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EDUCATIONAL REVIEW

Racial differences of early vascular aging in children and adolescents

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Abstract

The prevalence of non-communicable disease (NCDs) is rising globally, with a large burden recorded in sub-Saharan countries and populations of black race/ethnicity. Accelerated vascular deterioration, otherwise known as early vascular aging (EVA), is the underlying factor for highly prevalent NCDs such as hypertension. The etiology of EVA is multifactorial with a central component being arterial stiffness with subsequent development of hypertension and cardiovascular complications. Although arterial stiffness develops with increasing age, many children and adolescents are subjected to the premature development of arterial stiffness, due to genetic or epigenetic predispositions, lifestyle and behavioral risk factors, and early life programming. Race/ethnic differences in pediatric populations have also been reported with higher aortic stiffness in black (African American) compared with age-matched white (European American) counterparts independent of blood pressure, body mass index, or socioeconomic status. With known evidence of race/ethnic differences in EVA, the pathophysiological mechanisms underlying graded differences in the programming of EVA are still sparse and rarely explored. This educational review aims to address the early life determinants of EVA in children and adolescents with a particular focus on racial or ethnic differences.

Keywords Race · Ethnicity · Early vascular aging · Children · Adolescents · Arterial stiffness · Blood pressure · Endothelial dysfunction · Left ventricular hypertrophy · Cardiovascular disease

Introduction

Cardiovascular disease (CVD) is not only prevalent in adults and the elderly. Recent evidence highlighted the increasing trends of childhood and adolescent hypertension as well as related CVDs as future health challenges on a global scale with major economic implications [1–3]. Global evidence indicates that adult non-communicable diseases (NCDs), including CVD and type 2 diabetes, originate from early life or biological programming due to the interactions of environmental and genetic factors during a critical period of development, namely the first thousand days of life [4–6]. More importantly, even earlier changes in the biomechanical makeup of blood vessels may be compromised during fetal (intrauterine) development due to maternal nutrition [7], maternal smoking [8], maternal health (i.e., eclampsia, gestational diabetes) [9], access to health care (low socioeconomic status, lack of medical insurance) [10], and prematurity/low birthweight [11]. These early life determinants of CVD may predispose children and adolescents to accelerated biological aging, termed *early vascular aging* (EVA).

Aside from predispositions to genetic and environmental risk factors of certain phenotypes, there are also socioeconomic, sociocultural, and metabolic determinants to define an individual's health status. Alongside these determining risk factors for NCDs and especially CVD is the complexity of ethnic or racial differences that are regularly reported in CVD morbidity and mortality, with an increased burden among especially black (African and African-American) and Hispanic populations [12, 13] compared with white or Asian populations. Until now, genetics studies have not succeeded in explaining genetic predispositions to CVD among various racial or ethnic groups [14, 15]. In addition, clear biological definitions of ethnicity and race are still lacking. In an analysis from the 1998 South Africa Demographic Health Survey, authors highlighted unambiguous racial and income disparities among black African and white (European descent) South

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Africans. Black South Africans had less access to healthcare services and mostly fell in the lower socioeconomic classes compared with white South Africans [16]. Yet, 20 years later, this disproportion is still markedly unchanged in especially the sub-Saharan Africa context. Racial inequalities should remain a global social concern, since marked differences among race groups have been reported in health-related studies with no clear pathophysiological explanations. Evidence in this regard is lacking even more in pediatric and adolescent populations.

This review will focus on the evidence of EVA in children and adolescents, its characteristics, and multifactorial determinants with specific reference to race.

Definition and diagnosis of early vascular aging

The concept of premature vascular aging was described by Nilsson (1996) as the result of adverse psychosocial and environmental factors hindering the health-preserving mechanisms of human physiology [17]. Since then, the concept of EVA has been well demonstrated, but with limited focus in children, adolescents and young adults.

Definitions

With "normal" or *chronological* aging, biological changes manifest and may develop to disease states when an individual reaches the end stages of life. Chronological age is the number of years, months, or days lived since the day of birth and an obvious risk factor for CVD morbidity and mortality in the presence of established risk factors [18]. *Biological* aging is different from chronological aging as it reflects a number of factors contributing to a gradual decline in physiological and biochemical functionality of individuals across the lifespan. Some of these factors include genetics, lifestyle behaviors, and disease states such as hypertension, atherosclerosis, and diabetes mellitus. However, the aging process can be accelerated at a biological level, rendering a mismatch between the chronological and biological age. This dissociation between chronologic and biologic aging is termed EVA. EVA is therefore a state of accelerated adverse changes in the biochemical and cellular components of the vascular tree contributing to augmented forward pulse wave reflections at younger ages [19]. These early changes have particular detrimental effects on target organs such as the heart, brain, and kidneys.

Diagnosis

EVA can be diagnosed by the presence of abnormally high arterial stiffness (arteriosclerosis) for a specific age and sex [20]. Arterial stiffness is central to the development of EVA, whereby individuals with reduced arterial elasticity can be identified by non-invasive measurement of pulse wave velocity (PWV) [21]. Carotid-femoral PWV or aortic PWV is perhaps the most commonly used measure of arterial stiffness and is defined as the velocity of the arterial pulse wave travelling between two sites (distance × 0.8) along the arterial wall (transit time) [22]. In general, mostly in adult populations, higher (> 10 m/s) PWV indicates arterial stiffness and an increased risk for future cardiovascular events [23].

Clinical importance of early vascular aging

With increasing age, pulse pressure widens and systolic hypertension develops as long-term manifestations of arterial stiffening [24]. PWV is a sensitive technique to measure arterial stiffness and can detect early adverse changes in pulse wave reflections. By measuring PWV, EVA can be assessed to identify individuals (at younger ages) with accelerated aging or adverse medial layer morphological changes due to inherent features as well as interactions with environmental exposures [25]. The impact of these vascular changes and subsequent increased arterial (aortic) stiffness on cardiac remodeling is inevitable. Aortic stiffening increases left ventricular load as well as myocardial perfusion pressure, but limits the delivery of blood to the capillary beds during diastole. Evidently, increased arterial stiffness may contribute to myocardial ischemia [26] and cardiac failure [27]. Aside from the direct relationship between aortic stiffness and cardiac dysfunction and hypertrophy is also the downstream effects of arterial stiffening on the microvasculature within vital organs including the brain [28, 29] and kidneys [30, 31]. Therefore, the non-invasive measurement of PWV in a clinical setting may assist in the risk stratification of individuals (even in young asymptomatic individuals) and the possibility for primordial prevention. Carotid-femoral PWV by applanation tonometry has been established as a highly sensitive biomarker in identifying individuals with various phenotypes and can aid in therapeutic guidance [32, 33].

Not only does PWV assess arterial stiffness, but it also provides valuable predictive information for cardiovascular outcomes as an intermediate end-point and an independent predictor of cardiovascular events and all-cause mortality [34, 35]. The predictive power of PWV for CVD was first described in high-risk groups with chronic kidney disease (CKD), hypertension, or diabetes [36–38]. Later, in the general population [39], one standard deviation increase of PWV predicted a 30% increased risk for future cardiovascular events [34]. However, standardization of PWV measurements with various devices and across different populations still requires attention.

Etiology and prevalence of early vascular aging over the life course

In recent consortia and research, evidence led to the appreciation of the way in which early life (including pre-conception and intrauterine development) exposures to risk factors determine the origin and trajectories of disease across the life course [16]. The *life course* in this context refers to the reciprocal influences of especially environmental exposures on the biological determinants of health during the different stages of life including pre-pregnancy, gestation, infancy, adolescence, and adulthood [40].

In a statement by the Lancet Commission on hypertension, the concept of EVA was used to develop a life course strategy of CVD prevention and treatment, aiming to reduce cardiovascular risk factors, target organ damage and cardiovascular events throughout the different stages of life including childhood [6]. The authors highlighted that genetic susceptibility and epigenetic imprinting during fetal life can alter the life course trajectories and underlined the importance thereof in the management of raised blood pressure (BP) [6]. In an effort to further elucidate this concept, we adapted the life course trajectory approach (Fig. 1) to indicate that the presence of intrauterine risk factors (early life programming) already predisposes the fetus to increased future cardiovascular risk and the early onset of cardiovascular abnormalities in early childhood.

In Fig. 1, points A, B, and C indicate the relative risk of an individual on the health disease continuum based on the determinants and phenotype of fetal programming. The ideal life course is illustrated with a green line, and at point A, the risk of accelerated biological aging or EVA is much lower compared with an individual at points B and C. Such individuals (at point A) are theoretically defined as healthy or undergo supernormal vascular aging [20], with the least adverse cardiovascular disease manifestations throughout the life course. The majority of individuals intercepts the health disease continuum at point B, following an average life course in which hypertension and arterial stiffness manifests in late adulthood and middle age, with subsequent cardiovascular morbidity and mortality in advanced age. However, some individuals intercept the health-disease continuum at point C with accelerated biological aging and vascular compromise at very young ages, even in infancy, childhood, and adolescence. These individuals are believed to be subjected to maternal risk factors involved in the early life programming mismatch contributing to the increased relative risk of EVA, as discussed below.

Etiology

Evidence from BP tracking studies suggests that the development of blood vessel structure and function could be influenced by early somatic growth [41–44]. This may be the reason increased arterial wall stiffness (arteriosclerosis) and thickness (atherosclerosis) of large arteries are proposed to be present in children and adolescents in the early phases of elevated BP [45]. As with atherosclerosis, arterial stiffness is believed to start in early life on the basis of fetal programming of the medial elastin content of the arteries, as well as of other

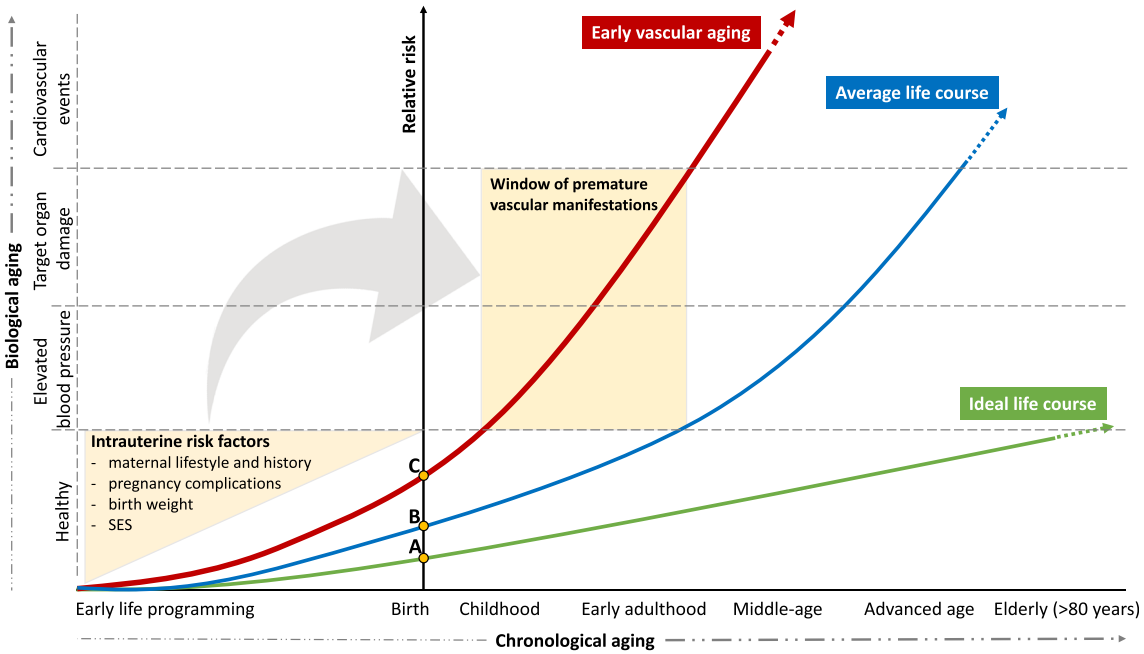

Fig. 1 An adapted life course model in the setting of early vascular aging and the consequences of early-life programming prior to birth. SES socioeconomic status, *Amended from Olsen et al., with permission from The Lancet [6]. Copyright ©2016, Elsevier

vasculature and capillaries [46, 47]. Therefore, EVA may start in utero as a result of adverse intrauterine environmental exposures for survival, which may contribute to an increased risk of vascular deterioration in early postnatal life [19].

Genetic-environmental interactions and ethnocultural influences may increase individual susceptibility to early-life programming of the vasculature [48–51]. For instance, fetal undernutrition is accompanied by suboptimal vascular growth and development with reduced elasticity, arterial compliance, and overall high peripheral resistance in the offspring [52]. Maternal nutrition and/or underlying disease states such as obesity and gestational diabetes can affect fetal nutrition and contribute to potential genetic changes during fetal development [53]. A population-based analysis indicated a 29% increased overall rate of early onset of CVD in offspring, if the mothers had diabetes during pregnancy [9]. In addition, reports have indicated higher risk of gestational diabetes among women from race groups other that non-Hispanic white race [54, 55].

Although the etiology of racial differences in early life programming is scant and perhaps only studied as biological fragments to understand the complexity of early life exposures on cardiovascular health and its future implications, evidence suggest that black children with lower birth weight compared with their white counterparts are at higher risk of having impaired vascular structure and function [56]. However, this may also be true for other race groups, as studies indicated that not only African-American babies (born at term) but also Indian, Pakistani, Bangladeshi, and black Caribbean offspring have lower birth weights than those from European ancestry [57, 58]. A study on prematurity also indicated that children born extremely preterm (compared with controls) have an increased future cardiovascular risk due to altered arterial hemodynamics of especially the smaller resistance blood vessels [59]. Systolic hypertension, elevated glucose levels, and hypercholesterolemia were also more prominent (compared with controls) as measured almost 6 years later in a group of preterm infants [60]. It appears that altered maternal lipid metabolism (higher triglycerides and total cholesterol) contributes to adverse prenatal programming of the hypothalamic-pituitary-adrenal axis by increasing a child's stress response as evidenced by greater cortisol reactivity [61]. This could be in part the mechanism to explain the link between the early life origin of CVD and the emotional functioning or psychological stress of a child [62]. In addition, researches have shown a clear association between multiple adverse childhood experiences and increased arterial stiffness as measured by PWV [63].

Prevalence of early vascular aging

The prevalence of arterial stiffness or rather EVA remains to be clearly defined, since evidence regarding the prevalence of EVA is limited in both adult and pediatric populations. Studies have indicated higher PWV values in low cardiovascular risk populations (under 30 years of age) and estimated the prevalence of EVA at 12.5% in Portugal ($n = 2542$; age 18–96 years) [64] and 37.3% in Austria ($n = 10\,973$; age 20–94 years) [65]. It is also believed that the prevalence of EVA is proportional to the prevalence of hypertension and related comorbidities such as obesity and type 2 diabetes mellitus, due to the latter being late manifestations of increased arterial stiffness [24]. From the USA, approximately 11% of children and adolescents have high BP [1], whereas in South Africa, the prevalence of childhood hypertension ranges between 7.5% and 22.3%, dependent on location, region, and culture [2]. Whether the prevalence of EVA relates to the prevalence of hypertension remains to be determined.

Although cardiovascular morbidity and mortality are traditionally attributed to numerous modifiable risk factors including unhealthy dietary and sedentary behaviors, low physical activity, psychosocial stress, hypertension, tobacco use, abnormal lipids, glucose intolerance, and obesity [66], there are other adverse risk factors often overlooked. Among these are low socioeconomic class, psychosocial stress, infectious diseases, lack of healthcare, and poor lifestyle choices as observed in low to middle-income countries have cumulative harmful effects on cardiovascular health, especially in populations with an exceptional proportion of ethnic and/or race variation [67, 68].

Race or ethnic differences in early vascular aging among children and adolescents

The etiology of racial differences in EVA is complex, but there is an appreciation of biological and socioeconomic factors that are at least partly involved [69]. Although many determinants of EVA could explain potential racial differences, there is limited evidence to unravel the origin of such differences in the early onset of CVD. In this section, we provide a brief overview of studies comparing components of EVA (BP, PWV, carotid intima media thickness, and left ventricular mass) from studies that included two or more race/ethnic groups in children and/or adolescents.

Analyses from the Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth (SHIP-AHOY) [70] has emphasized the importance of BP measurement in children, along with the most recent sets of guidelines for BP in pediatric populations [71, 72]. Moreover, target organ damage has already been observed in adolescents with BP levels below the current clinical definition for hypertension [73]. Differences in BP based on race/ethnicity are regularly reported in adults, yet limited, evidence of these differences exists in childhood and adolescents. These race/ethnic differences in BP have been described by potential differences in intrauterine growth, based on birth weight, followed by the

effects of early weight gain and growth in body height and current stature [74]. We summarized key studies that reported on BP differences by race (Table 1). The majority of studies comparing BP between different race groups are from the USA. These studies have reported mostly higher BP in black (African-American or African Caribbean) compared with children or adolescents from white or other (Asian, South Asian, Indian, Pakistan, Bangladesh) race groups. Many cross-sectional and longitudinal studies from the USA [56, 74–76, 78, 79, 81, 83, 84] and South Africa [82, 85] showed consistently higher BP (although inconsistent on whether the highest is systolic BP or diastolic BP) in the black compared with white population groups. The majority of these studies only compared BP without correcting for age, adiposity, stature, or other important confounders. In addition, a study from England [86] included large numbers of black, white, Asian, and other race groups and reported that black (African-Caribbean) children had similar mean systolic BP to white Europeans, but higher mean diastolic BP after correcting for age and sex. The same study also indicated that mean systolic BP tended to be slightly higher among black Caribbean, but lower among black Africans ($p = 0.004$); however, there was no heterogeneity for diastolic BP. Longitudinal studies mostly provide descriptive comparisons of the baseline BP profiles, and although these studies reported similar trends of higher BP in especially black children and adolescents, there are also inconsistencies. A multicenter study [77] performed an adjusted comparison between the black and white children that were born preterm and reported no race/ethnic differences, but after adjusting for neighborhood socioeconomic status, racial differences emerged over time. Similarly, studies from the USA [84, 87] and another from Brazil [88] indicated no differences in BP between black and white/non-black children and adolescents.

In a recent brief review, it became clear that studies investigating racial differences of arterial stiffness were mostly from the USA and some from Brazil and South Africa [89]. These studies reported that PWV was highest in especially black (African American, Brazilian, and South African) compared with the white groups. However, many of these studies were (i) inconsistent in reporting adjusted means of PWV, (ii) were mostly of cross-sectional design, or (iii) some studies only included one racial group. Additionally (Table 2), we provide an overview of comparative studies that measured PWV in children from different race/ethnicity.

Since there are no universal cutoffs for PWV in children and adolescents, comparative studies have proven useful in determining racial/ethnic differences in arterial stiffness and potentially EVA. Socioeconomic and psychosocial factors are becoming essential contributors to consider when investigating early manifestations of adverse vascular alterations in black populations. In a longitudinal study [87], Thurston et al. investigated association between race and socioeconomic (SES) with arterial stiffness in adolescents (age 14–16 years). The study found that PWV was higher in the black (African American) group as compared with the white group. A larger proportion in the black participants were from families with low household income, low levels of parental education, and had lower scores on the neighborhood SES assessment. Lower or medium family income and lower neighborhood SES were positively associated with PWV, even after adjustments for covariates. Despite a small sample size ($n = 107$, divided into black and white groups) (age 9–12 years), Lefferts et al. observed high PWV in black (African American) children as compared with white children after adjustments for covariates including age, sex, BMI, mean arterial pressure, and SES [81]. The study also noted a lower SES in the black children as compared their white counterparts.

Certain disease states may serve as facilitators for accelerated vascular aging in certain race/ethnic groups. In a population (age 11–26 years) with type 1 diabetes, a higher PWV was associated with non-Hispanic white race/ethnicity and higher in type 1 diabetes patients as compared with the controls; however, no comparative data was shown [90]. The regression analyses were adjusted for modifiable and non-modifiable risk factors. Furthermore, black (African American) adolescents with type 2 diabetes presented with a higher PWV compared with whites [91]. In the same study, multiple regression analyses further demonstrated that age, lipids, BP, and duration of diabetes were differently associated with arterial stiffness in individual race/ethnicity groups. A study in Brazil including both black and non-black children and adolescents (age 6–18 years) showed that in puberty and post-pubertal stages, black individuals had higher PWV as compared with the non-black group, even after adjustments for multiple confounders [88]. In black South African boys (age 6–8 years), there was a consistently higher PWV when measured across various segments of the vascular tree (Fig. 2) as compared with the white boys [82].

The contribution of heritability on racial/ethnic differences in arterial stiffness remains questionable. A twin study (age 11.9–30.0) reported that heritability traits did not display any differences between blacks and whites, despite black participants presenting with a higher PWV as compared with their white counterparts [78]. It is therefore clear that exposure to unfavorable environmental factors play a significant role in the prominence of higher PWV in black children and adolescents as compared with their white peers.

Carotid intima media thickness (CIMT), as a surrogate for the detection of atherosclerosis and early development of endothelial dysfunction [92], has also been reported as a determinant of EVA [93]. Only a few studies (mostly cross-sectional) have reported differences in CIMT among children and adolescents of different race/ethnicity (Table 3). The majority among these studies included comparisons between black (American, African,

Table 1 Studies comparing blood pressure in children and adolescents by race

Reference	Age (years)	Race, *N*	Blood pressure (SBP/DBP mmHg)	Type of study	Notes
Collins et al. 2008 [75] USA	12–21	Black 134 White 71	*Black* 112 ± 9/*61 ± 6* White 111 ± 9/59 ± 6	Cross-sectional	• No adjustments • Presented as means and standard deviations
Cruickshank et al. 2005 [74] USA	Baseline 3–4 Follow-up 15–17	Black 89 White 95 Black 89 White 95	Black girls 90.9 (88.4–93.4)/*56.2 (53.9–58.0)* White girls *93.9 (91.8–96.1)*/55.3 (53.5–57.1) *Black boys 93.4 (91.7–95.0)/54 (52.0–56.1)* White boys 92.1 (89.7–94.4)/52.8 (50.5–55.1) *Black girls 109.9 (106.6–113.1)/70.5 (68.4–72.6)* White girls 108.2 (105.6–110.8)/69.9 (67.9–71.9) *Black boys 116.3 (113.1–119.5)/70.6 (68.4–72.8)* White boys 112.9 (110.5–115.3)/68.7 (66.6–70.8)	Longitudinal	• Mean (95% CI) was reported for race differences in BP • Adjusted for current stature (height) and BMI, change in weight 4–17 years
Dekkers et al. 2002 [76] USA	8.2–27.5	Baseline Black 328 White 359	*Black girls 108.2 ± 9.0/59.9 ± 6.6* White girls 105.4 ± 8.8/58.1 ± 6.3 *Black boys 112.3 ± 11.1/59.1 ± 6.4* White boys 108.7 ± 9.0/56.7 ± 5.7	Longitudinal	• Mean and standard deviation were reported • Unadjusted analysis • No alpha level was indicated in descriptive comparisons • Means were reported of individuals with more than 4 out of 10 annual visits
Fuller-Rowell et al. 2017 [77] USA	2–6.5	Black 407 White 264	Black 100.2 ± 10.6/58.8 ± 8.9 White 101.2 ± 11.1/59.0 ± 10.2	Multicenter study	• Mean BP and standard deviation were reported • Longitudinal study of children born preterm • Adjusted for neighborhood SES which accounted for racial discrepancies in BP and BP change over time
Ge et al. 2007 [78] USA	11.9–30	Black 289 White 413	*Black women 110.7 ± 10.2/61.4 ± 6.9* White 107.7 ± 8.8/59.3 ± 6.3 *Black men 117.1 ± 11.1/59 ± 7* White 114.4 ± 10.3/57 ± 6.4	Longitudinal	• Mean and standard deviation were reported • No adjustments • Twin study
Heffernan et al. 2020 [79] USA	9–12	Black 154 White 115	*Black 115 ± 14*/68 ± 6 White 112 ± 10/67 ± 6	Cross-sectional	• Mean and standard deviation were reported • Unadjusted analysis • Significance for brachial SBP was indicated $p = 0.008$, no significant difference for brachial DBP
Hlaing et al. 2006 [80] USA	Baseline 6–8 Follow-up 16–18	Black 114 White 373	Baseline Black 102.4 ± 10.4/*59.9 ± 12.4* White *105 ± 13*/56.6 ± 13.8 Follow-up Black *113.1 ± 11.2*/64.6 ± 10.8 White 111.9 ± 11.3/*66.3 ± 10.3*	Longitudinal	• Mean and standard deviation were reported • 9-year follow-up • No adjustments
Lefferts et al. 2017 [81] USA	9–12	Black 54 White 53	*Black 116 ± 10/69 ± 6* White 113 ± 8/66 ± 6	Cross sectional	• No adjustment • BP presented as means and standard deviations
Mokwatsi et al. 2017 [82] South Africa	6–8	Black 40 White 41	*Black 105 ± 11/69.4 ± 8.96* White 102 ± 7.34/62.9 ± 7.79	Cross-sectional	• Mean and standard deviation were reported • Only boys were included in the study • Unadjusted comparison
Oberg et al. 2012 [56] USA	Adolescent twins 14	Black 465 White 562	*Black girls 110 ± 10.4/61 ± 7.0* White girls 106 ± 8.5/58 ± 5.4	Longitudinal	• Mean and standard deviations were reported • Adjusted for familial/parental factors

Table 1 (continued)

Reference	Age (years)	Race, *N*	Blood pressure (SBP/DBP mmHg)	Type of study	Notes
			Black boys 113 ± 10.5/59 ± 5.9 White boys 110 ± 9.3/56 ± 5.8		• Twin study
Philip et al. 2015 [83] USA	10–18	Black 89 White 100 Hispanic 103	Normal weight *Black 127 ± 10.2/75 ± 7.6* White 121 ± 11.3/73 ± 7.5 Hispanic 119 ± 11.7/70 ± 6 Overweight *Black 135 ± 14.4/77 ± 7.9* White 133 ± 12.3/75 ± 7.1 Hispanic 128 ± 128/72 ± 9.7	Prospective	• Mean and standard deviations were reported • Unadjusted analysis
Shah et al. 2012 [84] USA	10–23	Black 119 White 96	Black 123 ± 13/68 ± 13 White 121 ± 12/66 ± 12	Cross-sectional	• Mean and standard deviations were reported • No significant racial differences in BP
Steyn et al. 2000 [85] South Africa	5-year olds only	Black 852 Colored 70 Indian 19 White 23	*Black 108 ± 12/62 ± 8* Colored 105 ± 11/63 ± 8 Indian 100 ± 8/61 ± 9 White 100 ± 11/56 ± 8	Longitudinal	• Mean and standard deviations were reported • Limitation: underrepresentation of other race groups • Significance indicated at $p < 0.05$ between black, Indian, and white children
Thomas et al. 2012 [86] England	9–10	Black 1545 White 1318 South Asian 1497 Other (mixed race) 954	Black 104.9 (104.3–105.4)/63.2 (62.7–63.7) White 105.0 (104.4–105.6)/62.3 (61.7–62.8) South Asian 104.0 (103.3–104.6)/63.5 (62.9–64.0) Other Asian 105.4 (104.2–106.5)/64.6 (63.0–65) Other (mixed race) 105.3 (104.6–106.0)/63.1 (62.5–63.8)	Cross-sectional	• Mean and 95% CI were reported • Adjusted clustering: age, sex, observer, month, time of day, room temperature, and school. Significant trend for racial differences at $p < 0.01$ (for SBP) and $p < 0.003$ (for DBP)
Thurston et al. 2009 [87] USA	14–16	Black 81 White 78	Black 109.3 ± 9.1/63.4 ± 7.9 White 107.1 ± 8.6/63.1 ± 9.1	Longitudinal	• Mean and standard deviations were reported • No significant differences in SBP ($p = 0.12$) or DBP ($p = 0.81$) between two ethnic groups
Zaniqueli et al. 2017 [88] Brazil	6–18	Black 211 Non-black 560	Black 104 ± 9/62 ± 6 Non-black 104 ± 9/62 ± 7	Cross-sectional	• Mean and standard deviations were reported • Unadjusted analysis • No ethnic disparities between black and non-black children

Italic values indicate higher BP

BP blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Studies comparing pulse wave velocity in children and adolescents by race

Reference	Age (years)	Race, *N*	Pulse wave velocity	Type of study	Comments
Collins et al. 2008 [75] USA	12–21	Black 134 White 71	Ba-PWV (m/s) *Black 10.8 ± 1.34* White 10.4 ± 1.35	Cross-sectional	• Unadjusted analyses • Normal blood pressure and weight • Effect of age on Ba-PWV was greater in black adolescents and males than in white adolescents and females, however the differences were not statistically different
Ge et al. 2007 [78] USA	11.9–30.0	Black 289 White 413	Aorto-radial PWV (m/s) *Black men 6.65 ± 1.03* White men 6.38 ± 1.08 *Black women 6.68 ± 1.02* White women 6.28 ± 0.99 Aorto-dorsalis-pedis PWV (m/s) Black men 7.10 ± 0.83 White men 7.15 ± 0.91 *Black women 7.20 ± 081* White women 7.03 ± 0.84	Cross-sectional	• This was a genetic modeling twin study • Included monozygotic and dizygotic pairs • Unadjusted analyses
Lefferts et al. 2017 [81] USA	9–12	Black 54 White 53	CFPWV (m/s) *Black 4.70 ± 0.80* White 4.20 ± 0.80	Cross-sectional	• PWV measurements adjusted for age, sex, BMI, height, MAP, and SES • African American children were taller and heavier than white children, but not difference in BMI.
Mokwatsi et al. 2017 [82] South Africa	6–8	Black 40 White 41	Carotid-radial PWV (m/s) *Black 9.72 ± 1.72* White 8.21 ± 1.82 CFPWV (m/s) *Black 5.01 ± 0.68* White 4.42 ± 0.62 Carotid-dorsalis-pedis PWV (m/s) *Black 5.49 ± 0.62* White 5.01 ± 0.63	Cross-sectional	• PWV adjusted for MAP • 6–8-year age range chosen to avoid effects of prepubertal hormonal changes • Only boys were included in the study
Shah et al. 2012 [84] USA	10–23	Black 119 White 96	CFPWV (m/s) *Black 6.96 ± 1.30* White 6.21 ± 0.87	Cross-sectional	• Unadjusted analyses • 50% diagnosed with type 2 diabetes • Associations with cardiovascular risk factors differed in each race/ethnic group.
Thurston et al. 2009 [87] USA	14–16	Black 81 White 78	CFPWV (m/s) *Black 5.71 ± 1.22* White 5.25 ± 1.16	Longitudinal	• PWV only measured at follow-up, 3.30 (SD = 0.82, range 1.50–5.90) from baseline • Unadjusted comparisons analyses • PWV associated with African American race in adjusted linear regression
Zaniqueli et al. 2017 [88] Brazil	6–18	Black 211 Non-black 560	CFPWV (m/s) Unadjusted analyses *Black 5.80 ± 0.80* Non-black 5.60 ± 0.70 Adjusted analyses split by pubertal phase Prepubescent Black 5.40 ± 0.60 Non-black 5.30 ± 0.60 Pubescent *Black 5.90 ± 0.70* Non-black 5.60 ± 0.80 Post-pubescent *Black 6.10 ± 0.70* Non-black 5.30 ± 0.60	Cross-sectional	• Adjusted for sex, age, height, BMI, SBP, and heart rate • Suggested adolescence stage as a key period of manifestation of arterial stiffness in young black adults.

Italic values indicate significantly higher PWV

Ba-PWV brachial ankle PWV, *BMI* body mass index, *CFPWV* carotid femoral pulse wave velocity, *MAP* mean arterial pressure, *SBP* systolic blood pressure, *SD* standard deviation, *SES* socioeconomic status

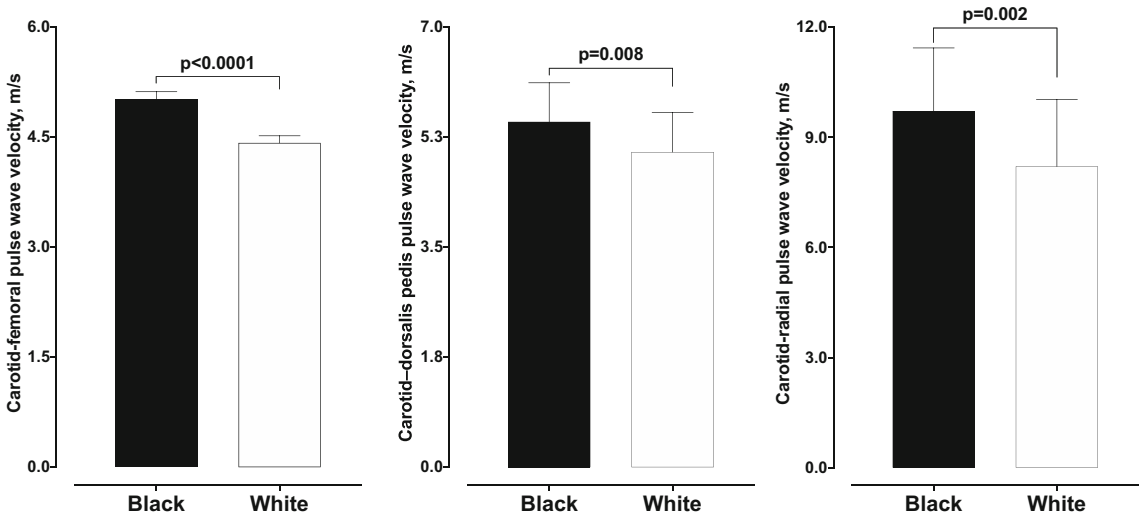

Fig. 2 Ethnic differences in pulse wave velocity between black and white boys (ages 6–8 years) from South Africa. Adapted from Mokwatsi et al. [82]

Caribbean) and white or Hispanic populations, with little comparative studies that included other racial or ethnic populations. Importantly, many of these studies reported on the unadjusted means of CIMT and did not necessarily consider any adjustment for BP, body composition, age, or sex. All studies from the USA reported significantly higher CIMT in black children [81, 95, 96] and/or adolescents [94], whereas one study reported borderline higher CIMT in the black compared with white group [87]. A UK study population, with multiple race/ethnic groups, reported higher CIMT in the black (African and Caribbean) compared with white, South Asian, Asian, and other (Indian, Pakistani, or Bangladeshi) race/ethnic groups, after adjustments for multiple covariates including age and sex [97]. From South Africa, one study reported higher CIMT in black compared with white boys, after adjustment for mean arterial pressure [82]. From the community of Bogalusa, USA, children (age 4–17 years) were cross-sectionally surveyed between 1973 and 2002 (not in Table 3) and were examined with CIMT as an additional measurement (not performed at baseline). The comparative analysis showed higher CIMT in black men (0.880 mm vs. 0.839 mm) and women (0.790 mm vs. 0.762 mm) compared with their white counterparts ($p < 0.00$) [98].

A recent systematic review reported on studies that investigated echocardiography in children and adolescents from various parts of the world and different race groups [99]. However, most of those studies did not perform any racial comparisons, making the current literature on the racial differences in these measurements highly limited, especially from countries other than the USA. Studies claim that children with left ventricular hypertrophy (LVH) are more likely to be of non-white race and have a higher BMI *z* score [100]. In Table 4, we listed studies in children and adolescents that compared left ventricular mass (LVM) between two or more race groups. Multiple studies from the USA reported higher unadjusted LVM in black compared with white children and adolescents [76, 79, 102, 108]. The higher LVM was more evident in black girls compared with boys for baseline and follow-up [105]. LVM adjusted for body surface area, stature, or body height to the power 2.7, yielded similar differences with higher LVM in black than white groups [79], along with the higher LVM in black girls and boys compared with their white counterparts [76, 105, 107]. Comparative studies have also reported no differences in LVM between black and white children or adolescents [106]. A longitudinal study with a very small sample size (black: $n = 25$ and white: $n = 36$), reported higher LVM (unadjusted and adjusted for body surface area) in white girls and black boys and after an approximate 6-year follow-up. LVM was higher in white boys and girls (unadjusted) and in white boys after considering indexing for body surface area compared with the black groups [101]. A retrospective study performed a racial/ethnic comparison of data from three different sites in the USA, and reported the highest LVM (indexed by body surface area) in the Hispanic group ($n = 20$) compared with the black and white groups [104]. Detail on age per race/ethnic group as well as secondary causes of hypertension per race/ethnic group were not reported in this analysis. One study from an Italian group also confirmed higher LVM in black ($n = 30$) compared with white ($n = 60$) adolescents, although this study was performed in athletes visiting Italy from Central or West Africa [103]. Based on the limited and inconsistent evidence, it remains uncertain whether LVM is universally higher in certain race/ethnic populations, especially in the context of EVA in children and adolescents.

Pathological determinants of early vascular aging

Similar to the multifactorial etiology of hypertension, EVA develops in the presence of cumulative risk factors in vulnerable populations such as children and adolescents, especially

Table 3 Studies comparing carotid intima media thickness in children and adolescents by race

Reference	Age (years)	Race, *N*	Carotid intima media thickness	Type of study	Notes
Breton et al. 2011 [94] USA	18–25	Asian 161 Black 38 Hispanic white 131 Non-Hispanic white 345 Other 93	CIMT (μm) Asian 587.5 (73.5) *Black 631.0 (61.0)* Hispanic white 588.5 (75.0) Non-Hispanic white 607.5 (79.0) Other 604.5 (95.0)	Cross-sectional	• Small *n* value for black students • Median and interquartile range were reported • Unadjusted analysis • The "other" race group was not defined in the study • Participants were included if they were lifetime non-smokers • *p* value was indicated for significance of trend at $p < 0.0001$
Chowdhury et al. 2014 [95] USA	4–21	Black 74 White 46	CIMT (mm) *Black 0.45 ± 0.03* White 0.43 ± 0.02	Cross-sectional	• Mean and standard deviation were reported • Unadjusted analysis • *p* value was indicated for significance at $p < 0.01$
Lefferts et al. 2017 [81] USA	9–12	Black 54 White 53	CIMT (mm) *Black = 0.41 ± 0.06* White = 0.39 ± 0.05	Longitudinal	• Mean and standard deviation were reported • Unadjusted analysis • *p* value was indicated for significance at $p < 0.05$
Mokwatsi et al. 2017 [82] South Africa	6–8	Black 40 White 41	CIMT (mm) *Black 0.47 ± 0.05* White 0.44 ± 0.05	Cross-sectional	• Mean and standard deviation were reported • Only boys were included in the study • Adjusted for mean arterial pressure • *p* value was indicated for significance at p 0.007
Thurston et al. 2009 [87] USA	14–16	Black 81 White 78	CIMT (mm) *Black 0.54 ± 0.03* White 0.53 ± 0.04	Cross-sectional	• Unadjusted analysis • Mean and standard deviation were reported • *p* value was indicated for significance at $p = 0.05$
Toledo-Corral et al. 2013 [96] USA	8–17	Black 55 Hispanic 101	CIMT (mm) *Black 0.644 ± 0.001* White 0.615 ± 0.001	Cross-sectional	• Mean and standard deviation were reported • Unadjusted analysis • *p* value was indicated for significance at $p < 0.0001$
Whincup et al. 2012 [97] UK	Only mean age was reported at 10.8 years	Black 240 White 208 South Asian 258 Asian other 63 Other 170*	CIMT (mm) *Black 0.487 (0.482–0.492)* White 0.472 (0.467–0.477) South Asian 0.469 (0.463–0.474) Asian other 0.476 (0.467–0.485) Other 0.475 (0.470–0.481)	Longitudinal	• Mean and 95% CI were reported • All means were adjusted for age, sex, month, and random effect for school • Black referred to black African and black Caribbean children • The authors noted that no marked differences were observed in CIMT levels between black African and black Caribbean children or between South Asian children of *Indian, *Pakistani, or *Bangladeshi origin—*data not shown* • CIMT was only measured at the second visit

Italic values indicate significantly higher CIMT

CI confidence intervals, *CIMT* carotid intima media thickness

Table 4 Studies comparing left ventricular mass in children and adolescents by race

Reference	Age (years)	Race, *N*	Left ventricular mass	Type of study	Notes
Allen et al. 1997 [101] USA	Children 8–10 Adolescents 15–17	Black 25 White 36 Black 20 White 34	LVM (g) Black girls 65.2 ± 4.7 *White girls 72.8 ± 3.5* *Black boys 82.2 ± 4.7* White boys 79.7 ± 5.0 LVM (g/m^2) Black girls 61.0 ± 3.3 *White girls 66.0 ± 2.8* *Black boys 74.4 ± 3.8* White boys 71.1 ± 2.8 LVM (g) Black girls 111.3 ± 8.4 *White girls 113.7 ± 6.8* Black boys 152.4 ± 12.9 *White boys 161.9 ± 8.1* LVM (g/m^2) Black girls 68.2 ± 3.7 White girls 68.6 ± 3.0 Black boys 79.4 ± 4.9 *White boys 88.2 ± 4.6*	Longitudinal	• Small *n* values • Mean and standard error were reported • Unadjusted analysis and body surface area adjusted LVM
Daniels et al. 1995 [102] USA	6–17	Black 89 White 103	LVM (g) *Black girls 81.4 ± 21.2* White girls 79.5 ± 24.1 *Black boys 101.6 ± 40.3* White boys 92.9 ± 31.5	Cross-sectional	• Unadjusted analyses • Mean and standard deviation were reported • LVM/LBM (g/kg) no significant difference by race (data not reported) • LVM/height^3 (g/m^3) no significant difference by race (data not reported)
Dekkers et al. 2002 [76] USA	8.2–27.5	Baseline Black 328 White 359	LVM (g) *Black girls 109.2 ± 31.6* White girls 102.8 ± 31.3 *Black boys 133.8 ± 41.5* White boys 123.9 ± 43.7 LVM (g/m^2) Black girls 66.7 ± 13.7 White girls 66.6 ± 13.5 *Black boys 80.5 ± 18.3* White boys 75.8 ± 16.8 LVM (g/m$^{2.7}$) *Black girls 31.3 ± 8.1* White girls 30.7 ± 8.0 *Black boys 35.7 ± 8.0* White boys 33.1 ± 8.5	Longitudinal	• Mean and standard deviation were reported • Unadjusted analysis, but also adjustments for body height to the power 2.7 and body surface area • No alpha level was indicated in descriptive comparisons • Means were reported of individuals with more than 4 out of 10 annual visits
Demola et al. 2019 [103] Italy	11.8–15.4	Black 30 White 60	LVM (g) *Black 175 ± 47* White 149 ± 46 LVM (g/m^2) *Black 106 ± 22* White 94 ± 18	Cross-sectional	• Mean and standard deviation were reported • Unadjusted analysis, but also adjustments for body height to the power 2.7 and body surface area • This study compared hemodynamic responses to physical exercise in adolescent athletes of black and white race

Table 4 (continued)

Reference	Age (years)	Race, *N*	Left ventricular mass	Type of study	Notes
			LVM (g/m$^{2.7}$) *Black 43 ± 9* White 38 ± 7		• Black children were all from the Central/West Africa, namely Burkina Faso, Cameroon, Ghana, Ivory Coast, Nigeria, and Senegal • Small *n* value for especially the black athletes
Hanevold et al. 2013 [104] USA	4.2–22	Black 49 White 60 Hispanic 20	LVM (g/m$^{2.7}$) Black 39.02 ± 1.83 White 32.21 ± 1.60 *Hispanic 41.14 ± 3.16*	Retrospective analysis from 3 sites in US	• Mean and standard error were reported • Adjustments for body height to the power 2.7 • Black referred to as African American • Children and adolescent were from different cities and backgrounds • Data from 1998–2003 pooled • Secondary causes of hypertension reported but with no race comparison • 55 patients received antihypertensive medication, but were not compared by race • Age was not provided per race group
Heffernan et al. 2020 [79] USA	9–12	Black 154 White 115	LVM (g) *Black 88.2 ± 23.7* White 82.4 ± 18.8 LVM (g/m) *Black 60.1 ± 14.2* White 57.0 ± 11.1 LVM (g/m^2) *Black 65.9 ± 10.7* White 63.7 ± 10.2 LVM (g/m$^{2.7}$) Black 31.8 ± 6.4 White 30.7 ± 5.5	Cross-sectional	• Mean and standard deviation were reported • Unadjusted analysis, but also adjustments for body height, body height to the power 2.7 and body surface area • Significance was lost for comparisons between black and white children with adjustments for body height ($p = 0.052$) and body height to the power 2.7 ($p = 0.16$)
Kapuku et al. 2008 [105] USA	14–18	Baseline Black 428 White 561 Follow-up Black 354 White 445	LVM (g) *Black girls 99.3 ± 21.3* White girls 93.9 ± 22.1 Black boys 115.9 ± 34.6 White boys 116.3 ± 33.9 LVM (g/m^2) *Black girls 28.5 ± 5.3* White girls 27.2 ± 5.7 Black boys 30.8 ± 6.4 White boys 30.2 ± 5.4 LVM (g) *Black girls 113.8 ± 24.5* White girls 110.4 ± 23.3 Black boys 151.9 ± 34.7 White boys 151.1 ± 35.2 LVM (g/m^2) *Black girls 30.5 ± 6.2* White girls 29.3 ± 6.1 Black boys 33.3 ± 7.0 White boys 33.0 ± 7.2	Longitudinal	• Mean and standard deviation were reported • This was a genetic modeling twin study with a follow-up time period of 4.1 ± 0.49 years (range 2.4–6.3 years) • Trend for racial differences in LVM (g) reported to be not significant • Trend for racial differences in LVM (g/m^2) reported at $p < 0.03$
Lamers et al. 2005 [106] USA	3–17	Black 50 White 72	LVM (g) *Black 85.91 ± 61.13* White 72.28 ± 36.29	Prospective	• Mean and standard deviation were reported • Only cross-sectional data reported • No statistical significance for LVM (g), $p = 0.49$ or LVM (g/m^2), $p = 0.67$

Table 4 (continued)

Reference	Age (years)	Race, *N*	Left ventricular mass	Type of study	Notes
			LVM (g/m^2) *Black 65.54 ± 23.37* White 63.92 ± 15.85		
Murro et al. 2013 [107] USA	15–19	Black 89 White 102	LVM ($g/m^{2.7}$) *Black girls 31 (18–56)* White girls 28 (21–40) Black boys 33 (22–60) White boys 32 (20–44)	Cross-sectional	• Mean and range were reported • LVM with height to the power 2.7 adjusted were the only reported measure
Schieken et al. 1998 [108] USA	11–17	*N* = 231 Exact *n* values not reported per race group. Black participants represent ~ 20% of the study sample.	LVM (g) *Black 87.9 ± 27.9* White 80.0 ± 23.1	Longitudinal	• A twin was selected randomly from each of the pairs of twins from the Medical College of Virginia Twin Study cohort • The sample sizes for each of the 5 study visits ranged from 231 subjects studied on at least 3 occasions, to 87 subjects studied on all 5 occasions • Significance at visit 1, $p < 0.01$ • Significance from visit 2 onwards was lost—due to *n* value limitations

Italic values indicate higher LV mass

LVM left ventricular mass

those with significant differences noted by race or ethnicity. It is becoming increasingly evident that early stages of CVD, such as hypertension and LVH, start to manifest in childhood and adolescence, with black children manifesting these risk factors earlier than white children [13, 82]. Therefore, race or ethnicity is considered risk factors of EVA and subsequent CVD. In low and middle-income countries, obesity and other NCDs are consequences of a combination of poverty, living environments, the availability of fast foods, and especially the consumption of energy-dense, but micronutrient-poor diets. However, there is substantial evidence to suggest that early life nutrition and intrauterine risk factors play a pivotal role in the progression towards adult NCDs [109].

Tracking studies have shown that children and adolescents with elevated BP have a higher risk of developing hypertension in early adulthood [45, 72, 110] and this transition to adult hypertension was mostly determined by modifiable cardiovascular risk factors including poor dietary habits (high dietary salt intake, fructose, processed and fast foods), poor sleep patterns, stress, and a lack of sufficient physical activity [45]. Furthermore, childhood nutrition is a major driver of child mortality and morbidity in countries with large ethnic inequities, with a substantial burden of under-and overnutrition, and a rapid growth of obesity, driven by the excessive consumption of sugar containing drinks, ultra-processed foods, and extensive sedentary lifestyle [16]. Underweight trends among children and adolescents are still alarmingly high especially in African and Southeast Asia compared with obesity. With obesity in children and adolescents reaching a plateau in high-income countries, the prevalence is still rising in low-income and middle-income countries. This has important consequences, including the short-term developments of psychiatric, psychological, and psychosocial disorders in childhood and the increased long-term risk of developing NCDs later in life [111].

In light of the abovementioned modifiable and non-modifiable risk factors contributing to EVA, EVA is typically felt to be manifest as the long-term development of endothelial dysfunction, arterial stiffness, LVH, and early kidney damage.

The vasculature

Arterial stiffness is defined as reduced arterial distensibility or compliance (in the *tunica media*) as a result of continuous adaptations in the molecular and biomechanical makeup of blood vessels [112, 113] and endothelial dysfunction. *Endothelial dysfunction* is defined as the state of impaired vasodilation due to proinflammation and prothrombic properties of the blood vessel walls [114]. Endothelial dysfunction is also associated with several CVDs in adults, including hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes mellitus, and CKD [114]. However, several mechanisms involved in reduced

vasodilatory responses of the endothelium are also evident in pediatric populations including reduced nitric oxide bioavailability, oxidative stress, and the activation of vasoactive peptides known to promote vasoconstriction. A study in black and white boys (mean age of 7.29 years) reported lower urinary nitrate-to-nitrite molar ratio, as a measure of nitric oxide bioavailability, in black boys compared with the white boys, suggesting a lower reabsorption rate of nitrite or lower nitric oxide generation and underlying sub-clinical endothelial dysfunction [115]. This result may further indicate genetic differences in renal carbonic anhydrase isoforms and anion transporters among children of black African ancestry. Furthermore, markers of oxidative stress (thiobarbituric acid-reactive substances and 8-hydroxy-2-deoxy guanosine) related to increased arterial stiffness and diastolic BP in boys with linked maternal lifestyle and cardiovascular risk factors, suggesting potential family-related early onset of increased cardiovascular risk [116]. Studies in children and adolescents reported higher arterial stiffness in black and Hispanic populations at ages as early as 6 years [80, 82, 84, 87] compared with white, non-Hispanic, and Asian children. Aside from studies that reported the higher BP, PWV, and CIMT in black and Hispanic populations, there are numerous intermediate determinants of EVA that contribute to the premature development of endothelial dysfunction and subsequent arterial stiffness. Increased aortic wall thickness and impaired vasomotor function was described as functions of increased arterial stiffness [117], as observed in preterm infants with systemic hypertension [118]. In addition, low birth weight and other complications such as bronchopulmonary dysplasia also contribute to the early onset of arterial stiffening [118].

Other determinants of endothelial dysfunction and arterial stiffness include metabolic factors (impaired glucose and lipid metabolism and insulin resistance), oxidative stress [119–121] and inflammation, as well as the increased deposition of matrix substances, all of which contribute to altered hemodynamics and subsequent hypertension [122–124]. In addition, increased carotid artery intima-media thickness and early atherosclerosis, capillary rarefaction and dysfunctional vascular regulation along with microvascular and macrovascular injury have been reported in children [125, 126], but ethnic-specific comparison studies are still limited. Metabolomics analyses also confirmed race/ethnic disparities, where PWV associated adversely with β-alanine, 1-methylhistidine, and L-proline in black South African children, which may suggest potential early compromise in cardioprotective metabolic pathways in children of African ancestry [127].

The heart and the kidneys

The vascular compromise in EVA has a direct impact on the heart and other target organs. Perhaps one of the most dynamic measures of increased cardiovascular risk is LVM. Increased LVM, also defined as LVH, is a prominent independent predictor of cardiovascular morbidity and mortality in adults [128, 129] and a sensitive marker of risk in children [130]. With exposure to various environmental factors (pollution, violence, poverty, availability to drugs, access to alcohol and cigarettes), aging, and lifestyle behaviors (exercise and dietary intake of healthy and unhealthy food), the wall of the left ventricle has the ability to remodel in response. LVM may be one of the earliest markers of hypertension mediated target organ damage or manifestations of EVA. From the Bogalusa Heart Study in Louisiana, adolescence was described as a critical age period for the development of LVH in later life due to the impact of BP trajectories in childhood on adult LVH and geometric patterns [131]. This study included a population of 65% white and 35% black children, adolescents, and adults (ages 4–51 years) and reported higher BP and LVM in the black participants, highlighting the reality of ethnic specific risks in the setting of EVA.

Underweight or overweight/obesity during childhood is an additional risk factor for the development of LVH as these markers of suboptimal nutrition are associated with accelerated CV deterioration and early vascular compromise. This has been confirmed by reports indicating LVH and left ventricular diastolic dysfunction in 9–19-year olds with obesity, prior to the development of sustained hypertension [132]. LVH is also a sensitive marker of target organ damage in children with high BP and CKD [130]. In children with CKD, LVH develops early and becomes more prevalent as renal function decreases; however, this may be dependent on BP as a study reported that a reduction in BP might predict a decline in LVH in children with CKD [133].

The degree of renal function is important—children with end-stage renal disease (ESRD) on dialysis had worse measures of arterial stiffness than those with a functional kidney transplant and healthy age-sex-matched controls [134, 135]. Litwin et al. even suggested partial reversal in CKD-associated arterial wall remodeling as patients displayed attenuation of arterial pathology after kidney transplantation than patients on dialysis irrespective of exposure to similar dialysis vintage [134]. In another study, PWV was not significantly different between children with mild CKD and healthy children, while in children with mild-to-moderate CKD, PWV was independently associated with increasing age, mean arterial pressure and black ethnicity [136].

Chronic kidney disease can also promote tissue growth and adversely impact left ventricular function via non-hemodynamic pathways such as chronic inflammation, vitamin D deficiency, and higher levels of parathyroid hormone [137, 138]. Vitamin D and its interactions with the renin-angiotensin-aldosterone system (RAAS) have been implicated in arterial stiffness. Vitamin D supplementation was shown to alleviate local arterial stiffness and improved flow-mediated

dilatation in children with CKD [106]. Fibroblast growth hormone-23 (FGF23), a hormone that is released from bone and works on the kidney has been positively associated with LVH in children aged 1–21 years [139, 140]. FGF23 increases activity of the RAAS by decreasing active vitamin D [141]. On the other hand, FGF23 may promote sodium retention and subsequently volume expansion independent of RAAS [142]. In the Framingham Heart Study (including the Offspring cohort and the Omni cohort), FGF23 was positively associated with African-American and Asian ethnicity [143]. However, in the CARDIA study, FGF23 was associated with an increase in BP over time and an increased incident of hypertension, with no racial/ethnic differences in hypertension [144].

Ethnic differences regarding the activity of RAAS are also well established with populations of African ancestry presenting with a suppressed RAAS across all ages [145–147]. The suppressed RAAS phenotype is not unique to individuals of African descent, but it is also common in Asians and elderly populations of other ethnicities [148, 149]. The low RAAS activity is due to, among others, retention of sodium and water, which increases the load against which the heart must work [146, 150]. In black boys with a mean age of 16 years, an increase in aldosterone was associated with decreased sodium excretion and increased BP and LVM [107]. Another study showed a stronger association between aldosterone and BP with aging from adolescence (mean age 10.6 years) to adulthood in black participants [147]. Early kidney damage and dysregulation in the RAAS may also stem from fetal conditions. Young adults born preterm present with smaller kidneys and higher angiotensin I, BP, and albumin-to-creatinine ratio compared with full-term controls [151], predisposing preterm babies to early vascular alterations and CVD development at young ages. A recent study developed a nomogram to predict aldosterone in children, which may improve assessment of RAAS dysfunction and treatment of pediatric hypertension to delay EVA [152]. Further studies in children and young adults from different ethnicities are needed to confirm if race-specific normal ranges are essential.

An increase is arterial stiffness was also observed in cases of children with acute post-streptococcal glomerulonephritis that progressed into CKD. Post-infectious glomerulonephritis (PIGN) is usually a result of group A streptococcal infections, and it is characterized by acute kidney injury, increased BP, glomerular hematuria, mild proteinuria, and edema [153]. Yu et al. demonstrated an association between arterial stiffness and PIGN in children [153]. The mechanisms are not yet clear, but may be due to the renal inflammatory response in PIGN [154, 155], and also suggest that glomerular changes may reflect vascular changes outside the kidney in response to infection. Rural and overcrowded communities are particularly vulnerable to epidemic clusters and outbreaks of PIGN [153]. PIGN used to be the most prevalent kidney disease in black South African children; however, focal glomerulosclerosis and rapidly progressive glomerulonephritis (mostly due to streptococcal infection) later became the first and second causes of renal failure requiring kidney transplantation [156].

Of importance, other factors contributing to the burden of kidney diseases in black South African children emanate from the quadruple burden of disease, which may not be unique to the South African context. Tuberculosis has been linked to focal glomerulosclerosis and Takayasu arteritis (inflammatory vasculitis of the aorta and its main branches), while HIV and its associated opportunistic infections, as well toxicity from antiretroviral drugs, have been implicated in kidney injury in children living with HIV [156–158]. Aboriginal children from Australia and New Zealand diagnosed with severe PIGN showed an increased risk to progress to advanced stages of renal damage and even ESRD as compared with the non-Aboriginal population [159–161]. It is not yet established if the ethnic-specific manifestations of acute kidney disease may accelerate vascular aging in children and young adults of certain race groups.

Future directions of early vascular aging and race/ethnicity in children and adolescents

While genetic studies have failed to distinguish ethnic or race-specific determinants of CVD risk [162], race/ethnicity remains one of the risk factors regularly reported in multiethnic population studies in relation to hypertension and cardiovascular disease states. Whether race/ethnicity by itself is a risk factor for EVA, or whether it is the convergence of multiple risk factors on the backdrop of race/ethnicity, remains to be confirmed.

In countries such as the USA, race/ethnic variations in health have been regularly reported, with differences in socioeconomic status as a major contributor to racial disparities in health [163]. However, in the recent 2018 World Bank report, South Africa was identified as the most unequal country in the world, with black South Africans reported to have the highest level of poverty, with less access to proper education, are most unemployed, have more female headed households, and have large families and many children per household [164]. With multiple discrepancies in environmental and sociocultural determinants that may adversely influence biological aging, research should be directed to larger, prospective, and standardized protocols to address racial differences in EVA, especially in low to middle-income countries with large ethnic diversity.

Finally, alongside the clinical treatment of the consequences of biological aging, focus should be shifted to the development of primordial prevention and educational programs to promote health from the beginning of life (starting with pregnant mothers, parents, pre-primary school children and teachers). The overall health and economic burden of

treating NCDs can be improved—especially in countries with large educational and sociocultural disparities and racial variation.

Conclusion

Although this is not an exhaustive review, the main features of EVA point to important racial differences in risk factors when evaluating the early life determinants of accelerated biological aging. The manifestations of EVA are of particular global and economic interest and should be targeted for primary prevention to curb the current escalating burden of cardiovascular disease, especially in children and adolescents at increased risk by race.

Key summary points

- Early life programming is an essential determinant of EVA in children and adolescents
- Children of black or Hispanic race are especially vulnerable to develop EVA due to predisposed risk in hemodynamic and end organ damage
- Ethnicity by itself can be considered a risk factor for EVA, but may be dependent on converging risk factors in early life

Multiple-choice questions

1. Early vascular aging can be defined as:

a) Premature CVD manifestation
b) Age-related biological deterioration
c) Age-related increases in cardiac function
d) Vascular degeneration
e) Premature deterioration of the vasculature

2. Which one of the following is the gold standard measure of EVA?

a) Carotid intima thickness
b) Blood pressure
c) Pulse wave velocity
d) Nitric oxide
e) Oxidative stress

3. The following are key characteristics of EVA except:

a) Increased pulse wave velocity
b) Oxidative stress
c) Increased elasticity of the arterial walls
d) Microvascular rarefaction
e) Increased vasoconstriction

4. Ethnic differences in intrauterine programming of early vascular aging may be linked to

a) Oxidative stress
b) Endothelial dysfunction
c) Epigenetic modifications
d) A and B only
e) All of the above

5. EVA and its associated cardiovascular risk can be mitigated by _____.

a) Intensifying treatment of hypertension, diabetes and renal diseases in resource poor settings
b) Timeous diagnosis and treatment of infectious diseases
c) Improving maternal and child health and nutrition
d) Both A and B
e) Options A, B, C

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Declarations None to declare.

References

1. Flynn JT (2018) High blood pressure in the young: why should we care? Acta Paediatr 107(1):14–19
2. Kagura J, Ong KK, Adair LS, Pettifor JM, Norris SA (2018) Paediatric hypertension in South Africa: an underestimated problem calling for action. S Afr Med J 108(9):708–709. https://doi.org/10.7196/SAMJ.2018.v108i9.13317
3. Shatat IF, Brady TM (2018) Editorial: Pediatric Hypertension: Update. Front Pediatr 6(209):209. https://doi.org/10.3389/fped.2018.00209
4. Barker D, Lampl M, Roseboom T, Winder N (2012) Resource allocation in utero and health in later life. Placenta 33:e30–e34
5. Calkins K, Devaskar SU (2011) Fetal origins of adult disease. Curr Probl Pediatr Adolesc Health Care 41(6):158–176
6. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, Damasceno A, Delles C, Gimenez-Roqueplo A-P, Hering D (2016) A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet 388(10060):2665–2712

7. Godfrey KM, Barker DJ (2000) Fetal nutrition and adult disease. Am J Clin Nutr 71(5 Suppl):1344S–1352S. https://doi.org/10.1093/ajcn/71.5.1344s
8. Taal HR, de Jonge LL, van Osch-Gevers L, Steegers EA, Hofman A, Helbing WA, van der Heijden AJ, Jaddoe VW (2013) Parental smoking during pregnancy and cardiovascular structures and function in childhood: the Generation R Study. Int J Epidemiol 42(5):1371–1380. https://doi.org/10.1093/ije/dyt178
9. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sorensen HT, Qin G, Li J (2019) Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. BMJ 367:l6398. https://doi.org/10.1136/bmj.l6398
10. Silva LM, Coolman M, Steegers EA, Jaddoe VW, Moll HA, Hofman A, Mackenbach JP, Raat H (2008) Low socioeconomic status is a risk factor for preeclampsia: the Generation R Study. J Hypertens 26(6):1200–1208. https://doi.org/10.1097/HJH.0b013e3282fcc36e
11. Barker DJ (2004) The developmental origins of chronic adult disease. Acta Paediatr Suppl 93(446):26–33. https://doi.org/10.1111/j.1651-2227.2004.tb00236.x
12. Pool LR, Ning H, Lloyd-Jones DM, Allen NB (2017) Trends in racial/ethnic disparities in cardiovascular health among US adults From 1999-2012. J Am Heart Assoc 6(9). https://doi.org/10.1161/JAHA.117.006027
13. Schutte AE, Botha S, Fourie CMT, Gafane-Matemane LF, Kruger R, Lammertyn L, Malan L, Mels CMC, Schutte R, Smith W, van Rooyen JM, Ware LJ, Huisman HW (2017) Recent advances in understanding hypertension development in sub-Saharan Africa. J Hum Hypertens 31(8):491–500. https://doi.org/10.1038/jhh.2017.18
14. Ordovas JM (2007) Medicine, genetics and race: the case of cardiovascular diseases. Perinat Med 4(1):1–6. https://doi.org/10.2217/17410541.4.1.1
15. Race, Ethnicity, and Genetics Working Group (2005) The use of racial, ethnic, and ancestral categories in human genetics research. Am J Hum Genet 77(4):519–532
16. Lake L, Shung-King M, Hendricks M, Heywood M, Nannan N, Laubscher R, Bradshaw D, Mathews C, Goga A, Ramraj T, Chirinda W (2019) Prioritising child and adolescent health: a human rights imperative. Child and adolescent health, Cape Town
17. Nilsson P (1996) Premature ageing: the link between psychosocial risk factors and disease. Med Hypotheses 47(1):39–42
18. Sniderman AD, Furberg CD (2008) Age as a modifiable risk factor for cardiovascular disease. Lancet 371(9623):1547–1549
19. Nilsson PM (2008) Early vascular aging (EVA): consequences and prevention. Vasc Health Risk Manag 4(3):547–552. https://doi.org/10.2147/vhrm.s1094
20. Laurent S, Boutouyrie P, Cunha PG, Lacolley P, Nilsson PM (2019) Concept of extremes in vascular aging: from early vascular aging to supernormal vascular aging. Hypertension 74(2):218–228
21. Kotsis V, Antza C, Doundoulakis I, Stabouli S (2017) Markers of early vascular ageing. Curr Pharm Des 23(22):3200–3204. https://doi.org/10.2174/1381612823666170328142433
22. Zhong Q, Hu M-J, Cui Y-J, Liang L, Zhou M-M, Yang Y-W, Huang F (2018) Carotid–femoral pulse wave velocity in the prediction of cardiovascular events and mortality: an updated systematic review and meta-analysis. Angiology 69(7):617–629
23. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank J, De Backer T, Filipovsky J, Huybrechts S, Mattace-Raso FU, Protogerou AD (2012) Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. J Hypertens 30(3):445–448
24. Izzo JL, Shykoff BE (2019) Arterial stiffness: clinical relevance, measurement, and treatment. Rev Cardiovasc Med 2(1):29–40
25. Cunha PG, Boutouyrie P, Nilsson PM, Laurent S (2017) Early vascular ageing (EVA): definitions and clinical applicability. Curr Hypertens Rev 13(1):8–15. https://doi.org/10.2174/1573402113666170413094319
26. Kingwell BA (2002) Large artery stiffness: implications for exercise capacity and cardiovascular risk. Clin Exp Pharmacol Physiol 29(3):214–217
27. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC (2001) Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol 38(3):796–802
28. Maillard P, Mitchell GF, Himali JJ, Beiser A, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C (2016) Effects of arterial stiffness on brain integrity in young adults from the Framingham Heart Study. Stroke 47(4):1030–1036. https://doi.org/10.1161/strokeaha.116.012949
29. Saji N, Toba K, Sakurai T (2015) Cerebral small vessel disease and arterial stiffness: tsunami effect in the brain. Pulse 3(3-4):182–189
30. Briet M (2019) Large artery remodelling and stiffening in moderate chronic kidney disease. Artery Res 5(4):137–137
31. Georgianos PI, Sarafidis PA, Liakopoulos V (2015) Arterial stiffness: a novel risk factor for kidney injury progression? Am J Hypertens 28(8):958–965
32. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A (2014) 2013 ESH/ESC Practice guidelines for the management of arterial hypertension: ESH-ESC The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press 23(1):3–16
33. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, De Carlo M, Gallino A, Landmesser U, Laurent S (2015) The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. Atherosclerosis 241(2):507–532
34. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB (2014) Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol 63(7):636–646. https://doi.org/10.1016/j.jacc.2013.09.063
35. Townsend RR (2016) Arterial stiffness: recommendations and standardization. Pulse 4(Suppl. 1):3–7
36. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM (1998) Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 32(3):570–574
37. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37(5):1236–1241
38. Levisianou D, Foussas S, Skopelitis E, Adamopoulou E, Xenopoulou T, Destounis A, Koukoulis G, Skoularigis I,

Melidonis A, Triposkiadis F (2013) Arterial stiffness predicts risk for long-term recurrence in patients with type 2 diabetes admitted for acute coronary event. Diabetes Res Clin Pract 99(3):315–320
39. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J (2006) Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 113(5):664–670. https://doi.org/10.1161/circulationaha.105.579342
40. Lynch J, Smith GD (2005) A life course approach to chronic disease epidemiology. Annu Rev Public Health 26:1–35. https://doi.org/10.1146/annurev.publhealth.26.021304.144505
41. Gillman MW, Rosner B, Evans DA, Smith LA, Taylor JO, Hennekens CH, Keough ME (1991) Use of multiple visits to increase blood pressure tracking correlations in childhood. Pediatrics 87(5):708–711
42. Kagura J, Adair LS, Musa MG, Pettifor JM, Norris SA (2015) Blood pressure tracking in urban black South African children: birth to twenty cohort. BMC Pediatr 15(1):78. https://doi.org/10.1186/s12887-015-0402-z
43. Lauer RM, Clarke WR (1988) A longitudinal view of blood pressure during childhood: the Muscatine Study. Stat Med 7(1-2):47–57. https://doi.org/10.1002/sim.4780070109
44. Shear CL, Burke GL, Freedman DS, Berenson GS (1986) Value of childhood blood pressure measurements and family history in predicting future blood pressure status: results from 8 years of follow-up in the Bogalusa Heart Study. Pediatrics 77(6):862–869
45. Falkner B (2015) Recent clinical and translational advances in pediatric hypertension. Hypertension 65(5):926–931
46. Cattell MA, Anderson JC, Hasleton PS (1996) Age-related changes in amounts and concentrations of collagen and elastin in normotensive human thoracic aorta. Clin Chim Acta 245(1):73–84. https://doi.org/10.1016/0009-8981(95)06174-6
47. Martyn CN, Greenwald SE (1997) Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. Lancet (London, England) 350(9082):953–955. https://doi.org/10.1016/s0140-6736(96)10508-0
48. Bansal N (2006) Maternal and early life determinants of serum lipids and vascular function in pre-school children. The University of Manchester (United Kingdom),
49. Islam M, Jafar TH, Bux R, Hashmi S, Chaturvedi N, Hughes AD (2014) Association of parental blood pressure with retinal microcirculatory abnormalities indicative of endothelial dysfunction in children. J Hypertens 32(3):598–605. https://doi.org/10.1097/hjh.0000000000000063
50. Stirrat LI, Reynolds RM (2014) Effects of maternal obesity on early and long-term outcomes for offspring. Res Rep Neonatol 4:43
51. van Os J, Rutten BP, Poulton R (2010) Gene–environment interactions for searchers: collaboration between epidemiology and molecular genetics. In: Advances in Schizophrenia Research 2009. Springer, pp 19-50
52. Clough GF (2011) Developmental conditioning of the vasculature. Compr Physiol 5(1):397–438
53. Kuh D, Smith GD (2004) disease: an historical perspective with particular reference to coronary. A life course approach to chronic disease epidemiology (2):15
54. Hedderson MM, Darbinian JA, Ferrara A (2010) Disparities in the risk of gestational diabetes by race-ethnicity and country of birth. Paediatr Perinat Epidemiol 24(5):441–448. https://doi.org/10.1111/j.1365-3016.2010.01140.x
55. Savitz DA, Janevic TM, Engel SM, Kaufman JS, Herring AH (2008) Ethnicity and gestational diabetes in New York City, 1995-2003. BJOG 115(8):969–978. https://doi.org/10.1111/j.1471-0528.2008.01763.x
56. Oberg S, Ge D, Cnattingius S, Svensson A, Treiber FA, Snieder H, Iliadou A (2007) Ethnic differences in the association of birth weight and blood pressure: the Georgia cardiovascular twin study. Am J Hypertens 20(12):1235–1241. https://doi.org/10.1016/j.amjhyper.2007.07.012
57. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J (2003) US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics 111(1):e61–e66. https://doi.org/10.1542/peds.111.1.e61
58. Harding S, Rosato M, Cruickshank J (2004) Lack of change in birthweights of infants by generational status among Indian, Pakistani, Bangladeshi, Black Caribbean, and Black African mothers in a British cohort study. Int J Epidemiol 33(6):1279–1285
59. McEniery CM, Bolton CE, Fawke J, Hennessy E, Stocks J, Wilkinson IB, Cockcroft JR, Marlow N (2011) Cardiovascular consequences of extreme prematurity: the EPICure study. J Hypertens 29(7):1367–1373. https://doi.org/10.1097/HJH.0b013e328347e333
60. Posod A, Odri Komazec I, Kager K, Pupp Peglow U, Griesmaier E, Schermer E, Wurtinger P, Baumgartner D, Kiechl-Kohlendorfer U (2016) Former very preterm infants show an unfavorable cardiovascular risk profile at a preschool age. PLoS One 11(12):e0168162. https://doi.org/10.1371/journal.pone.0168162
61. Mina TH, Lahti M, Drake AJ, Forbes S, Denison FC, Raikkonen K, Norman JE, Reynolds RM (2017) Maternal lipids in pregnancy are associated with increased offspring cortisol reactivity in childhood. Psychoneuroendocrinology 83:79–83. https://doi.org/10.1016/j.psyneuen.2017.04.018
62. Carey LP (2018) Childhood emotional functioning and arterial stiffness in young adulthood. ProQuest Dissertations Publishing, State University of New York at Albany
63. Klassen SA, Chirico D, O'Leary DD, Cairney J, Wade TJ (2016) Linking systemic arterial stiffness among adolescents to adverse childhood experiences. Child Abuse Negl 56:1–10. https://doi.org/10.1016/j.chiabu.2016.04.002
64. Cunha PG, Cotter J, Oliveira P, Vila I, Boutouyrie P, Laurent S, Nilsson PM, Scuteri A, Sousa N (2015) Pulse wave velocity distribution in a cohort study: from arterial stiffness to early vascular aging. J Hypertens 33(7):1438–1445
65. Danninger K, Hafez A, Binder RK, Aichberger M, Hametner B, Wassertheurer S, Weber T (2019) High prevalence of hypertension and early vascular aging: a screening program in pharmacies in Upper Austria. J Hum Hypertens:1–9
66. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet (London, England) 364(9438):937–952. https://doi.org/10.1016/S0140-6736(04)17018-9
67. Braveman P, Gottlieb L (2014) The social determinants of health: it's time to consider the causes of the causes. Public Health Rep 129(1_suppl2):19–31
68. Rosengren A, Smyth A, Rangarajan S, Ramasundarahettige C, Bangdiwala SI, AlHabib KF, Avezum A, Boström KB, Chifamba J, Gulec S (2019) Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. Lancet Glob Health 7(6):e748–e760
69. Cruickshank JK, Silva MJ, Molaodi OR, Enayat ZE, Cassidy A, Karamanos A, Read UM, Faconti L, Dall P, Stansfield B, Harding S (2016) Ethnic differences in and childhood influences on early adult pulse wave velocity: the determinants of adolescent, now young adult, social wellbeing, and health longitudinal study.

Hypertension 67(6):1133–1141. https://doi.org/10.1161/HYPERTENSIONAHA.115.07079
70. Mendizabal B, Urbina EM, Becker R, Daniels SR, Falkner BE, Hamdani G, Hanevold CD, Hooper SR, Ingelfinger JR, Lande M, Martin LJ, Meyers K, Mitsnefes M, Rosner B, Samuels JA, Flynn JT (2018) SHIP-AHOY (Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth). Hypertension 72(3):625–631. https://doi.org/10.1161/HYPERTENSIONAHA.118.11434
71. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM, Subcommittee on screening and management of high blood pressure in children (2017) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 140 (3):e20171904. doi:https://doi.org/10.1542/peds.2017-1904
72. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, Invitti C, Litwin M, Mancia G, Pall D, Rascher W, Redon J, Schaefer F, Seeman T, Sinha M, Stabouli S, Webb NJ, Wuhl E, Zanchetti A (2016) 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 34(10):1887–1920. https://doi.org/10.1097/HJH.0000000000001039
73. Urbina EM, Khoury PR, Bazzano L, Burns TL, Daniels S, Dwyer T, Hu T, Jacobs DR Jr, Juonala M, Prineas R, Raitakari O, Steinberger J, Venn A, Woo JG, Sinaiko A (2019) Relation of blood pressure in childhood to self-reported hypertension in adulthood. Hypertension 73(6):1224–1230. https://doi.org/10.1161/HYPERTENSIONAHA.118.12334
74. Cruickshank JK, Mzayek F, Liu L, Kieltyka L, Sherwin R, Webber LS, Srinavasan SR, Berenson GS (2005) Origins of the "black/white" difference in blood pressure: roles of birth weight, postnatal growth, early blood pressure, and adolescent body size: the Bogalusa heart study. Circulation 111(15):1932–1937. https://doi.org/10.1161/01.CIR.0000161960.78745.33
75. Collins RT, Somes GW, Alpert BS (2008) Differences in arterial compliance among normotensive adolescent groups: Collins arterial compliance in adolescents. Pediatr Cardiol 29(5):929–934. https://doi.org/10.1007/s00246-008-9239-7
76. Dekkers C, Treiber FA, Kapuku G, Van Den Oord EJ, Snieder H (2002) Growth of left ventricular mass in African American and European American youth. Hypertension 39(5):943–951. https://doi.org/10.1161/01.hyp.0000015612.73413.91
77. Fuller-Rowell TE, Curtis DS, Klebanov PK, Brooks-Gunn J, Evans GW (2017) Racial disparities in blood pressure trajectories of preterm children: the role of family and neighborhood socioeconomic status. Am J Epidemiol 185(10):888–897
78. Ge D, Young TW, Wang X, Kapuku GK, Treiber FA, Snieder H (2007) Heritability of arterial stiffness in black and white American youth and young adults. Am J Hypertens 20(10):1065–1072. https://doi.org/10.1016/j.amjhyper.2007.05.013
79. Heffernan KS, Lefferts WK, Atallah-Yunes NH, Glasgow AC, Gump BB (2020) Racial differences in left ventricular mass and wave reflection intensity in children. Front Pediatr 8:132. https://doi.org/10.3389/fped.2020.00132
80. Hlaing WM, Prineas RJ (2006) Arterial stiffness variations by gender in African-American and Caucasian children. J Natl Med Assoc 98(2):181–189
81. Lefferts WK, Augustine JA, Spartano NL, Atallah-Yunes NH, Heffernan KS, Gump BB (2017) Racial differences in aortic stiffness in children. J Pediatr 180:62–67. https://doi.org/10.1016/j.jpeds.2016.09.071
82. Mokwatsi GG, Schutte AE, Kruger R (2017) Ethnic differences regarding arterial stiffness of 6-8-year-old black and white boys. J Hypertens 35(5):960–967. https://doi.org/10.1097/HJH.0000000000001267
83. Philip R, Alpert BS, Schwingshackl A, Huang X, Blakely D, Rovnaghi CR, Tran QT, Arevalo A, Anand KJ (2015) Inverse relationship between cardio-ankle vascular index and body mass index in healthy children. J Pediatr 167(2):361–365. e361
84. Shah AS, Dolan LM, Gao Z, Kimball TR, Urbina EM (2012) Racial differences in arterial stiffness among adolescents and young adults with type 2 diabetes. Pediatr Diabetes 13(2):170–175
85. Steyn K, de Wet T, Richter L, Cameron N, Levitt NS, Morrell C (2000) Cardiovascular disease risk factors in 5-year-old urban South African children—the Birth to Ten Study. S Afr Med J 90(7):719–726
86. Thomas C, Nightingale CM, Donin AS, Rudnicka AR, Owen CG, Cook DG, Whincup PH (2012) Ethnic and socioeconomic influences on childhood blood pressure: the Child Heart and Health Study in England. J Hypertens 30(11):2090–2097
87. Thurston RC, Matthews KA (2009) Racial and socioeconomic disparities in arterial stiffness and intima media thickness among adolescents. Soc Sci Med 68(5):807–813
88. Zaniqueli D, Alvim RO, Luiz SG, Oliosa PR, de Sa CR, Mill JG (2017) Ethnicity and arterial stiffness in children and adolescents from a Brazilian population. J Hypertens 35(11):2257–2261. https://doi.org/10.1097/HJH.0000000000001444
89. Schutte AE, Kruger R, Gafane-Matemane LF, Breet Y, Strauss-Kruger M, Cruickshank JK (2020) Ethnicity and arterial stiffness. Arterioscler Thromb Vasc Biol 40(5):1044–1054. https://doi.org/10.1161/ATVBAHA.120.313133
90. Shah AS, Wadwa RP, Dabelea D, Hamman RF, D'Agostino R Jr, Marcovina S, Daniels SR, Dolan LM, Fino NF, Urbina EM (2015) Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. Pediatr Diabetes 16(5):367–374. https://doi.org/10.1111/pedi.12279
91. Shah AS, El Ghormli L, Gidding SS, Bacha F, Nadeau KJ, Levitt Katz LE, Tryggestad JB, Leibel N, Hale DE, Urbina EM (2018) Prevalence of arterial stiffness in adolescents with type 2 diabetes in the TODAY cohort: Relationships to glycemic control and other risk factors. J Diabetes Complicat 32(8):740–745. https://doi.org/10.1016/j.jdiacomp.2018.05.013
92. Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, Chen W, Srinivasan SR, Daniels SR, Kahonen M, Laitinen T, Taittonen L, Berenson GS, Viikari JS, Raitakari OT (2010) Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation 122(24):2514–2520. https://doi.org/10.1161/CIRCULATIONAHA.110.966465
93. Litwin M, Feber J, Ruzicka M (2016) Vascular aging: lessons from pediatric hypertension. Can J Cardiol 32(5):642–649. https://doi.org/10.1016/j.cjca.2016.02.064
94. Breton CV, Wang X, Mack WJ, Berhane K, Lopez M, Islam TS, Feng M, Hodis HN, Kunzli N, Avol E (2011) Carotid artery intima-media thickness in college students: race/ethnicity matters. Atherosclerosis 217(2):441–446. https://doi.org/10.1016/j.atherosclerosis.2011.05.022
95. Chowdhury SM, Henshaw MH, Friedman B, Saul JP, Shirali GS, Carter J, Levitan BM, Hulsey T (2014) Lean body mass may explain apparent racial differences in carotid intima-media thickness in obese children. J Am Soc Echocardiogr 27(5):561–567. https://doi.org/10.1016/j.echo.2014.01.007
96. Toledo-Corral CM, Myers SJ, Li Y, Hodis HN, Goran MI, Weigensberg MJ (2013) Blunted nocturnal cortisol rise is

associated with higher carotid artery intima-media thickness (CIMT) in overweight African American and Latino youth. Psychoneuroendocrinology 38(9):1658–1667. https://doi.org/10.1016/j.psyneuen.2013.01.011

97. Whincup PH, Nightingale CM, Owen CG, Rapala A, Bhowruth DJ, Prescott MH, Ellins EA, Donin AS, Masi S, Rudnicka AR (2012) Ethnic differences in carotid intima-media thickness between UK children of black African-Caribbean and white European origin. Stroke 43(7):1747–1754
98. Li S, Chen W, Srinivasan SR, Tang R, Bond MG, Berenson GS (2007) Race (black-white) and gender divergences in the relationship of childhood cardiovascular risk factors to carotid artery intima-media thickness in adulthood: the Bogalusa Heart Study. Atherosclerosis 194(2):421–425. https://doi.org/10.1016/j.atherosclerosis.2006.08.026
99. Majonga ED, Norrish G, Rehman AM, Kranzer K, Mujuru HA, Nathoo K, Odland JO, Kaski JP, Ferrand RA (2018) Racial variation in echocardiographic reference ranges for left chamber dimensions in children and adolescents: a systematic review. Pediatr Cardiol 39(5):859–868. https://doi.org/10.1007/s00246-018-1873-0
100. Brady TM, Fivush B, Flynn JT, Parekh R (2008) Ability of blood pressure to predict left ventricular hypertrophy in children with primary hypertension. J Pediatr 152(1):73–78 e71. https://doi.org/10.1016/j.jpeds.2007.05.053
101. Allen MT, Matthews KA, Sherman FS (1997) Cardiovascular reactivity to stress and left ventricular mass in youth. Hypertension 30(4):782–787. https://doi.org/10.1161/01.hyp.30.4.782
102. Daniels SR, Kimball TR, Morrison JA, Khoury P, Meyer RA (1995) Indexing left ventricular mass to account for differences in body size in children and adolescents without cardiovascular disease. Am J Cardiol 76(10):699–701
103. Demola P, Crocamo A, Ceriello L, Botti A, Cremonini I, Pattoneri P, Corradi D, Visioli F, Goldoni M, Pela G (2019) Hemodynamic and ECG responses to stress test in early adolescent athletes explain ethnicity-related cardiac differences. Int J Cardiol 289:125–130. https://doi.org/10.1016/j.ijcard.2019.04.084
104. Hanevold C, Waller J, Daniels S, Portman R, Sorof J, International Pediatric Hypertension Association (2004) The effects of obesity, gender, and ethnic group on left ventricular hypertrophy and geometry in hypertensive children: a collaborative study of the International Pediatric Hypertension Association. Pediatrics 113(2):328–333. https://doi.org/10.1542/peds.113.2.328
105. Kapuku GK, Ge D, Vemulapalli S, Harshfield GA, Treiber FA, Snieder H (2008) Change of genetic determinants of left ventricular structure in adolescence: longitudinal evidence from the Georgia cardiovascular twin study. Am J Hypertens 21(7):799–805. https://doi.org/10.1038/ajh.2008.178
106. Lamers L, Ensing G, Pignatelli R, Goldberg C, Bezold L, Ayres N, Gajarski R (2005) A prospective assessment of myocardial contractility in young African Americans: does ethnicity impact the wall stress-heart rate-corrected velocity of circumferential fiber shortening relationship? J Am Soc Echocardiogr 18(7):743–748
107. Murro DG, Beavers M, Harshfield GA, Kapuku GK (2013) Aldosterone contributes to elevated left ventricular mass in black boys. Pediatr Nephrol 28(4):655–660. https://doi.org/10.1007/s00467-012-2367-6
108. Schieken RM, Schwartz PF, Goble MM (1998) Tracking of left ventricular mass in children: race and sex comparisons: the MCV Twin Study. Medical College of Virginia. Circulation 97(19):1901–1906. https://doi.org/10.1161/01.cir.97.19.1901
109. El-Heis S, Lillycrop KA, Burdge GC, Gluckman PD, Hanson MA, Godfrey KM (2018) Early-life nutrition, epigenetics and prevention of obesity. In: Epigenetics in Human Disease. Elsevier, pp 427-456
110. Lurbe E, Torro MI, Alvarez-Pitti J, Redon P, Redon J (2016) Central blood pressure and pulse wave amplification across the spectrum of peripheral blood pressure in overweight and obese youth. J Hypertens 34(7):1389–1395
111. Ahmad FS, Cai X, Kunkel K, Ricardo AC, Lash JP, Raj DS, He J, Anderson AH, Budoff MJ, Wright Nunes JA, Roy J, Wright JT Jr, Go AS, St John Sutton MG, Kusek JW, Isakova T, Wolf M, Keane MG, Investigators CRIC (2017) Racial/ethnic differences in left ventricular structure and function in chronic kidney disease: the chronic renal insufficiency cohort. Am J Hypertens 30(8):822–829. https://doi.org/10.1093/ajh/hpx058
112. O'Rourke MF, Hashimoto J (2007) Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 50(1):1–13. https://doi.org/10.1016/j.jacc.2006.12.050
113. Vlachopoulos C, O'Rourke M, Nichols WW (2011) McDonald's blood flow in arteries: theoretical, experimental and clinical principles. CRC press
114. Endemann DH, Schiffrin EL (2004) Endothelial dysfunction. J Am Soc Nephrol 15(8):1983–1992. https://doi.org/10.1097/01.ASN.0000132474.50966.DA
115. Tsikas D, Hanff E, Bollenbach A, Kruger R, Pham VV, Chobanyan-Jürgens K, Wedekind D, Arndt T, Jörns A, Berbée JF (2018) Results, meta-analysis and a first evaluation of U NOx R, the urinary nitrate-to-nitrite molar ratio, as a measure of nitrite reabsorption in experimental and clinical settings. Amino Acids 50(7):799–821
116. Craig A, Mels CMC, Kruger R (2018) Thiobarbituric acid-reactive substances relate to arterial stiffness and blood pressure in 6 to 8-year-old boys stratified by maternal risk. Free Radic Res 52(2):180–187. https://doi.org/10.1080/10715762.2017.1421314
117. Tauzin L, Rossi P, Giusano B, Gaudart J, Boussuges A, Fraisse A, Simeoni U (2006) Characteristics of arterial stiffness in very low birth weight premature infants. Pediatr Res 60(5):592–596. https://doi.org/10.1203/01.pdr.0000242264.68586.28
118. Sehgal A, Malikiwi A, Paul E, Tan K, Menahem S (2016) Systemic arterial stiffness in infants with bronchopulmonary dysplasia: potential cause of systemic hypertension. J Perinatol 36(7):564–569. https://doi.org/10.1038/jp.2016.10
119. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Vessby B, Basu S, Tracy R, Jacobs DR Jr (2005) Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. Circulation 111(15):1985–1991
120. Śladowska-Kozłowska J, Litwin M, Niemirska A, Płudowski P, Wierzbicka A, Skorupa E, Wawer ZT, Janas R (2012) Oxidative stress in hypertensive children before and after 1 year of antihypertensive therapy. Pediatr Nephrol 27(10):1943–1951
121. Túri S, Friedman A, Bereczki C, Papp F, Kovàcs J, Karg E, Németh I (2003) Oxidative stress in juvenile essential hypertension. J Hypertens 21(1):145–152
122. Daniels SR (2019) Understanding the global prevalence of hypertension in children and adolescents. JAMA Pediatr 173(12):1133–1134
123. Hinton TC, Adams ZH, Baker RP, Hope KA, Paton JF, Hart EC, Nightingale AK (2020) Investigation and treatment of high blood pressure in young people: too much medicine or appropriate risk reduction? Hypertension 75(1):16–22
124. Mynard JP, Goldsmith G, Springall G, Eastaugh L, Lane GK, Zannino D, Smolich JJ, Avolio A, Cheung MM (2020) Central aortic blood pressure estimation in children and adolescents: results of the KidCoreBP study. J Hypertens 38(5):821–828
125. Köchli S, Endes K, Steiner R, Engler L, Infanger D, Schmidt-Trucksäss A, Zahner L, Hanssen H (2019) Obesity, high blood pressure, and physical activity determine vascular phenotype in

young children: the EXAMIN YOUTH study. Hypertension 73(1):153–161
126. Laigaard PP, Larsen M, Hansen MH, Jeppesen J, Olsen EM, Skovgaard AM, Munch IC (2020) Retinal arteriolar wall-to-lumen ratios at 16–17 years in the Copenhagen Child Cohort 2000 Study. J Hypertens 38(4):731–736
127. Erasmus D, Mels CMC, Louw R, Lindeque JZ, Kruger R (2018) Urinary metabolites and their link with premature arterial stiffness in black boys: the ASOS study. Pulse 6(3):144–153. https://doi.org/10.1159/000492155
128. Benjamin EJ, Levy D (1999) Why is left ventricular hypertrophy so predictive of morbidity and mortality? Am J Med Sci 317(3):168–175
129. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP (1990) Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 322(22):1561–1566
130. Kavey RE (2013) Left ventricular hypertrophy in hypertensive children and adolescents: predictors and prevalence. Curr Hypertens Rep 15(5):453–457. https://doi.org/10.1007/s11906-013-0370-3
131. Zhang T, Li S, Bazzano L, He J, Whelton P, Chen W (2018) Trajectories of childhood blood pressure and adult left ventricular hypertrophy: the Bogalusa Heart Study. Hypertension 72(1):93–101. https://doi.org/10.1161/HYPERTENSIONAHA.118.10975
132. Dusan P, Tamara I, Goran V, Gordana ML, Amira PA (2015) Left ventricular mass and diastolic function in obese children and adolescents. Pediatr Nephrol 30(4):645–652. https://doi.org/10.1007/s00467-014-2992-3
133. Kupferman JC, Aronson Friedman L, Cox C, Flynn J, Furth S, Warady B, Mitsnefes M, CKiD Group (2014) BP control and left ventricular hypertrophy regression in children with CKD. J Am Soc Nephrol 25(1):167–174. https://doi.org/10.1681/ASN.2012121197
134. Litwin M, Wuhl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, Jobs K, Grenda R, Wawer ZT, Rajszys P, Troger J, Mehls O, Schaefer F (2005) Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. J Am Soc Nephrol 16(5):1494–1500. https://doi.org/10.1681/ASN.2004110932
135. Tawadrous H, Kamran H, Salciccioli L, Schoeneman MJ, Lazar J (2012) Evaluation of arterial structure and function in pediatric patients with end-stage renal disease on dialysis and after renal transplantation. Pediatr Transplant 16(5):480–485. https://doi.org/10.1111/j.1399-3046.2012.01721.x
136. Savant JD, Betoko A, Meyers KE, Mitsnefes M, Flynn JT, Townsend RR, Greenbaum LA, Dart A, Warady B, Furth SL (2017) Vascular stiffness in children with chronic kidney disease. Hypertension 69(5):863–869. https://doi.org/10.1161/HYPERTENSIONAHA.116.07653
137. Amann K, Ritz E, Wiest G, Klaus G, Mall G (1994) A role of parathyroid hormone for the activation of cardiac fibroblasts in uremia. J Am Soc Nephrol 4(10):1814–1819
138. Pecoits-Filho R, Lindholm B, Stenvinkel P (2002) The malnutrition, inflammation, and atherosclerosis (MIA) syndrome—the heart of the matter. Nephrol Dial Transplant 17(suppl_11):28–31
139. Mitsnefes MM, Betoko A, Schneider MF, Salusky IB, Wolf MS, Juppner H, Warady BA, Furth SL, Portale AA (2018) FGF23 and left ventricular hypertrophy in children with CKD. Clin J Am Soc Nephrol 13(1):45–52. https://doi.org/10.2215/CJN.02110217
140. Seeherunvong W, Abitbol CL, Chandar J, Rusconi P, Zilleruelo GE, Freundlich M (2012) Fibroblast growth factor 23 and left ventricular hypertrophy in children on dialysis. Pediatr Nephrol 27(11):2129–2136. https://doi.org/10.1007/s00467-012-2224-7
141. de Borst MH, Vervloet MG, ter Wee PM, Navis G (2011) Cross talk between the renin-angiotensin-aldosterone system and vitamin D-FGF-23-klotho in chronic kidney disease. J Am Soc Nephrol 22(9):1603–1609. https://doi.org/10.1681/ASN.2010121251
142. Andrukhova O, Slavic S, Smorodchenko A, Zeitz U, Shalhoub V, Lanske B, Pohl EE, Erben RG (2014) FGF23 regulates renal sodium handling and blood pressure. EMBO Mol Med 6(6):744–759. https://doi.org/10.1002/emmm.201303716
143. Haring R, Enserro D, Xanthakis V, Mitchell GF, Benjamin EJ, Hamburg NM, Sullivan L, Nauck M, Wallaschofski H, Vasan RS (2016) Plasma fibroblast growth factor 23: clinical correlates and association with cardiovascular disease and mortality in the Framingham Heart Study. J Am Heart Assoc 5(7):e003486. https://doi.org/10.1161/JAHA.116.003486
144. Akhabue E, Montag S, Reis JP, Pool LR, Mehta R, Yancy CW, Zhao L, Wolf M, Gutierrez OM, Carnethon MR, Isakova T (2018) FGF23 (Fibroblast Growth Factor-23) and incident hypertension in young and middle-aged adults: the CARDIA study. Hypertension 72(1):70–76. https://doi.org/10.1161/HYPERTENSIONAHA.118.11060
145. Gafane LF, Schutte R, Van Rooyen JM, Schutte AE (2016) Plasma renin and cardiovascular responses to the cold pressor test differ in black and white populations: the SABPA study. J Hum Hypertens 30(5):346–351. https://doi.org/10.1038/jhh.2015.88
146. Spence JD, Rayner BL (2018) Hypertension in blacks: individualized therapy based on renin/aldosterone phenotyping. Hypertension 72(2):263–269. https://doi.org/10.1161/HYPERTENSIONAHA.118.11064
147. Tu W, Eckert GJ, Hannon TS, Liu H, Pratt LM, Wagner MA, Dimeglio LA, Jung J, Pratt JH (2014) Racial differences in sensitivity of blood pressure to aldosterone. Hypertension 63(6):1212–1218. https://doi.org/10.1161/HYPERTENSIONAHA.113.02989
148. Higashi Y, Oshima T, Ozono R, Nakano Y, Matsuura H, Kambe M, Kajiyama G (1997) Nocturnal decline in blood pressure is attenuated by NaCl loading in salt-sensitive patients with essential hypertension: noninvasive 24-hour ambulatory blood pressure monitoring. Hypertension 30(2):163–167
149. Sagnella GA (2001) Why is plasma renin activity lower in populations of African origin? J Hum Hypertens 15(1):17–25. https://doi.org/10.1038/sj.jhh.1001127
150. Stewart AD, Millasseau SC, Dawes M, Kyd PA, Chambers JB, Ritter JM, Chowienczyk PJ (2006) Aldosterone and left ventricular hypertrophy in Afro-Caribbean subjects with low renin hypertension. Am J Hypertens 19(1):19–24. https://doi.org/10.1016/j.amjhyper.2005.06.035
151. Paquette K, Fernandes RO, Xie LF, Cloutier A, Fallaha C, Girard-Bock C, Mian MOR, Lukaszewski M-A, Mâsse B, El-Jalbout R (2018) Kidney size, renal function, Ang (angiotensin) peptides, and blood pressure in young adults born preterm: the HAPI study. Hypertension 72(4):918–928
152. Martinez-Aguayo AG, Campino C, Rodriguez-Fernandez M, Poggi H, D'apremont I, Moore R, Garcia H, Solari S, Allende F, Peredo S (2020) Urinary sodium-to-potassium ratio and plasma renin and aldosterone concentrations in normotensive children: implications for the interpretation of results. J Hypertens 38(4):671–678
153. Yu MC, Yu MS, Yu MK, Lee F, Huang WH (2011) Acute reversible changes of brachial-ankle pulse wave velocity in children with acute poststreptococcal glomerulonephritis. Pediatr Nephrol 26(2):233–239. https://doi.org/10.1007/s00467-010-1590-2
154. Sie MP, Mattace-Raso FU, Uitterlinden AG, Arp PP, Hofman A, Pols HA, Hoeks AP, Reneman RS, Asmar R, van Duijn CM, Witteman JC (2008) The interleukin-6-174 G/C promoter polymorphism and arterial stiffness; the Rotterdam Study. Vasc Health Risk Manag 4(4):863–869. https://doi.org/10.2147/vhrm.s1693
155. Viera N, Pedreanez A, Rincon J, Mosquera J (2007) Streptococcal exotoxin B increases interleukin-6, tumor necrosis factor alpha, interleukin-8 and transforming growth factor beta-1 in leukocytes.

Pediatr Nephrol 22(9):1273–1281. https://doi.org/10.1007/s00467-007-0501-7
156. Thomson PD (1997) Renal problems in black South African children. Pediatr Nephrol 11(4):508–512
157. Jindal AK, Tiewsoh K, Pilania RK (2018) A review of renal disease in children with HIV infection. Infect Dis (Lond) 50(1):1–12. https://doi.org/10.1080/23744235.2017.1371852
158. McCulloch MI, Ray PE (2008) Kidney disease in HIV-positive children. In: Seminars in nephrology, vol 6. Elsevier, pp 585-594
159. Van Buynder PG, Gaggin JA, Martin D, Pugsley D, Mathews JD (1992) Streptococcal infection and renal disease markers in Australian aboriginal children. Med J Aust 156(8):537–540
160. White AV, Hoy WE, McCredie DA (2001) Childhood post-streptococcal glomerulonephritis as a risk factor for chronic renal disease in later life. Med J Aust 174(10):492–496
161. Wong W, Morris MC, Zwi J (2009) Outcome of severe acute post-streptococcal glomerulonephritis in New Zealand children. Pediatr Nephrol 24(5):1021–1026. https://doi.org/10.1007/s00467-008-1086-5
162. Risch N, Burchard E, Ziv E, Tang H (2002) Categorization of humans in biomedical research: genes, race and disease. Genome Biol 3(7):comment2007. https://doi.org/10.1186/gb-2002-3-7-comment2007
163. Williams DR, Mohammed SA, Leavell J, Collins C (2010) Race, socioeconomic status, and health: complexities, ongoing challenges, and research opportunities. Ann N Y Acad Sci 1186:69–101. https://doi.org/10.1111/j.1749-6632.2009.05339.x
164. Sulla V, Zikhali P (2018) Overcoming poverty and inequality in South Africa : an assessment of drivers, constraints and opportunities, vol 1. World Bank Group, Washington, D.C.

Answers

1. e; 2. c; 3. c; 4. e; 5. e