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Is There a Role for Imaging Youth at Risk of Atherosclerosis?

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Abstract

Purpose of Review Cardiovascular (CV) risk factors such as dyslipidemia, hypertension, diabetes, and obesity are associated with an increased risk for CV events in adults. Noninvasive measures of vascular health are associated with these CV events and can potentially help risk stratify children with CV risk factors. The purpose of this review is to summarize recent literature regarding vascular health in children with cardiovascular risk factors.

Recent Findings Adverse changes in pulse wave velocity, pulse wave analysis, arterial distensibility, and carotid intima-media thickness are seen in children with CV risk factors supporting potential utility in risk stratification. Assessing vascular health in children can be challenging due to growth-related changes in vasculature, multiple assessment modalities, and differences in normative data.

Summary Vascular health assessment in children with cardiovascular risk factors can be a valuable tool for risk stratification and help identify opportunities for early intervention. Future areas of research include increasing normative data, improving conversion of data between different modalities, and increasing longitudinal studies in children linking childhood risk factors to adult CV outcomes.

Keywords Pediatrics · Pulse wave velocity · Pulse wave analysis · Carotid intima-media thickness · Dyslipidemia · Hypertension · Diabetes · Obesity

Introduction: Evidence for Origins of Atherosclerosis in Youth

It is well established that adults with cardiovascular (CV) risk factors such as dyslipidemia, hypertension, obesity, and diabetes have an increased risk for CV events [1–5]. Vascular changes are associated with these hard CV outcomes with adverse changes in large artery stiffness, arterial distensibility, and arterial wave reflections seen in adult studies [6–10]. Indeed, carotid-femoral pulse wave velocity (cfPWV), a measure of arterial stiffness, is independently associated with CV events in adults [6, 10]. Similarly, adverse changes in arterial distensibility and arterial wave reflections are associated with increased CV risk factors and events [7–9, 11]. The question then is if similar vascular changes occur in children with CV risk factors.

There is evidence that atherosclerosis develops even in youth. The Bogalusa Heart Study performed autopsies in young individuals (aged 2–39 years) who died from various causes (mostly trauma) and found that around 50% of subjects aged 2–15 years had fatty streaks in the coronary arteries with the percentage significantly increasing to 85% between age 21 and 39 years ($P = 0.01$) [12]. Furthermore, individuals with 3 or 4 adverse risk factors including body mass index (BMI), systolic blood pressure (SBP), serum triglyceride, and serum low-density lipoprotein cholesterol (LDL-C) had a higher prevalence of fatty streaks and fibrous plaques in the aorta and coronary arteries compared to those with no adverse risk factors.

The multi-center Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study also performed autopsies in young individuals (aged 15–34 years) and had similar

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findings to the Bogalusa Heart Study [13]. Fatty streaks and raised lesions were present even in the 15–19 year age group and became more extensive in size with increasing age. The findings of the Bogalusa Heart Study and the PDAY study show that the genesis of atherosclerosis occurs in youth and that progression continues with age. The findings from these studies underpin the use of noninvasive measures of vascular health to evaluate for arterial changes in youth with CV risk factors.

Effects of Cardiovascular Risk Factors on Vascular Health

Pulse Wave Velocity

Obesity during childhood predisposes individuals to various comorbid conditions [14]. However, the impact of obesity can also be seen on the vasculature as obese children exhibit increased PWV compared to lean children [15–17]. PWV can be evaluated using several methods including applanation tonometry, ultrasound, photoplethysmography, and cardiac magnetic resonance imaging (MRI). Despite the variety of PWV measurement modalities used in studies, meta-analyses of results showed overall increased arterial stiffness in obese children compared to controls [17, 18]. Cardiac MRI assessment of aortic PWV could potentially be more sensitive to arterial changes as differences in mean aortic PWV between obese youth and controls were noted on cardiac MRI even when no differences were seen on carotid-femoral PWV (cfPWV) measured by the usual standard, applanation tonometry [19].

PWV differences can also be seen with dyslipidemia in children though results are mixed. A study of children with hypercholesterolemia showed significantly higher local PWV in the carotid artery compared to controls [20]. Supporting these findings, a study of children with familial hypercholesterolemia (FH) also found significantly increased aortic (ascending to descending) PWV when assessed by cardiac MRI [21]. However, a recent meta-analysis of PWV in patients with FH found no significant difference in PWV between FH patients versus controls when including studies of both adults and children [22].

While hypertension and obesity are often comorbid conditions, children with hypertension exhibit increased PWV independent of obesity [23, 24]. Furthermore, PWV rises incrementally per unit increase in blood pressure (BP) [25] and across BP categories from normotensive to prehypertensive to hypertensive youth [26].

Children with diabetes also show changes in arterial stiffness. Adolescent and young adult patients with type 1 diabetes (T1D) had significantly higher cfPWV compared to controls independent of risk factors such as adiposity, hypertension, dyslipidemia, and microalbuminuria [27]. Similar findings are seen in young adults with youth-onset type 2 diabetes (T2D) compared to lean controls [28]. When examining contributing factors to PWV in diabetic patients, the duration of diabetic disease [29, 30] and lower insulin sensitivity [31] appear to be strong determinants of arterial stiffness.

Other conditions with increased CV risk are associated with adverse alterations in arterial stiffness. Subjects with tetralogy of Fallot, heart transplant, transposition of the great arteries, and aortic coarctation have been found to have significantly higher PWV even after repair compared to controls [32–37]. Kawasaki disease is associated with higher PWV compared to controls [38, 39]. End-stage renal disease (ESRD) requiring dialysis also results in higher PWV in children with changes persisting even 6 months after renal transplantation suggesting large artery structural changes in these patients [40–42]. Acute changes in renal function appear to affect arterial stiffness with elevated PWV measurements in children with post-streptococcal glomerulonephritis resolving after improvement of renal function [43]. Blood pressure elevation in children with renal disease may explain some of the changes in arterial parameters [44, 45].

Pulse Wave Analysis

The effect of obesity on measures of pulse wave analysis varies between studies. Augmentation index (AIx) was significantly higher in obese youth compared to lean controls in a large, multiethnic study including children and young adults aged 10–24 years [16]. Contrasting these findings, a study of younger children aged 5–15 years found that AIx was significantly lower in obese children than in lean controls [46] supporting the concept of age-related changes in arterial wave reflections from childhood into adulthood. When examining the effects of obesity on the forward pulse wave amplitude (Pf) and backward pulse wave amplitude (Pb) of the aortic pressure wave, Pf [46, 47] and Pb [46] have been found to be significantly higher in obese children compared to lean controls.

Dyslipidemia and hypertension appear to be associated with adverse changes in pulse wave analysis in children. Youth with high LDL-C levels were found to have significantly increased AIx compared to controls [20]. Triglyceride (TG) level and TG to high-density lipoprotein cholesterol (HDL-C) ratio also appear to influence AIx [48, 49]. When examining the effects of BP in children, AIx increases across BP categories of normotension, prehypertension, and hypertension [26] with differences also seen when evaluating elevated central blood pressures compared to controls [48].

Similar to its effects on PWV, diabetes is associated with adverse changes in pulse wave analysis in youth and young adults. These changes are seen in both T1D and T2D subjects with significantly increased AIx in both groups compared to non-diabetic controls [27, 28, 30, 50]. However, it appears that these vascular changes are not present in subjects with prediabetes supporting potentially lower vascular risk in these patients [51].

Changes in AIx are also seen in other high CV risk conditions. AIx is higher in cyanotic congenital heart disease [35, 52], ESRD [41], cystic fibrosis [53], and sickle cell disease [54]. These findings across a wide range of diseases support the potential utility of arterial assessment for risk stratification.

Distensibility

Obesity in children is associated with decreased (more adverse) arterial distensibility. Distensibility measured at both carotid and brachial regions was significantly decreased in obese children compared to normal weight controls [16, 55]. Furthermore, the degree of obesity impacts arterial distensibility with severe obesity in adolescents and young adults associated with lower brachial distensibility compared to those with non-severe obesity [56]. These vascular changes appear to start around age 13–16 years showing the importance of early intervention in preventing adverse arterial changes [57].

Similar adverse changes in arterial distensibility are seen in dyslipidemia, hypertension, and diabetes. Lipid levels have been found to be independent determinants of arterial distensibility, particularly of the brachial artery [49, 57, 58]. However, the effect of hypercholesterolemia on arterial distensibility appears to vary by site and by age. Studies of young patients with FH have found increased distensibility and compliance in the aorta [21, 59, 60] but with decreased measurements in the carotid artery [61]. By adulthood, this effect is gone and aortic distensibility is worse compared to controls [62]. Blood pressure is an independent determinant of arterial distensibility [55, 57], and brachial distensibility worsens across increasing BP categories from normotension to prehypertension to hypertension [26]. Similarly, adolescents with T1D and T2D had worse arterial distensibility and compliance versus controls [27–29].

Carotid Intima-Media Thickness

Increased carotid intima-media thickness (cIMT) is also found in high CV risk conditions. Obese children were found to have significantly higher cIMT compared to non-obese controls [63]. The degree of obesity also impacts cIMT as children in the severe obesity classification (>120% of the 95th percentile BMI) have higher cIMT than non-severely

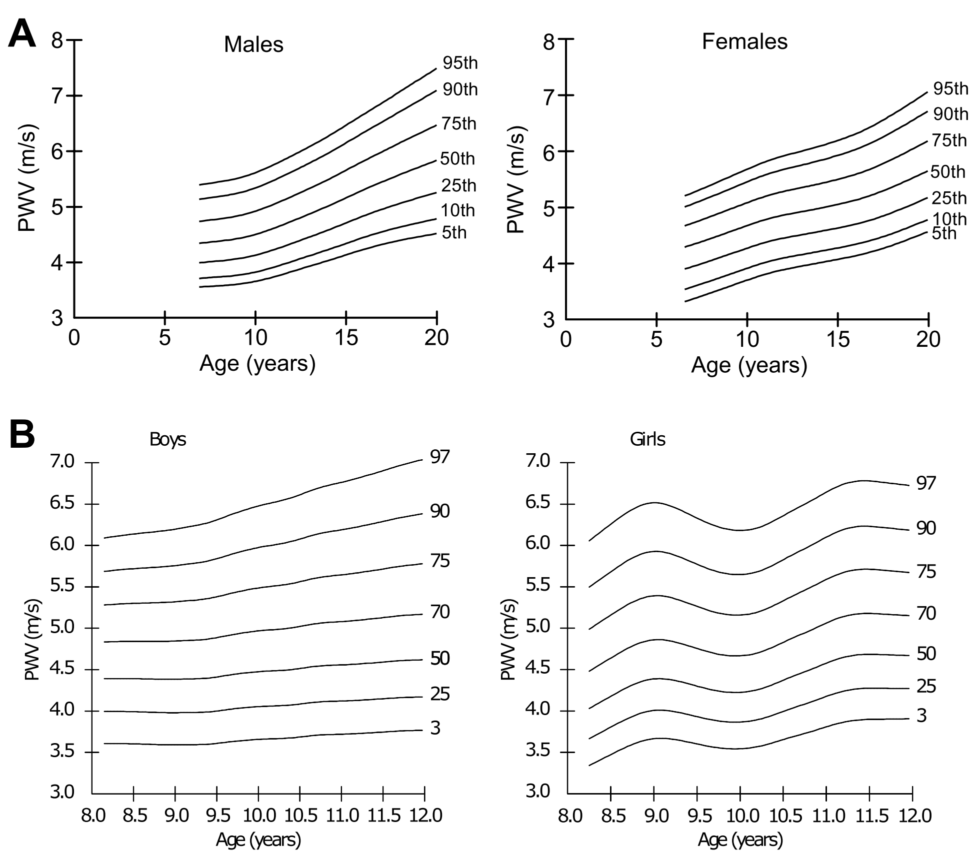

Fig. 1 Comparison of gender-specific carotid-femoral pulse wave velocity (cfPWV) percentile curves by applanation tonometry. **A** cfPWV curves by age from Reusz et al. [73]. **B** cfPWV curves by age from Mora-Urda et al. [78]. **A** with permission from Reusz GS et al. Hypertension. 2010; 56:217e224. https://doi.org/10.1161/HYPERTENSIONAHA.110.152686) [73]; **B** with permission from Mora-Urda AI et al. J Clinic Hypertens. 2017; 19:227e234. https://doi.org/10.1111/jch.12899 [78])

obese children [64]. Exercise and diet interventions in obese children appear to decrease cIMT [63, 65] suggesting that the vascular changes are reversible.

The presence of dyslipidemia and lifetime dyslipidemia trends also affect cIMT. Children with FH have increased cIMT and carotid plaques compared to controls [66]. Additionally, children with persistently high non-HDL-C from childhood into adulthood had a significantly increased risk for high cIMT as adults compared to subjects with persistently normal non-HDL-C levels [67••]. However, subjects with normal non-HDL-C levels in childhood who then developed high non-HDL-C in adulthood also had an increased risk for high cIMT. Normalization of non-HDL-C in adulthood was associated with decreased risk for high cIMT with no significant difference in risk between the normalized non-HDL-C group compared to the persistently normal non-HDL-C group.

Hypertension and diabetes are both associated with adverse cIMT changes. A recent large study of 4709 subjects evaluated cIMT during childhood and again after an 11-year follow-up finding that hypertension and obesity were associated with increased risk for high cIMT both cross-sectionally and longitudinally [68•]. Similar to the long-term effects of dyslipidemia on cIMT, long-term BP elevation from childhood into adulthood increases the risk for high cIMT as an adult [69]. Those who had normal childhood BP but then developed elevated BP during adulthood had an increased risk for high cIMT as well. Reassuringly, children who had elevated BP but then normalized the BP in adulthood had no increased risk for high cIMT further supporting the importance of early intervention of CV risk factors in children. Prediabetes was found to be a significant determinant of cIMT and brachial distensibility in youth [51] and diabetes has also been found in multiple studies to be associated with increased cIMT compared to controls [66].

Challenges in the Vascular Assessment of Children

Despite the abundance of data showing the value of vascular assessment in determining CV risk, there are challenges to performing these assessments in children. As children grow, there is a lengthening of the aorta and other vasculature which affects wave reflection sites. Additionally, there are arterial wall changes that occur in large artery development with elastogenesis extending from mid-gestation into adolescence [70, 71].

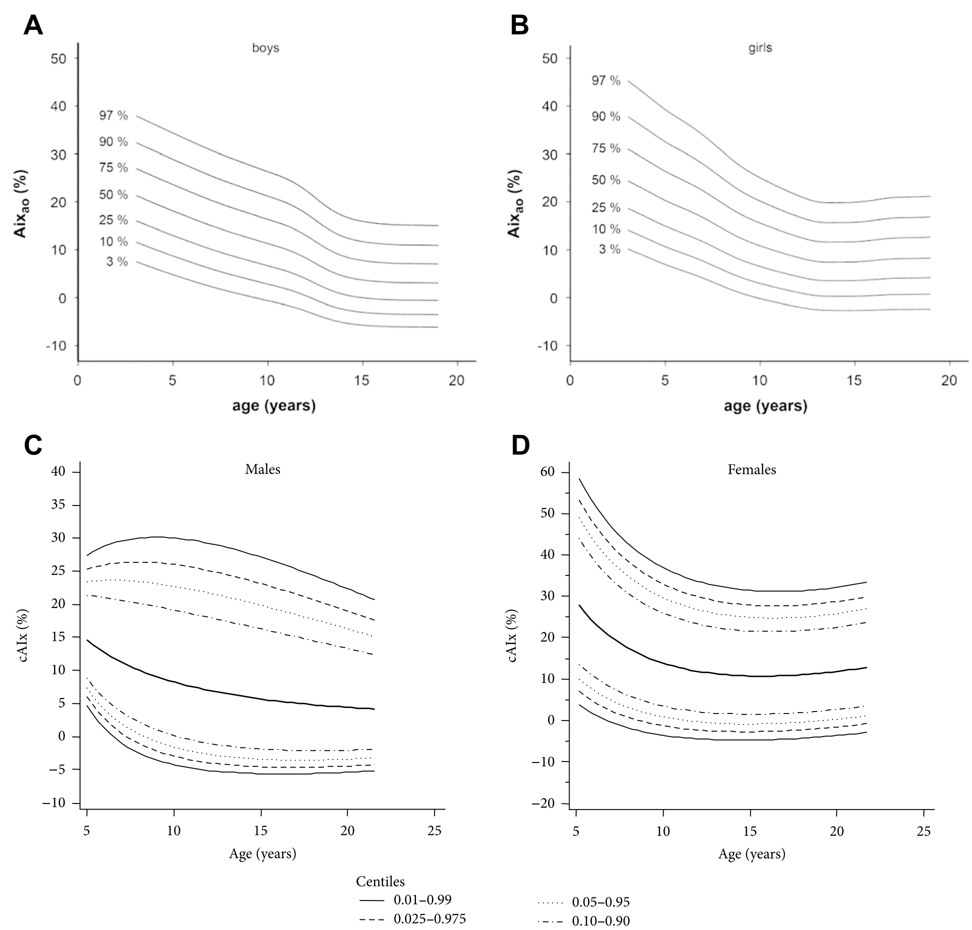

Fig. 2 Comparison of gender-specific augmentation index (AIx) percentile curves by age. Percentile curves from Hidvegi et al. [79] for boys (**A**) and girls (**B**) are shown. Percentile curves from Diaz et al. [80] for males (**C**) and females (**D**) are shown (figures with permission from Hidvégi EV et al. J Hum Hypertens. 2015; 9:495e501. https://doi.org/10.1038/jhh.2014.118 [79]; and Diaz A et al. Int J Hypertens. 2018; 2018:1469651. https://doi.org/10.1155/2018/1469651 [80])

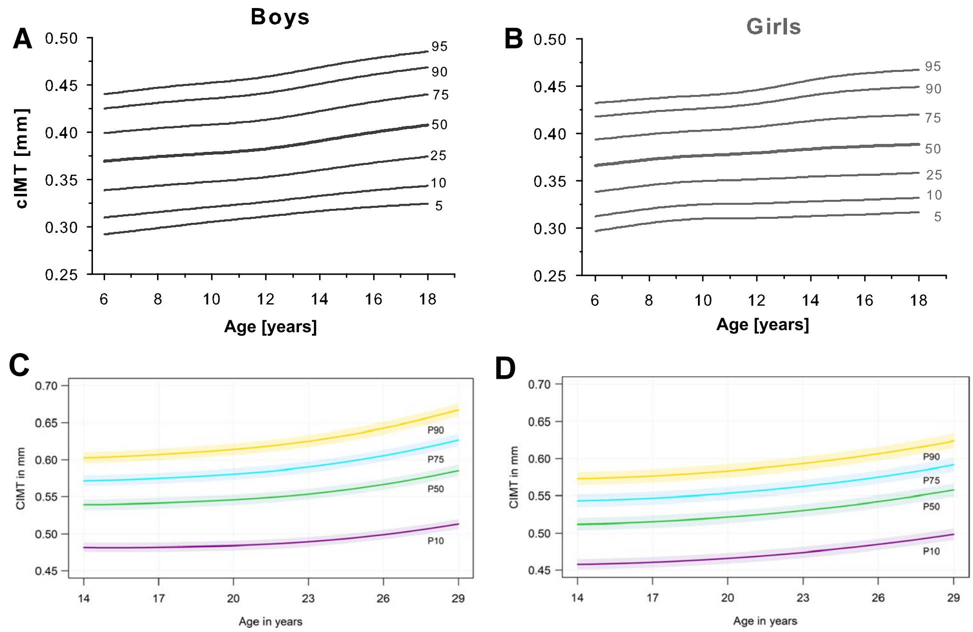

Fig. 3 Comparison of gender-specific carotid intima-media thickness (cIMT) percentile curves by age. Percentile curves from Doyon et al. [81] are shown for boys (**A**) and girls (**B**). Percentile curves at median height from Neuhauser et al. [68•] are shown for males (**C**) and females (**D**) with shaded corridors reflecting the cIMT range between the 10th and 90th height percentiles (figures with permission from Doyon A, et al. Hypertension. 2013; 62:550e556. https://doi.org/10.1161/HYPERTENSIONAHA.113.01297 [81]; and Neuhauser HK, et al. Hypertension. 2022;79:1167-1176. https://doi.org/10.1161/hypertensionaha.121.18521 [68•])

The vascular changes that occur throughout childhood also necessitate age-adjusted normal values for vascular parameters. There is an additional difficulty in defining normal values due to multiple methods and devices to assess vascular measures. For instance, PWV can be measured in multiple ways with values differing between modalities. The current gold standard of measuring PWV is using applanation tonometry to measure cfPWV [72]. Reference curves for cfPWV have been established with the largest study thus far by Reusz et al. [73] in 1008 children (Fig. 1). However, the study population primarily consisted of Hungarian, Italian, and Algerian children which may limit generalizing these values to other races and ethnicities. Mora-Urda et al. [74] also created reference curves for cfPWV using applanation tonometry but focused on a younger age group (8–11 years) in Spanish children (Fig. 1). Reference curves also exist for PWV measured by oscillometric devices [75, 76]; however, this method of PWV assessment is not currently recommended due to lack of longitudinal outcomes evidence [72]. Aortic PWV measured by cardiac MRI is also possible,

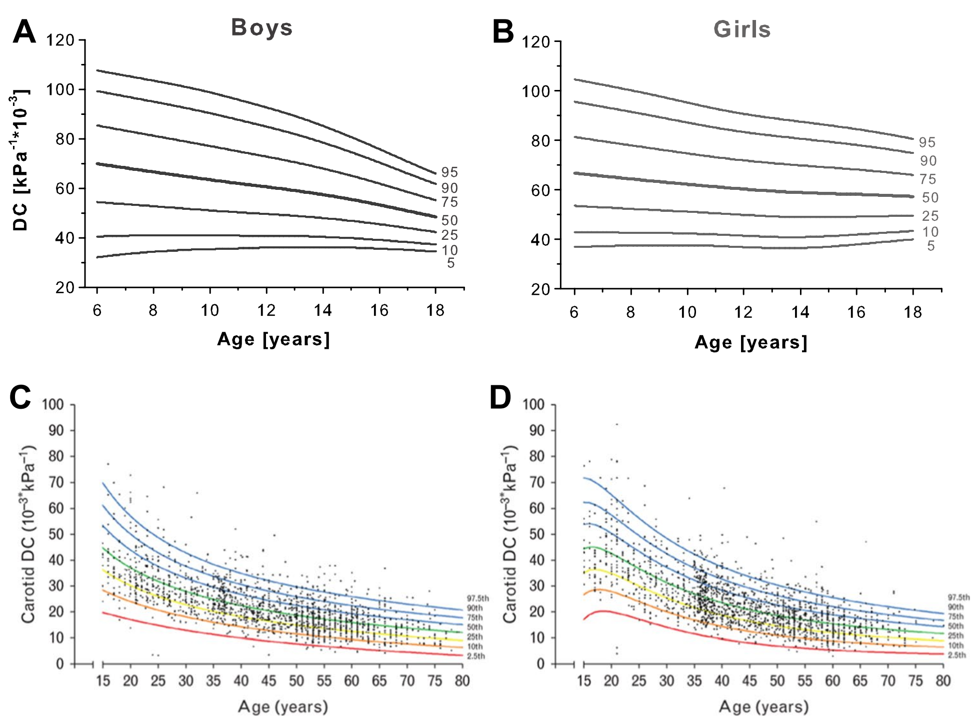

Fig. 4 Comparison of gender-specific percentile curves for carotid distensibility coefficient by age. Percentile curves from Doyon et al. [81] are shown for boys (**A**) and girls (**B**). Percentile curves from Engelen et al. [82] are shown for males (**C**) and females (**D**) (figures with permission from Doyon A et al. Hypertension. 2013; 62:550e556. https://doi.org/10.1161/HYPERTENSIONAHA.113.01297 [81]; and Engelen L, et al. J Hypertens. 2015;33:1981-96. https://doi.org/10.1097/hjh.0000000000000654 [82])

but there is limited reference data for children [77]. Overall, there appears to be an increase in PWV with age.

There is a similar variety in reference curves for pulse wave analysis with various techniques used for measurement. Hidvegi et al. [79] established reference curves for AIx using oscillometry whereas Diaz et al. [80] published reference values using applanation tonometry (Fig. 2). While there are slight differences between the two studies, AIx appears to be higher in females compared to males, likely due to shorter height in females, and decreases with increasing age.

For cIMT, Doyon et al. [81] published reference values for children and adolescents from a large group of non-obese and non-hypertensive subjects (Fig. 3). A recent study by Neuhauser et al. [68•] of German subjects established age-based reference values from age 14 to 29 years also showed a gradual increase in cIMT with advancing age. Males had higher cIMT at all ages compared to females. Reference curves by Neuhauser et al. [•68] have higher values than those from Doyon et al which may be explained by Neuhauser et al. [68•] including subjects with obesity and hypertension.

Regarding arterial distensibility, reference curves are available for both measurements using ultrasound and MRI. Doyon et al. [81] and Engelen et al. [82] determined distensibility coefficient reference curves for the carotid artery with values overall decreasing with age in both males and females (Fig. 4). Aortic distensibility reference values at different aortic regions are limited but also available for MRI [77].

Future Directions

There is an increasing body of literature showing early vascular changes in children with CV risk factors. Furthermore, the long-term effects of these risk factors on vascular health are becoming clearer with more longitudinal studies. These findings continue to support early intervention in children with risk factors to reduce future CV risk. Additional normative data across age, sex, and race/ethnicity are needed for pediatric vascular assessment modalities to improve the applicability of reference values. Further research into the conversion of values between different devices will also help guide the interpretation and clinical application of these vascular assessment modalities. Additional longitudinal studies will also help more strongly link childhood risk factors to adult CV outcomes and thereby help improve prevention strategies. Vascular health assessment continues to grow more valuable as a tool to determine risk in children with the goal of improving CV risk prevention.

Declarations

Conflict of Interest Dr. Tran has nothing to disclose.
Dr. Urbina reports personal fees from Targus Medical and Astellas Pharma, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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