein levels in youth have declined, although the reason(s) remain unclear [40, 41, 42•] [1••, 97••]. Nationally, representative data show the prevalence of any abnormal cholesterol level being roughly 20% and abnormal levels of TC, triglycerides (TG), HDL-C, and LDL-C of 7.1%, 10.2%, 12.1%, and 6.4%, respectively. [41, 42•] While levels of lipids and lipoprotein in overweight and obese children are elevated, it should be noted that children who are lean may also be at risk. Indeed a substantial proportion of youth, particularly those with unhealthy lifestyles and genetic variants, have elevated lipids yet a normal weight. Focusing exclusively on excess weight as a trigger for cholesterol screening will miss a substantial proportion of those with significant dyslipidemia who would benefit from intervention, including use of lipid-lowering medication [42•]. Girls are more likely to have elevated LDL-C than boys, while boys have higher HDL-C and TG [1••]. In general, Asian children have higher levels of TC, LDL-C, and TG, while Hispanic children have the lowest levels of HDL-C and Black children lower TG [1••].

Classification and Diagnosis

Categorically, disorders of lipid and lipoprotein metabolism are the result of one or more of the following: unhealthy lifestyles, genetic predisposition, the effects of medications, and medical conditions. Atherogenic dyslipidemia, commonly seen in children who are overweight or obese, is defined as the triad of elevated TG, low HDL-C, and increased number of small, dense LDL particles, while LDL C is generally normal or modestly increased. Genetic variants, such as those that cause FH, are commonly characterized by isolated elevation of total and LDL-C, with normal TGs and HLD-C [21]. With the high prevalence of FH (1:200) in the general population and the rising prevalence of childhood obesity, these "classic" lipid profiles have begun to overlap.

The primary genetic lipid disorders include FH, familial combined hyperlipidemia (FCH), and familial severe hypertriglyceridemia (HTG). FH is an autosomal codominant disorder [43, 44]. While the vast majority of children with heterozygous FH (HeFH) are asymptomatic, those with homozygous FH (HoFH) can present in early childhood with xanthomas commonly involving the extensor surfaces of the knees and elbows. Although rare (1:250,000), individuals with HoFH may experience ASCVD-related events within the first two decades of life. In contrast, HeFH is very common (~0.4%) with one child born with a heterozygous variant every minute.

Although less often recognized in the pediatric population, the prevalence of FCH approaches 1%. Youth with HeFH and FCH are frequently asymptomatic during childhood; nonetheless, the risk of a fatal or nonfatal MI is approximately 20 to 100 times higher than the general population [43, 44].

Although the role of familial HTG in premature ASCVD remains unclear, youth and adults with severely elevated TGs (> 1000 mg/dL) are susceptible to acute and recurrent episodes of pancreatitis throughout the lifecourse [21]. A review of lipid and lipoprotein abnormality secondary to medication or medical conditions is beyond the scope of this review.

Screening

Lipid screening during childhood primarily aims to identify youth with genetically induced hypercholesterolemia, especially HeFH [21, 43]. Screening guidelines, first published in 1992, have evolved from targeted screening based upon

family history to including other individual risk factors and medical conditions [2, 21]. Supporting this evolution are studies showing screening based upon family history misses 30–60% of children with elevated lipid levels many of whom would benefit from early intervention, including use of lipid-lowering medication [45]. The 2011 NHLBI guidelines recommended (1) universal cholesterol screening for children beginning at 9–11 years of age and, if normal, repeated at 17–21 years of age and (2) targeted cholesterol screening for children ≥ 2 years old with risk and risk conditions [21]. The rates of universal screening in clinical practice, however, remain low, justified by some based upon a lack of decades-long data which demonstrate cholesterol screening in childhood decreases future ASCVD events, a presumed, but unproven, stigma following a lipid-related diagnosis, anxiety related to dietary habits, and cost. As a result, the US Preventive Services Task Force review assigned universal childhood lipid screening an "I" rating (insufficient data) [27]. It should be noted, however, that the USPSTF did not reject the potential benefit of cholesterol screening but was unable to come to a definitive conclusion for or against cholesterol screening due to a lack of published outcome data. Thus far, provider screening of children for lipid-related disorders has failed to identify the expected proportion with heFH [46]. Barriers to cholesterol screening identified by pediatric providers include a lack of guideline awareness, discomfort with managing lipid disorders, and opposition to the use of lipid-lowering medication in children [47].

Early diagnosis and management are critically important if we are to improve outcomes in this vulnerable population. A key study from a Dutch HeFH cohort found offspring with proper therapy in early life was almost completely protected from coronary events before 40 years of age compared to their parents, in whom treatment was delayed until later in life and, as a consequence, was substantially affected by coronary events prior to 40 years of age [7•]. A combined meta-analysis compared ASCVD events between trials of statins versus LDL-C lowering genetic polymorphisms and showed that the latter were substantially more effective, suggesting lifelong lower LDL-C levels are more cardioprotective [8]. Chronic exposure to elevated LDL-C increases the risk for ASCVD events and is modifiable [6••].

Management

Lifestyle modifications is the cornerstone of dyslipidemia management in children, with or without weight loss [21, 48, 49]. The NHBLI Cardiovascular Health Integrated Lifestyle Diet (CHILD-2) is recommended for youth with persistently elevated LDL-C (clinically suspected or genetically confirmed FH), limiting saturated fat to < 7% total calories and dietary cholesterol to < 200 mg/day, and incorporating dietary psyllium fiber and plant sterols. For patients with elevated TGs, the CHILD-2 TG diet recommends eliminating SSB and added sugars while replacing simple carbohydrates with whole grains and complex carbohydrates. Children should participate in 5 h of moderate-to-vigorous exercise weekly and limit daily sedentary screen times to less than 2 h per day [21].

Pharmacological therapy is indicated in youth who failed to reach their lipid goal with lifestyle intervention alone, especially in those with family history or other ASCVD risk factors. Several publications evaluating pharmacotherapy for HeFH have concluded that statin use decreases ASCVD-related events and slows progression of atherosclerosis [7•, 44]. With respect to side effects, a Cochrane review of nine randomized placebo control trials of statins in children showed no differences in liver enzyme levels, incidence of rhabdomyolysis, or alterations in sexual maturation from cholesterol-derived sex hormones [50]. Nonetheless, it is important to remain vigilant. Of note, there is evidence in children that statin use may be rarely associated with the development of type 2 diabetes similar to adults [51].

Hypertension

Epidemiology, Tracking, and Temporal Trends

Elevated blood pressure (BP) is the strongest modifiable cause of ASCVD [52, 53]. Evidence-based recommendations for BP management in youth are contained within the 2011 NHLBI integrated cardiovascular risk reduction guidelines and the 2017 AAP BP guidelines [21, 54]. Despite the rise in rates of obesity in youth since the 1970s, the average systolic blood pressure in the population has declined. Reduced lead exposure has been linked to declining BP in US children [55]. Meanwhile, in parallel with the rise in obesity, the proportion of youth with abnormal BP has increased, with ample evidence showing BMI exerts strong effects on BP [56, 57]. According to the 2017 AAP BP guidelines, about 14% of adolescents have an elevated BP [58]. Hypertension is more prevalent in boys than girls and amongst Blacks and Hispanics compared with Whites and Asians [59]. Meta-analysis demonstrates BP tracks from childhood to adulthood and is greater for adolescents than younger children [4]. Critically, multiple studies show hypertension during adolescence predicts all-cause mortality and ASCVD in adulthood [6••, 60, 61]. Better BP control in children may avert elevated BP in young adulthood and its related consequences [62].

Diagnosis and Classification

The diagnosis and classification of hypertension in youth are challenging due to the need for age-sex-height-dependent

normative references and the common occurrence of white coat (WCH)/anxiety-induced/reactive hypertension or masked hypertension (MH). Studies have suggested that the prevalence of WCH in youth studies is approximately 32%, varying significantly across various study populations [63]. MH, estimated to be present approximately 7% of youth, is defined as a normal BP recorded during a clinic visit yet elevated when recorded by 24-h ambulatory BP monitoring [63].

Ambulatory blood pressure monitoring (ABPM) is deemed superior to office or home BP monitoring in classifying true versus WCH hypertension [54, 63]. Several studies show a strong relationship between ABPM-defined hypertension and target organ damage, such as elevated left ventricular (LV) mass, thicker carotid artery thickness, and increased arterial stiffness [64–66]. Updated guidelines on the use of ABPM and the interpretation of its results have been published, including use in youth who are obese and those with sleep apnea and certain forms of congenital heart disease [63]. ABPM use has been demonstrated cost-effectiveness in children and adults with suspected hypertension [67, 68].

A complete history and physical examination help distinguish between primary and secondary hypertension. In evaluating the causes of hypertension, a study in a tertiary pediatric hypertension clinic found secondary hypertension in 100% patients of infants, 80% of 1–5 years old, and ~ 50% of ≥ 6 years old [69]. Secondary causes of hypertension are often suggested by a history of premature birth, frequent urinary tract infections, or a lack of ABPM evidence showing attenuation of BP during sleep [54, 63]. Adolescents with prevalent ASCVD risk factors (e.g., elevated BMI, unhealthy diet, or physical inactivity) can be assumed to have essential hypertension barring abnormal history or exam findings or until BP does not improve in expected fashion [54].

Management

Management of hypertension in youth starts with adoption of a heart healthy lifestyle with particular focus on improving dietary quality, increasing physical activity, and achieving/maintaining a healthy weight [21, 70]. The Dietary Approaches to Stop Hypertension (DASH) diet has consistently shown improved BP measurements across various subpopulation [70, 71]. The DASH diet focuses on intake of whole grains, vegetables, and fruits high in fiber, potassium, magnesium, and calcium, as well as lean meats, fat-free dairy, and minimizing added sugars and sodium.

Data in youth on the relation between physical activity and BP has been incompletely established due to study design or limited participation. One meta-analysis showed that exercise reduced SBP and DBP by 1% and 3%, respectively, but did not meet statistical significance [72]. Activity data from youth measured utilizing wearable technology confirmed that higher PA was associated with lower BP and suggested that activity amount may be more important than the intensity [73]. School-based intervention strategies improving PA improved BP in children [74].

Current guidelines recommend initiation of pharmacologic treatment in youth if adequate lifestyle changes alone fail to improve BP after 6 months and more acutely in those with severely elevated BP [54]. Calcium channel blockers (CCB), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor antagonists (ARB) are the first-line choices for goal-directed medical therapy. Of note, thiazide diuretics and beta-blockers should be used cautiously as they can impair glucose metabolism, placing patients at risk for developing diabetes mellitus [75]. The rarity of ASCVD events in childhood prevents outcome-based therapy goals, making reduction to population percentile-based "normal" levels, either below 90 percentile for age-sex or below 130/80, as the goal of therapy [54]. Causes of secondary hypertension should be identified and addressed if present. The utility of vascular or cardiac assessments or goal-directed therapy on future ASCVD risk events needs to be defined.

Congenital heart disease

CHD is the most common form of birth defect, affecting roughly 8 in every 1000 live births [9]. Of these children, roughly 30% will require a procedural intervention during early life [9]. CHD can affect any structure within the developing heart and often occurs in multiple combinations, resulting in a wide array of cardiac lesions. While many classification schemes exist, for purposes of this discussion, CHD is classified into three main categories. First are septal defects that allow blood to escape the intended route, resulting in either cyanosis secondary to inadequate flow to the lungs or, alternatively, excessive flow to the lungs which over time can lead to pulmonary artery changes that impede flow and cause cyanosis and heart failure. The second category is narrowing of the heart valves thereby impeding blood flow into and/or out of the ventricles, often resulting in diminutive chamber sizes, hence the maxim "no flow, no grow." Finally, abnormalities can exist in large blood vessels through which blood is pumped from the heart, especially the aorta, leading to narrowing (coarctation) or anatomic interruption of the aorta. Further complicating this panoply of anatomic and function disorders is procedural interventions which have their own effects and side effects. Each unique type of CHD has its own natural history, altered by the type of treatment-rendered and treatment-related side effects. These can alter the natural history and may mitigate future ASCVD-related risk (Table 1) [11]. The increasing

Table 1 Excess risk of atherosclerotic cardiovascular disease type by congenital heart disease type

Type of congenital heart disease	Coronary artery disease	Cerebrovascular disease	Vascular disease
Coronary anomalies	↑	-	-
Transposition of the great arteries	↑	-	↑
Coarctation of the aorta	↑	↑	↑
Aortic valve disease	↑	-	↑
Septal defects	-	↑	-
Eisenmenger syndrome	-	↑	↑
Cyanotic heart disease	-	↑	↑

Up arrow indicates higher risk than general population. *Dash* indicates no evidence of increased risk

prevalence of youth who survive CHD reinforces the importance of focusing on ASCVD risk factors [10]. Advances in care have resulted in > 90% improvement in youth who survive CHD into adulthood. [10, 11, 76] Indeed, epidemiology suggests that in countries with high per capita income, the number of adults currently living with CHD outnumbers the number of youth who had survived CHD [10]. Given the preponderance of evidence, some studies suggest CHD survivors face new challenges related to higher risk of early ASCVD [11, 77–81]. Guidelines for adults with CHD, including those for ASCVD risk factor screening, confirmation, and treatment, generally recommend goal-directed medical therapy (GDMT) [11].

Reports suggest 70 to 80% of adult CHD survivors have at least 1 ASCVD risk factors [77, 79, 80]. It should be noted, however, that current data regarding adult-onset ASCVD in CHD survivors reflect older forms of CHD treatment, many of which have been supplanted by substantially newer and novel forms of treatment. In addition, individuals not living in countries with high per capita income often lack availability of adequate treatment for CHD and access to qualified pediatric cardiologists, which results in higher proportions of this disadvantage population being exposed to lifelong ASCVD risk factors [76]. Even in populations with higher incomes, conventional social determinants of health affect care in those with CHD and, as a consequence, cause variation within subpopulations. Interacting with these baseline risks, the altered natural history of CHD can add special risks for ASCVD events including coronary artery atherosclerosis, atherothrombosis, stroke, vascular occlusion, or vascular rupture.

Fundamentally, ASCVD creates a mismatch between the demand for oxygen and the cardiovascular system's ability to meet that need, whether to the heart, brain, or other vital organs [1••]. In CHD, this mismatch can occur due to changes in arterial blood flow or increases in tissue demand [82]. First, the anatomy or location of coronary arteries which supply the heart can be significantly altered by congenital abnormalities or post-procedural complications. As an example, during in utero development, the pulmonary artery may give rise to an anomalous left coronary artery, the latter forming collateral vessels which join to the normal right coronary system. When the left coronary artery is attached to the pulmonary artery, (1) some of the blood flowing into the coronary artery flows back into the pulmonary artery, thus "stealing" the blood from the heart, and (2) the blood which reaches the heart is deoxygenated. This combination leads to myocardial infarction in infancy, progression to permanent ischemic cardiomyopathy, and/or rupture of the mitral valve papillary muscle with a flail mitral valve, the latter due to the tip of the mitral papillary muscle being the most distant and, therefore, the most vulnerable [83, 84].

Alternatively, some abnormal origins of the coronary arteries can be innocuous until they are surgically altered. Examples include an arterial switch for transposition of the great arteries, pulmonary autograft (Ross), or an aortic root replacement (Bentall) wherein the coronary vessels are surgically reimplanted into a neoaortic vessels [85]. Although such surgeries are conscientiously performed with attention to avoiding scar lines at the coronary ostia, obstructions still occur, and subsequent abnormal flow dynamics can induce coronary atherosclerosis.

Coarctation is a narrowing of the aorta characterized by hypertension proximal to the lesion and lower BP distal to the lesion [86]. Studies show that despite optimal repair, hypertension is more prevalent than the general population [87–89]. Consequently, survivors of coarctation have been shown to be at higher risk of ASCVD [11, 90, 91]. Stroke may be related to berry aneurysms of the cerebral vasculature, with some evidence that screening in at an early age for these vascular anomalies may be warranted [90, 92]. In children with persistent systolic hypertension, the afterload induces compensatory hypertrophy of the ventricular myocardium [93]. The crescendo demand of this progressive ventricular hypertrophy eventually leads to inadequate oxygen delivery, characteristically causing infarction of the subendocardial myocardium.

Likewise, valvar, subvalvar, and supravalvar aortic stenosis represent forms of ventricular afterload leading to consequent ventricular hypertrophy and inadequacy of supply and demand. Supravalvar aortic stenosis can be associated with genetic disorders, like Williams syndrome, which is also associated with coronary ostial stenosis impairing myocardial oxygen delivery and/or renal artery stenosis leading to systemic hypertension and consequent ventricular hypertrophy [94]. Progression or degeneration of the native or repaired heart valve can lead to stenosis or regurgitation, sending ineffective excessive blood flow to and fro. This excess flow can cause increases in size of the ventricle or

aorta. When the size of the ventricle increases, it can lead to myocardial hypertrophy, but when an aneurysmal dilation occurs in the aorta, there is no muscular layer to compensate, raising the risk of vessel rupture [11].

With respect to residual septal defects (patent foramen ovale, atrial septal defect, atrioventricular septal defect, or ventricular septal defect), blood flows from higher to lower pressure left side to right side, although transient right to left flow is possible [77, 79]. This transient right to left flow allows for systemic venous thromboses to embolize, traverse the defect from right to left, bypass the lungs, and obstruct the cerebral arteries, causing stroke. Septal defects are the most common form of CHD associated with ASCVD [79].

Cyanotic heart lesions are readily identified and repaired in childhood, making ASCVD more likely to occur following rather than prior to surgical repair [95, 96]. Late cyanosis, therefore, occurs infrequently in unrepaired heart disease. When present, it can be due to residual ventricular septal defect coupled with obstruction to pulmonary blood flow and consequent flow of cyanotic blood from right to left ventricle (Eisenmenger syndrome). Chronic cyanosis induces polycythemia. Intriguingly, these patients have no excess risk of coronary disease but are at higher risk of stroke [11, 81, 95, 96]. Stroke risk is attributed to the combination of residual right-to-left blood flow through the septal defect and hyperviscosity secondary to cyanosis-induced polycythemia.

In light of this myriad of unique vulnerabilities, meticulous assessment and management of ASCVD risk factors are required [11, 78, 80, 81]. Special focus is needed to resolve the so-called vulnerable-child phenomenon wherein CHD survivors have internalized a learned helplessness preventing participation in vigorous activity [97••]. Recent guidelines demonstrate a paradigm shift toward encouraging as much activity as permissible within the constraints imposed by the functional safety limitations of CHD [11].

Conclusion

CHD, the most prevalent birth defect, often necessitates a procedural intervention during early life. Greater than 90% of children with CHD survive into adulthood, resulting in more adults than children with a history of CHD. ASCVD risk factors are highly prevalent in children, including those born with structural heart disease. Data suggests that each type of CHD has special risks for ASCVD. Pediatric healthcare providers should focus on maintaining the health of children with CHD by early identification and optimum management of all modifiable ASCVD-associated risk factors. Current guidelines support managing risk factors in those with CHD similarly to the general population, with special attention to encouraging physical activity under the constraints of each particular CHD. Further work is needed to better understand phenotypic variation and the effects of ASCVD risk modification in children who survive CHD.

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Declarations

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