Arterial stiffness is a strong predictor of cardiovascular events and all-cause mortality in middle-aged and older adults. Arterial stiffness has been limited to being an intermediate marker of atherosclerotic cardiovascular events in adolescents and young adult studies. The paucity of normative longitudinal data and repeated gold-standard assessments of arterial stiffness among the young population has occasioned a huge knowledge gap in its clinical utility. This review summarizes recent longitudinal evidence in a large adolescent population, supporting the value of arterial stiffness as a novel risk factor for hypertension, overweight/obesity and insulin resistance. Preventing or decreasing arterial stiffness during adolescence may confer cardiometabolic health benefits in later life, but further pathological and mechanistic research is needed. The review also offers suggestions for incorporating arterial stiffness measures into routine paediatric and young adult clinical practice.

**Keywords:** adolescent, arteriосlerosis, dyslipidaemia, hyperglycaemia, hyperinsulinemia, metabolic syndrome, obesity, paediatrics, preventive cardiology, vascular ageing, young adults

**Abbreviations:** ALSPAC, Avon Longitudinal Study of Parents and Children; cPWV, Carotid-Femoral Pulse Wave Velocity; CI, Confidence Interval

### INTRODUCTION

Arterial stiffness increases with ageing as described a century ago by Bramwell and Hill [1], although they measured carotid-radial pulse wave velocity: a muscular arterial segment assessment from the upper arm. It is now established that the assessment of the elastic arterial stiffness in middle-aged and older adults strongly predicts cardiovascular events and all-cause mortality [2–4]. Therefore, carotid-femoral pulse wave velocity (cPWV) is considered the gold standard for assessing arterial stiffness [5]. On the basis of evidence among middle-aged and older adults, interventions aimed at preventing arterial stiffness are currently ongoing or proposed to mitigate stiffness-related disease epidemics [6–8]. Unfortunately, arterial stiffness research as a predictor of diseases among adolescents and young adults lags [4,9]. Several studies conducted among young population have utilized arterial stiffness as a surrogate atherosclerotic cardiovascular outcome, such that hypertension, obesity, hyperglycaemia, insulin resistance and other cardiometabolic diseases predicted higher arterial stiffness [4,9–14]. The paucity of normative longitudinal data based on age, sex, body size and hypertensive state among adolescents and young adults may have limited the clinical utility of arterial stiffness measures in paediatric clinical practice [9,11,12,15–19]. Longitudinal findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) suggest that arterial stiffness, measured with cPWV, could be an independent predictor of several risk factors for cardiometabolic diseases in a very large cohort of adolescents [20–22]. Extensive details of arterial stiffness assessments, haemodynamics, physics and mechanobiology have been published earlier [5,6,9,23]. This review summarizes recent epidemiological evidence on arterial stiffness usefulness in young population [20–22,24] and proposes future directions.

### A BRIEF SYNOPSIS OF ARTERIAL STIFFNESS HAEMODYNAMICS

During cardiac contraction, pressure waves travel along the arterial tree and the speed is measured as pulse wave velocity (PWV). An earlier return of the reflected pulse wave to the proximal aorta increases cardiac afterload. Stiffening increases the power associated with a given flow, which may damage the microcirculation, such as small arteries and arterioles. This damage seems to be more prominent in high-flow organs [1,4,6]. The forward traveling pressure and flow waves are initiated by cardiac contractions, and partial wave reflection occurs when a forward wave encounters regions of impedance mismatch leading to the returned or backward wave. Arterial characteristic impedance is the proportion of a forward traveling pressure wave to the returned or backward wave. Arterial characteristic impedance is the proportion of a forward traveling pressure wave speed in early systole, that is the change in pressure for a given change in flow, prior to the return of prominent wave reflections. In young healthy adults, low
impedance ensures that nominal ventricular ejection produces a low amplitude forward travelling pressure wave moving down the aorta at a relatively low PWV. However, as arteries stiffen with age, impedance and forward travelling pressure increase leading to higher PWV [4,6,7,25].

**ARTERIAL STIFFNESS WITH THE RISK OF ELEVATED BLOOD PRESSURE AND HYPERTENSION**

The prevalence of age-adjusted elevated blood pressure and hypertension in 1522 U.S. adolescents aged 13–17 years accessed between 2007 and 2010 was 9.5 and 4.6%, respectively [26]. The male to female ratio for diagnosed arterial hypertension in the U.S. adolescent cohort was 3:1 [26]. Moreover, the prevalence of elevated systolic blood pressure and hypertension among 3862 British adolescents aged 17.7 years accessed between 2008 and 2010 is 21.3 and 6.3%, respectively [20]. The male to female ratio for elevated SBP in the British cohort at age 17.7 and 24.5 years was 5:1 and 3:1, respectively [20]. The disparity in the prevalence of elevated blood pressure between the U.S. and British studies is due to the mean ages of study participants, that is 13–17 versus 17.7–24.5 years [20,26]. A recent review reported that the prevalence of primary hypertension among 18-year-old adolescents was 10–11%, but among male adolescents, the prevalence is 16–21% [27]. This increasing prevalence of hypertension in late adolescence and young adulthood and its sequelae, especially among male adolescents, warrants further study [16,27,28].

A systematic review and meta-analysis of prospective studies reported that elevated blood pressure in the young was associated with an intermediate marker of cardiovascular disease, high PWV, in adulthood [odds ratio (OR) 1.83; 95% confidence interval (CI), 1.39–2.40] [28]. However, none of the included longitudinal studies in the meta-analysis had baseline measures of PWV and thus could not examine plausible causal inference (i.e., the direction of the association) [28]. The authors suggested that early life arterial thickening and stiffening may cause elevated blood pressure (reverse causation), but the sequence of events may be less likely at young versus older ages [28]. A cross-sectional evidence from the ENIGMA study conducted in 2005 among 1028 healthy university students in Cambridge and Wales, aged 17–27 years, suggests that arterial stiffness may be an underlying major haemodynamic abnormality for essential hypertension [29].

Recently, longitudinal evidence from repeated measures of cfPWV in 3862 apparently healthy adolescents revealed that adolescent arterial stiffness may causally precede elevated blood pressure and hypertension in young adulthood [20] contrary to the systematic review and meta-analysis report [28]. The mean (SD) cfPWV for boys at 17.7 and 24.5 years was 6.03 (0.70) and 6.71 (1.19) m/s, respectively, whilst that of girls was 5.54 (0.62) m/s at 17.7 years and 6.09 (1.01) m/s at 24.5 years (Fig. 1) [20]. The authors found that among boys, a higher cfPWV at 17.7 years predicted elevated SBP and/or hypertension [OR 1.31 (CI 1.02–1.70)] and elevated DBP and/or hypertension [OR 2.18 (CI 1.49–3.19)] at 24.5 years but not among girls [OR 1.09 (CI 0.83–1.42)] and [OR 1.40 (CI 0.91–2.16)], respectively [20]. Adolescents in the highest quartile of cfPWV at 17.7 and 24.5 years had a two-fold increase in SBP and DBP during the 7-year observation period when compared with those at the lower second quartile of cfPWV (Fig. 2) [20]. It is expected that a true risk factor is implicated in the causal path of a disease process. On the contrary, a risk marker is associated with the disease process without being in the causal pathway [30]. Temporal relationship is a critical initial step in establishing causation but not necessarily sufficient; therefore, strong evidence for causal inference must additionally test the strength of association, consistency, presence of a dose-response relationship and a plausible pathogenic pathway between the cause and effect [30]. Using several advanced statistical models, such as the mixed-effect hierarchical model and cross-lagged autoregressive structural equation models, the ALSPAC study among adolescents reported a plausible temporal causal relationship between arterial stiffness and elevated blood pressure/hypertension, tested the strength of associations, consistency and dose-response relationships (Figs. 1 and 2) [20]. All analyses were controlled for risk factors measured both at baseline and follow-up such as age, sex, low-density lipoprotein cholesterol, insulin, triglyceride, high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, heart rate, glucose, fat mass, lean mass, smoking status, family history of hypertension/diabetes/high cholesterol/vascular disease and moderate to vigorous physical activity.

Arterial stiffness increases with age across the life course, excessive stiffening could lead to early organ dysfunction and damage [4,6,7,9,31,32]. The origin of arterial stiffness in early life remains a huge debate, whether it is vascular structure driven or a consequence of prenatal disorders in either vascular smooth muscle tone or volume expansion.
The genetic contribution to arterial stiffening is moderate with an estimated 40% heritability of high cfPWV [35]. Perinatal sclerotic lesions in foetal arteries have been observed in babies of mothers who are smokers just as telomere length has been suggested to influence intrauterine programming of arterial dysfunction in postnatal life [36,37]. About three decades ago, passive smoking was associated with early arterial damage assessed as dose-related impairment of endothelium-dependent dilatation in healthy young adults [38]. Recently, it was observed in the ALSPAC cohort that smoking exposure from ages 13 through 17 years, even at low levels of less than 20 cigarettes in a lifetime, was associated with higher cfPWV at 17 years of age [39]. Existing background metabolic diseases have been associated with higher arterial stiffness in youths [24,40]. Longitudinal studies among adults have shown that arterial stiffening may also be caused by the combined effect of elevated heart rate and blood pressure due to increased mechanical stress fatigue in the arterial wall [32,41–45]. A high sodium intake has been associated with arterial stiffness, development of extracellular matrix and alteration in secretory properties of vascular smooth muscle cells independent of blood pressure [44]. It was suggested that endothelial cells lining the artery lumen may serve as sensors of modified dietary salt intake for generating signal-transduction events that lead to growth factor production, shear stress modification and potentially arterial stiffness [44]. Safar et al. [44] comprehensively reviewed the plausible causal role of dietary salt intake on arterial stiffness. Over a decade ago, Fernhall et al. [34], in a review, discussed the origin of arterial function in youth, which might be a window into cardiovascular risk. The present review summarises current evidence, which answers some of Fernhall et al. [34] proposed future research questions among youths.

Elastic artery stiffening results in rapid backflow of blood to the heart, early return of wave reflections, increased pulsatile load and cardiac output. This increased pulsatile power results in hyper-perfusion of high-flow organs causing microvascular damage. Arterial stiffening increases forward pressure waveform and pulse pressure resulting in elevated systolic pressure and subsequent diastolic dysfunction via concentric left ventricular remodeling and hypertrophy [4,6,7,9,31,32]. In a healthy adolescent and young adult, the highly elastic aorta stores energy during systole, which is released during elastic recoil in diastole. There is a dampening of this elastic recoil when arteries stiffen due to reduced atrioventricular plane displacement [4,6,31]. This may be evident in the recent study wherein participants who were consistently in the highest quartile of cfPWV from adolescence through young adulthood had a two-fold higher SBP and DBP increase over the 7 years when compared with those who had optimal cfPWV [20]. It is thus necessary that future studies investigate whether adolescent arterial stiffness temporally precedes ventricular hypertrophy, and cardiac diastolic and systolic dysfunction in young adulthood, independent of blood pressure and heart rate. Evidence from mouse studies indicates that impairment of elastin expression leads to arterial stiffening and constriction, prior to the increase in blood pressure and that the increase in blood pressure is inversely associated with arterial elastin content [32,45].
Moreover, young participants diagnosed with elastin haploinsufficiency syndrome have been observed to have elevated arterial stiffness before developing hypertension [46]. Consistent with the foregoing, adolescent arterial stiffness may be the ‘egg or cause’ and young adulthood elevated blood pressure/hypertension the ‘chicken or effect’ [20, 29, 32]. Existing vicious cycle between arterial stiffness and high blood pressure suggests a blood pressure-dependent arterial stiffness. Arterial stiffness in adolescence and young adulthood may also be a consequence of higher blood pressure in childhood [47–49]. However, careful and accurate assessment is warranted to investigate the temporal relationships between arterial stiffness and elevated blood pressure from infancy through young adulthood.

**ARTERIAL STIFFNESS WITH THE RISK OF OVERWEIGHT AND OBESITY**

The prevalence of adolescent obesity is on the rise [50], and several efforts targeted at decreasing this trend in the long term have yielded limited success [51]. Among 3862 adolescents from the ALSPAC study, it was reported that boys had a significant increase in overweight and obesity compared with girls during the 7-year observation period [20]. Several studies have reported the inconsistent effects of overweight and obesity on arterial stiffness during adolescence and young adulthood [10, 18, 52–55]. Although the mechanism through which obesity influences arterial stiffening in early life remains incompletely elucidated, it was postulated that autonomic and metabolic dysfunction may alter sympathovagal balance via effects on arterial smooth muscle [52]. Moreover, vascular adipose and immune cell dysfunction have been associated with obesity-induced arterial stiffness [56]. Studies in animal models have shown that increased obesity in mice fed with a high-fat and high-sucrose diet was associated with stiffer arteries within a month and that arterial stiffening occurred due to activation of inflammatory markers, oxidative stress and reduced bioavailability of nitric oxide [57]. This evidence suggests that obesity may temporally precede arterial stiffness.

However, most human studies that have related measures of obesity with arterial stiffness have used BMI, BMI-Z-scores and percentiles as measures of body composition [10, 18]. These measures of body composition do not clearly distinguish the role of fat mass from muscle mass in their relationships with arterial stiffness. Recently, it was reported that cumulative fat mass from age 9 through 17 years directly measured using dual-energy X-ray absorptiometry was associated with higher arterial stiffness at 17 years of age [53]. Similarly, another study in the same population showed that cumulative fat mass from ages 9 through 24 years was associated with higher arterial stiffness at 24 years of age [54]. However, the cumulative fat mass measured from ages 9 through 24 years was not associated with the 7-year increase or progression in arterial stiffness from ages 17 through 24 years [47]. Nonetheless, overweight/obese girls had statistically significantly higher cfPWV at 17 and 24 years in contrast to normal-weight girls [20]. On the contrary, overweight/obese boys had lower cfPWV at age 24 years in comparison with normal-weight males, although not statistically significant [20]. The disparities in the prospective studies [18, 47, 53, 54] suggest that the dynamic changes in fat mass from childhood through young adulthood may not be directly associated with arterial stiffness progression, especially in a healthy young population. There were significant differences in cfPWV values classified based on weight categories across different longitudinal cohorts, that is ALSPAC and Cincinnati Cohort [20, 24] (Table 1). These differences may be due to weight classification, that is BMI percentiles versus BMI cut-points, the combination of overweight and obese categories in the ALSPAC cohort in relation to the normal weight and the combination of normal and overweight in the Cincinnati cohort versus obese categories [20, 24]. Another important difference between the two studies is that the Cincinnati cohort used the robust measurement of aortic PWV by arterial tonometry (SphygmoCor), while the ALSPAC cohort used the oscillometric cuff derived PWV (Vicorder) [20, 24]. In youth, Vicorder aortic PWV values were similar to those obtained by SphygmoCor applanation tonometry with the best agreement between devices obtained in the aortic tree path length [58]. An excellent intra and interobserver repeatability and measurements ease make Vicorder appropriate for large young population studies [58]. Nonetheless, clinical outcome studies that utilized oscillometric aortic PWV measures are limited [9].

The ALSPAC cohort had a longer follow-up period of 7 years in contrast to 5 years in the Cincinnati cohort, although the baseline ages were similar [20, 24]. Also, in both longitudinal cohorts, cfPWV was elevated in the overweight and/or obese categories [20, 24] (Table 1).

Understanding the complex and possibly vascular adaptive relationships between obesity and arterial stiffness warrants temporal longitudinal studies [20]. The first-ever temporal longitudinal report revealed that higher cfPWV in adolescence independently predicted a nearly 20% increased risk of either total or trunk fat mass overweight/obesity in young adulthood [20]. Moreover, the cross-lagged temporal

**TABLE 1. Comparison of carotid-femoral pulse wave velocity values according to weight categories across longitudinal cohorts**

| Timeline     | Weight Category | Age in years | Sample size | cfPWV (m/s) Mean (SD) | Age in years | Sample size | cfPWV (m/s) Mean (SD) |
|--------------|-----------------|--------------|-------------|-----------------------|--------------|-------------|-----------------------|
| Baseline     | Normal weight   | 17.7         | 3038        | 5.76 (0.71)           | 17.2         | 141         | 5.3 (0.66)           |
|              | Overweight/Obese| 17.7         | 767         | 5.77 (0.66)           | 17.6         | 156         | 6.2 (1.1)            |
| Follow-up    | Normal weight   | 24.5         | 1022        | 6.29 (1.09)           | 22.5         | 141         | 5.5 (0.81)           |
|              | Overweight/Obese| 24.6         | 618         | 6.39 (1.17)           | 23.1         | 156         | 6.4 (1.2)            |

cfPWV, carotid-femoral pulse wave velocity.
findings showed that bidirectional relationships exist between arterial stiffness and total or trunk fat mass (Fig. 3), although the relationship was two-fold stronger when total or trunk fat mass predicted higher cfPWV [20]. Obesity is a high-flow condition that promotes arterial remodelling via a decrease in elastic fibre thickness with a resultant elevation in stress and strain [6]. The increased strain leads to higher collagen deposit, higher wall stiffness and raised cfPWV [6]. It was also reported that the 7-year increase in cfPWV was paradoxically associated with the 7-year decrease in total or trunk fat mass [20]. This finding suggests that arterial stiffness may play a role in fat metabolism and deposit since increased arterial stiffness leads to high-flow low-resistance microvascular organ damage in the liver and pancreas, but further longitudinal, pathological and mechanistic studies are needed.

ARTERIAL STIFFNESS WITH THE RISK OF HYPERGLYCAEMIA AND INSULIN RESISTANCE

The precursors of young-onset type 2 diabetes, that is type 2 diabetes diagnosed before the age of 40 years, are elevated insulin resistance, hyperglycaemia and altered metabolic milieu [59–61]. The global prevalence of young-onset type 2 diabetes is rising, and recent evidence among adolescents diagnosed with the disease reported several early organ damages within a mean time of $13.3 \pm 1.8$ years [61,62]. In addition, recent randomized controlled trials, metformin monotherapy and/or lifestyle modification have been unsuccessful in treating young-onset type 2 diabetes, warranting further research on ways to reduce the risk in early life [63,64]. Established precursors and consequences of young-onset type 2 diabetes are high blood pressure, dyslipidaemia and family history of diabetes [61–64]. Longitudinal studies have reported higher cfPWV in adolescents with type 1 and 2 diabetes [24,65,66]. Therefore, identifying other preventable risk factors of young-onset type 2 diabetes may help ameliorate the incidence of the disease, particularly among adolescents and young adults [61,62].

About a year and a half ago, it was reported among 14 159 healthy Chinese adults aged $48.3 \pm 12.0$ years, followed up for 3.72 years, that higher arterial stiffness may temporal precede higher fasting blood glucose and could be causally associated with incident type 2 diabetes [67]. In the same Chinese cohort, among 11 156 middle-aged adults, it was recently shown that arterial stiffness had a better predictive ability than hypertension in predicting type 2 diabetes and that the pathological path between arterial stiffness and diabetes may not be modified by the ageing process of inflammation and oxidation [68]. Earlier, in a Swedish elderly cohort of 2450 individuals aged $71.9 \pm 5.6$ years, followed up for $4.43 \pm 1.40$ years, it was
observed that increased cfPWV was associated with increased incidence of diabetes, independent of other risk factors [69]. These adult studies suggest that arterial stiffness may be a novel risk factor for young-onset type 2 diabetes or its precursor among adolescents and young adults is unknown. Emerging evidence among 3862 healthy adolescents from the ALSPAC study suggests that arterial stiffness may predict hyperinsulinemia in young adulthood, after a 7-year follow-up [21]. Further extensive investigation of the same cohort employing advanced statistical models revealed that arterial stiffness may temporally precede insulin resistance and hyperinsulinemia (Fig. 5) [22]. Due to few incidences of young-onset type 2 diabetes in the cohort, the authors could not examine the temporal causal association between arterial stiffness and incident young-onset type 2 diabetes among adolescents [21,22].

In contrast to the Chinese adult study [67], arterial stiffness among adolescents does not appear to precede hyperglycaemia in the causal path [22], probably because the adult study employed an assessment of arterial stiffness (brachial-ankle PWV) that includes a considerable muscular component, which may limit the specificity of the measurement. Moreover, the adult study analyses did not account for participants’ insulin levels despite evidence that insulin at physiologic concentrations acutely diminishes arterial stiffness greater than those controlling peripheral vascular resistance [67,70]. The study that purportedly demonstrated that insulin decreases large artery stiffness used augmentation index as a measure of aortic stiffness [70]. Augmentation index is related to the propagation of the reflected waves and is not an accurate index of arterial stiffness, depending mainly on heart rate and peripheral resistance, and slightly on arterial stiffness [6,9]. As central arterial stiffness predicts hard cardiovascular events, it may be clinically useful in additionally predicting early risk of young-onset type 2 diabetes (hyperinsulinemia and insulin resistance) [2–4,21,22]. Considering that previous randomized controlled trials on the treatment of young-onset type 2 diabetes have been unsuccessful [63,64], these emerging longitudinal evidence among adolescents [21,22] and adults [67] suggest that future intervention aimed at treating young-onset type 2 diabetes may consider a concurrent reduction of arterial stiffness in addition to diabetes therapy [22]. Evidence from the ALSPAC study revealed that irrespective of sex, cfPWV and fasting insulin levels were significantly higher among overweight/obese and elevated blood pressure/hypertensive youths, both at 17 and 24 years of age [20]. Moreover, arterial stiffness progression (predictor) was close to having a statistically significant association with the 7-year increase in fasting insulin (outcome), among overweight/obese participants who made up one-fifth of the adolescent population [22]. These findings suggest that arterial stiffness, obesity and insulin resistance may be inextricably linked in the development of type 2 diabetes mellitus, with arterial stiffness potentially initiating the disease cascade [6,20,22,67,71,72]. Increased proinflammatory cytokines especially from higher visceral adiposity have been associated with altered insulin metabolic signalling, insulin-mediated nitric oxide production and arterial stiffening [72,73]. Nonetheless, accounting for high-sensitivity C reactive protein, an inflammatory marker, in the analyses did not alter the temporal relationships between arterial stiffness and insulin resistance [20–22]. Of note, the effect of smoking status, physical activity levels, sedentary behaviour, family history of diabetes, dyslipidaemia and cardiovascular diseases on the temporal associations were not significant, probably because most adolescents were apparently healthy [22]. Arterial stiffness preceding hyperinsulinemia and insulin resistance (Fig. 3) implicates insulin response rather than production. Therefore, the known effects of aortic stiffness on microvascular reactivity in the periphery may explain the association of aortic stiffness with subsequent insulin resistance/diabetes [4,22,67]. Nonetheless, the pathological mechanism by which arterial stiffness may independently contribute to metabolic alterations warrants further research.

**ARTERIAL STIFFNESS WITH THE RISK OF DYSLIPIDAEMIA**

Longitudinal studies relating dyslipidaemia with worsening arterial stiffness among youth are few, and the relationships attenuate after controlling for conventional risk factors [6,24,74,75]. It is postulated that subendothelial lipid deposit, increased atheroma deposit and lipid peroxidation are potential pathophysiological mechanisms that support lipid-induced atherosclerosis, which could simultaneously occur with arterial stiffening depending on the arterial site [6,76]. There is no evidence of the longitudinal associations of repeated measures of cfPWV and repeated lipid measures, and whether lipid alteration temporally precedes arterial stiffness was largely unknown. Again, the ALSPAC study involving 3862 adolescents followed up for 7 years bridged the gap in knowledge by reporting that temporal or bidirectional associations of either low-density lipoprotein cholesterol and triglyceride with arterial stiffness may not exist, particularly among apparently healthy youths [22]. These temporal causal findings may explain why clinical trials aimed at reducing arterial stiffness from lipid-lowering drugs have been mildly effective, nearly 6.8% reduction [67,77,78]. Nonetheless, it seems likely that adolescent arterial stiffness may temporally precede decreased high-density lipoprotein cholesterol in young adulthood in the causal path [22]. It was reported that a 1 m/s rise in cfPWV during adolescence was independently associated with a −0.3 mmol decrease in high-density lipoprotein cholesterol (P = 0.051) in young adulthood after accounting for cardiometabolic and lifestyle factors [22]. Further longitudinal analysis revealed that the 7-year increase in arterial stiffness was directly associated with a 7-year increase in triglyceride, although not in the causal path. Taken together, it appears that arterial stiffness progression may be associated with reduced high-density lipoprotein cholesterol and elevated triglyceride, but the mechanism by which arterial stiffness alters lipid metabolism remains uncertain.

**ARTERIAL STIFFNESS, OBESITY, HYPERTENSION AND INSULIN RESISTANCE**

Higher arterial stiffness has been reported among youths with obesity, hypertension, insulin resistance and diabetes
Arterial stiffness precedes hypertension and metabolic risks in youth

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Guidelines did not recommend the routine assessment of cFPWV in youth with suspected hypertension [19]. The recent availability of normative longitudinal data on cFPWV based on age, sex, body size and hypertensive state among 3862 adolescents and young adults [20,22] from the ALSPAC study and 448 adolescents and young Cincinnati cohort [24] (Table 1 and Figs. 1 and 2) could be useful in updating existing reference values for cFPWV in healthy adolescents and clinical guidelines, such as the European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension and the American Academy of Pediatrics Clinical Practice Guidelines [9,12,15–17,19,83–87]. However, normative cFPWV data among adolescents from diverse ethnic or racial backgrounds are still limited [20,24,88].

Studies examining arterial stiffness temporal progression with early organ damage such as the brain, heart, liver, pancreas and kidney are warranted among adolescents and young adults, as temporal associations have been demonstrated in adult studies [4,6,7,9,16,89]. It is also pertinent to determine the primary risk factor for worsening arterial stiffness in an apparently healthy adolescents, apart from age and sex. Temporal longitudinal studies of arterial stiffness progression in relation to cardiometabolic alterations are needed in a multiethnic adolescent population because arterial stiffness has been strongly associated with ethnicity [88]. Future basic and clinical studies are required to examine how secreted metabolites released by adipose tissues among normal-weight and obese individuals explain the contribution of excess adiposity to insulin resistance and pathogenesis of hypertension and arterial stiffening in the young population [6,51,71,72]. Several dietary and exercise clinical trials have failed to lower arterial stiffness in the young population [90–92]. A recent meta-analysis on the acute effect of exercise on arterial stiffness in healthy participants also reported a null exercise effect on cFPWV after 24 h [93]. Recently, a randomized, placebo-controlled, double-blind clinical trial that examined the effect of angiotensin-converting enzyme inhibitors and/or statins on vascular phenotypes among adolescents with type 1 diabetes reported no effect on cFPWV [94]. Nonetheless, arterial stiffness has emerged as a major novel risk factor for the development of hypertension, total and truncal obesity, hyperinsulinemia, insulin resistance, type 2 diabetes, and possibly dyslipidaemia among apparently healthy adolescents, young adults [6,20,22,29,89], (Fig. 3) and middle-aged adults [67,68]; therefore, new strategies [51] and interventional trials to mitigate arterial stiffness in youth are urgently needed [95–98]. Assessment of arterial stiffening can be conducted across the paediatric insulin resistance and relative case compared with an electrocardiogram [7,9,17,82,83], and these observational studies [20–22,29] provide arterial stiffness normative data that could be utilized in patient management [89]. There is now a strong theoretical argument to include arterial stiffness as a trigger to initiate antihypertensive therapy in paediatric and young adult populations [19,89]. Lastly, arterial stiffness may not be considered only as hypertension-induced target organ damage, or signs of early vascular ageing [9,16,17,19,83,89] but may be clinically defined and treated as a potential cause of elevated blood pressure/
hypertension and altered cardiometabolic functions in youths having no prior disease risks.

CONCLUSION

Higher arterial stiffness in adolescence may potentially be a novel risk factor for young adulthood hypertensive and metabolic disease, which is now being established among adults [6,22,67—69]. Higher arterial stiffness in early life may result from maternal smoking habits, early life smoking patterns, high salt intake, genetic programming, obesity, elevated blood pressure and other poor cardiometabolic and lifestyle factors [4,6,54,56,71,72]. This review summarizes recent advances in the study of arterial stiffness in young [14,20,22,24,34,40] and proposes future directions. It must be noted that high-calorie intake and physical inactivity remain the primary cause of metabolic disorders in our current society [10,51,56,71,72]. The observation that arterial stiffening precedes metabolic alteration or cholesterol metabolism [20,22] could indicate arterial stiffening as an early marker of a series of biological alterations finally leading to disease formation such as type 2 diabetes mellitus [4,67,68]. Thus, the underlying mechanisms for which arterial stiffness contributes to metabolic disorder in youth require urgent clinical studies and basic research.

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Conflicts of interest

There are no conflicts of interest.

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