Significance of High-Normal Blood Pressure for Children and Adolescents: Postprint

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Abstract

Currently, the definition of hypertension in nearly all pediatric hypertension guidelines issued by countries and organizations is based on the P95 of the blood pressure distribution in healthy children and adolescents. However, substantial data have demonstrated that target organ damage associated with hypertension can be identified at levels classified as high-normal blood pressure according to current guidelines. This review summarizes the blood pressure classification for children and adolescents across different countries, the prevalence of hypertension and high-normal blood pressure, the rate of progression from high-normal blood pressure to hypertension, and the target organ damage of hypertension at high-normal blood pressure levels. We contend that pediatricians should place greater emphasis on high-normal blood pressure, and that future efforts should focus on refining the definitions of high-normal blood pressure and hypertension, as well as investigating the potential roles of pharmacological treatment and lifestyle modifications in the development of hypertension among adolescents with high-normal blood pressure.

Full Text

Significance of High Normal Blood Pressure in Children and Adolescents

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Abstract

Currently, the definition of hypertension in nearly all pediatric hypertension guidelines issued by countries and organizations is based on the 95th percentile (P95) of blood pressure distribution in healthy children and adolescents. However, substantial data demonstrate that target organ damage from hypertension can be confirmed at levels considered high-normal blood pressure by current guidelines. This review summarizes blood pressure classification systems for children and adolescents across different countries, the prevalence of hypertension and high-normal blood pressure, the rate of progression from high-normal blood pressure to hypertension, and target organ damage occurring at high-normal blood pressure levels. We argue that pediatricians should pay greater attention to high-normal blood pressure, and future efforts should focus on refining the definitions of high-normal blood pressure and hypertension and exploring the potential roles of pharmacological treatment and lifestyle modifications in preventing hypertension development among adolescents with high-normal blood pressure.

Keywords: high-normal blood pressure; hypertension; children and adolescents; target organ

Introduction

Hypertension in children represents a considerable public health challenge worldwide, with observed increases in prevalence over the past two decades. Defining pediatric hypertension and assessing its prevalence present inherent challenges because blood pressure naturally rises with age and height. Since cardiovascular disease incidence is extremely low in children and adolescents, it is impossible to link blood pressure to events such as heart failure, renal failure, stroke, or death decades later, making it unfeasible to establish a specific blood pressure cutoff that increases cardiovascular risk in adulthood.

Our review of pediatric blood pressure guidelines from various countries and organizations reveals that nearly all are based on percentile methods derived from healthy children and adolescents, defining high-normal blood pressure and hypertension as blood pressure values between P90–P95 and ≥P95, respectively, corresponding to gender, age, and height levels. Some guidelines refer to high-normal blood pressure as "prehypertension" or "elevated blood pressure" ; for

clarity, this review uniformly uses the term "high-normal blood pressure" [1-4]. Evidence of target organ damage and high progression rates to hypertension from high-normal blood pressure suggests that blood pressure values beginning at P90 warrant clinical attention.

Blood Pressure Classification Systems

China According to the Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revision), building upon the 2010 Chinese pediatric blood pressure reference standards, the guidelines incorporate height' s influence on blood pressure to establish reference standards for Chinese children and adolescents aged 3–17 years based on age, gender, and height percentiles. Blood pressure levels are determined using P50, P90, P95, and P99 values corresponding to different height levels for each age group. Specific blood pressure classifications are shown in .

United States The 2017 American Academy of Pediatrics (AAP) Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents updated the 2004 Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. The guideline uses the term "elevated blood pressure" instead of "prehypertension" and analyzes blood pressure levels using P50, P90, P95, and P99 values corresponding to gender, age, and height levels. Notably, the guideline created new standardized blood pressure tables based on children and adolescents with normal body mass index (BMI $<$ 85th percentile), excluding data from overweight or obese individuals, as overweight and obesity are strongly associated with elevated blood pressure and hypertension, and their inclusion would bias the reference tables. Consequently, the new standardized tables contain lower blood pressure values than the Fourth Report. For children $ $13 years, the classification aligns with adult hypertension guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC), facilitating management of hypertensive adolescents. Specific classifications are shown in .

Europe The 2016 European Society of Hypertension (ESH) Guidelines for the Management of High Blood Pressure in Children and Adolescents analyze blood pressure levels using P50, P90, P95, and P99 values corresponding to gender, age, and height levels. Specific classifications are shown in . Due to diagnostic discrepancies, the European hypertension guidelines consensus states that for adolescents aged 16 years or older, hypertension should no longer be defined based on the 95th percentile of standardized blood pressure values but rather on adult hypertension thresholds. Using age-, gender-, and height-specific P95 values as hypertension definitions creates inconsistencies: a 16-year-old boy' s hypertension P95 value corresponds to a systolic pressure of 137–140 mmHg,

while a 16-year-old girl at the same height level has a hypertension P95 systolic value of 132 mmHg. Two years later, according to adult hypertension guidelines, these values would be classified as high-normal blood pressure, with even greater diagnostic differences in adolescents below the 95th height percentile.

Canada According to Canada' s 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children, pediatric hypertension diagnosis is based on gender-, age-, and height-specific blood pressure percentiles or simplified diagnostic criteria derived from the Bogalusa Heart Study. Hypertension is diagnosed when a child' s systolic or diastolic blood pressure reaches P95 or higher on at least three separate measurements, or when blood pressure exceeds 120/80 mmHg in children aged 6–11 years or 130/85 mmHg in children aged 12–17 years. Stage 1 hypertension is defined as P95 to P95+12 mmHg, and Stage 2 hypertension as >P95+12 mmHg.

Prevalence and Progression

Nearly all pediatric blood pressure guidelines worldwide define hypertension as blood pressure values consistently at or above P95 derived from healthy children and adolescents. The Bogalusa Heart Study [5] provided simplified definitions for pediatric prehypertension and hypertension in a cohort of 1,225 adults followed from childhood (mean follow-up 27.1 years). For children aged 6–11 years, prehypertension was defined as $110/70 \leq \text{BP} < 120/80$ mmHg and hypertension as $\text{BP} \geq 120/80$ mmHg. For adolescents aged 12–17 years, prehypertension was defined as $120/80 \leq \text{BP} < 130/85$ mmHg and hypertension as $\text{BP} \geq 130/85$ mmHg. The study found that these simplified blood pressure definitions predicted adult hypertension and subclinical cardiovascular disease (including carotid intima-media thickness, pulse wave velocity, and left ventricular hypertrophy) as effectively as percentile-based definitions. Compared to children with normal blood pressure, those with high-normal blood pressure and hypertension had higher risks of developing hypertension and subclinical cardiovascular disease in adulthood. Based on gender-, age-, and height-specific percentiles, 110/70 mmHg approximates P90 for 6-year-old children, while 120/80 mmHg approximates P90 for 12-year-old children, indicating that blood pressure values beginning at P90 merit attention.

A systematic review and meta-analysis of global pediatric hypertension prevalence [7] included 47 articles, reporting a combined hypertension prevalence of 4.00% (95% CI, 3.29%–4.78%) and high-normal blood pressure prevalence of 9.67% (95% CI, 7.26%–12.38%) in children under 19 years. Stage 1 hypertension prevalence was 4.00% (95% CI, 2.10%–6.48%) and Stage 2 hypertension 0.95% (95% CI, 0.48%–1.57%). Over the past two decades, pediatric hypertension prevalence has shown an upward trend, with a relative increase of 75–79%

between 2000–2015. Another meta-analysis [8] reported hypertension prevalence increasing from 8.5% (95% CI, 7.4–9.7) to 19.2% (95% CI, 16.9–21.7) by 2015.

Chen Xiaoli et al. [9] confirmed blood pressure tracking phenomena in a meta-analysis of 50 published cohort studies representing diverse populations. Their analysis demonstrated an overall mean tracking coefficient of 0.38 for systolic blood pressure and 0.28 for diastolic blood pressure, confirming that higher childhood blood pressure levels correlate with higher adult blood pressure levels. Furthermore, the Bogalusa Heart Study [10] showed that children with elevated blood pressure (≥P80) were 2–3 times more likely to develop hypertension in adulthood than those with normal blood pressure.

Falkner et al. [11] identified a cohort of adolescents in the National High Blood Pressure Database with repeated blood pressure measurements at 2- and 4-year intervals. Among adolescents initially in the high-normal blood pressure range, the estimated progression rate to hypertension was approximately 7% per year. Redwine et al. [12] studied 1,006 adolescent participants over a mean follow-up of 2.1 years, finding an overall hypertension development rate of 0.7% per year. The rate was 0.3% per year among adolescents with normal blood pressure at initial diagnosis versus 1.1% per year among those with high-normal blood pressure. Adolescents who remained in the high-normal range across three follow-up visits had a hypertension development rate of 6.6% per year.

Target Organ Damage

The Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revision) identifies target organ damage as a crucial component of hypertension diagnostic evaluation, emphasizing early detection of asymptomatic subclinical target organ damage. Hypertension-mediated target organ damage refers to structural and functional changes in corresponding organs at an early, potentially reversible stage, representing a critical intervention point [13,14]. Target organs include the brain, heart, kidneys, central and peripheral arteries, and eyes. Common assessments include carotid intima-media thickness (cIMT), pulse wave velocity (PWV), left ventricular hypertrophy (LVH), estimated glomerular filtration rate (eGFR), microalbuminuria, urinary albumin excretion or urinary albumin-to-creatinine ratio (UACR), fundoscopy, and neuroimaging. Recent studies have demonstrated that hypertension-related target organ changes can occur even at high-normal blood pressure levels in children and adolescents, challenging the current P95-based definition of pediatric hypertension.

Vascular System The vascular system has received increasing attention as a critical target organ in hypertension. Endothelial dysfunction is considered an early event in essential hypertension pathophysiology that may lead to subclinical target organ damage and atherosclerosis progression [15]. In hyperten-

sive patients, sustained elevation of microvascular pressure causes endothelial cell dysfunction, while endothelial cells produce multiple substances that maintain vascular homeostasis [16]. Flow-mediated dilation is the most commonly used technique to evaluate endothelial cell function, representing nitric oxide-mediated, endothelium-dependent vasodilation [17]. Impaired vasodilation is associated with increased susceptibility to atherosclerosis and cardiovascular disease, representing an early stage of subclinical target organ damage preceding clinical events [18]. Large artery stiffness is considered an important determinant of cardiovascular complications and a cardiovascular risk factor [19], with carotid-femoral pulse wave velocity (PWV) serving as the gold standard measure of arterial stiffness—the higher the aortic stiffness, the higher the PWV. cIMT is a recognized marker of subclinical atherosclerosis, easily measured by vascular ultrasound and representing a significant indicator of vascular injury caused by hypertension [20].

In a Swiss study of 1,171 children (mean age 7 years) [21], blood pressure was classified according to American Academy of Pediatrics guidelines: normal blood pressure <P90, high-normal blood pressure P90–P95, and hypertension ≥P95. Participants with high-normal blood pressure had higher PWV (4.44 [4.39–4.49] m/s) and those with hypertension had higher PWV (4.56 [4.51–4.60] m/s) compared to normotensive peers (4.30 [4.28–4.32] m/s), P<0.001. Another study [22] included 382 adolescents (aged 11–19 years; mean 15.6$\pm$1.8$years$)$stratifiedbysystolicbloodpressureintolow-risk(<P75, n=155)$, $moderate-risk(P80–P90, n=88)$, $andhigh-risk($ \$P90, n=139) groups. The study demonstrated a consistent increase in PWV with blood pressure, indicating that high-normal blood pressure, even before clinical hypertension diagnosis, is associated with vascular injury in adolescents.

Lurbe et al. [23] studied a cohort of children (mean age 12.6 years) with 501 participants, finding that PWV in those with blood pressure in the high-normal range did not differ statistically from hypertensive youth. Blood pressure was an independent predictor of PWV, with each one standard deviation increase in systolic blood pressure associated with a 0.329 m/s increase in PWV.

Urbina et al. [24] recruited 723 adolescents and young adults aged 10–23 years (29% with type 2 diabetes), classifying blood pressure using the Fourth Report and JNC 7 criteria into normal (n=53), high-normal (n=65), and hypertensive (n=127) groups. High-normal participants exhibited cIMT similar to hypertensive patients and showed reduced brachial artery dilation and accelerated PWV compared to normotensive individuals. In multivariate analysis, high-normal blood pressure remained an independent predictor of target organ damage (assessed by cIMT, PWV, and left ventricular mass) even after adjusting for cardiovascular risk factors including BMI.

An International Pediatric Cardiovascular Consortium study examined different blood pressure categories and subclinical atherosclerosis prediction, determining that childhood systolic blood pressure, mean arterial pressure, and pulse pressure were all significantly associated with increased adult cIMT [25]. The

authors calculated childhood systolic blood pressure cutoffs associated with increased cIMT across age groups, ranging from 105 mmHg in boys aged 3–5 years to 123 mmHg in boys aged 13–18 years—values below the P90 threshold in the 2017 American Academy of Pediatrics guideline. These findings again suggest that current blood pressure levels at P90 in children may warrant greater clinical attention.

Cardiac System Chronic increased left ventricular load in hypertensive patients can lead to LVH, impaired left ventricular diastolic function, left atrial enlargement, arrhythmias (particularly atrial fibrillation), and increased heart failure risk. LVH represents an adaptive response to hemodynamic overload from elevated peripheral blood pressure and is a predictor of cardiovascular events. Left ventricular diastolic dysfunction generally precedes LVH and represents the first manifestation of early cardiac damage. In hypertensive patients, left ventricular diastolic dysfunction results primarily from altered left ventricular morphology and function, impaired myocardial relaxation, and increased arterial stiffness, with hypertension-mediated arterial stiffness promoting the development and progression of diastolic dysfunction.

The Urbina et al. study [24] demonstrated that high-normal blood pressure may have detrimental cardiac effects in young people. The researchers examined cardiac structure and function in 723 adolescents and young adults (aged 10–23 years, mean age 19 years), finding that 10% had blood pressure in the high-normal range (P90–P95). High-normal participants had left ventricular mass intermediate between normotensive and hypertensive participants and showed diastolic dysfunction (lower mitral E/A ratio) compared to normotensive individuals.

Falkner et al. recruited 301 Black adolescents aged 13–18 years, stratified by normal blood pressure versus elevated blood pressure ($ $120/80 mmHg) and obesity status, undergoing standard echocardiography. They found a stepwise increase in left ventricular mass, with the lowest mass in those with normal blood pressure and BMI and the highest in those with elevated blood pressure and BMI. Importantly, LVH was observed within the high-normal blood pressure range, with participants having systolic blood pressure in the P75–P90 range showing three times higher LVH risk than those with systolic blood pressure <P75.

Stabouli et al. [29] reported similar findings in a cohort of children aged 5–18 years evaluated for suspected hypertension, including 89 normotensive, 10 high-normal, and 25 hypertensive individuals. Left ventricular mass index increased sequentially, with final LVH prevalence in high-normal and hypertensive children (20% each) higher than in normotensive children (6.7%). Ambulatory blood pressure studies [30,31] also found that children and adolescents with ambulatory blood pressure in the P90 range exhibited LVH prevalence similar to those with sustained hypertension.

The SHIP-AHOY (Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth) project [32] recruited approximately 400 adolescents aged 11–18 years with blood pressure ranging from normal to Stage 1 hypertension to assess blood pressure-related target organ effects. Researchers calculated the sensitivity and specificity of different blood pressure levels for predicting LVH, finding that at systolic blood pressure P90, sensitivity and specificity reached optimal balance. While P95 provided greater specificity for LVH prediction, sensitivity decreased by nearly half compared to P90. They concluded that echocardiographic evaluation should begin at systolic blood pressure ≥P90 for optimal LVH detection.

A SHIP-AHOY-based study [33] also examined the relationship between cardiac function and blood pressure levels in adolescents, applying advanced echocardiographic analysis in 346 subjects (mean age 15 years). Compared to participants with lower blood pressure, those with systolic blood pressure ≥P90 showed significantly reduced systolic ejection fraction, global longitudinal strain, left ventricular fractional shortening, and diastolic function. These changes correlated linearly with systolic blood pressure levels without a specific threshold for functional abnormalities. All these subclinical markers of left ventricular dysfunction are associated with adverse cardiovascular outcomes in adults [34]. The fact that these abnormalities can be detected in adolescents with high-normal blood pressure raises questions about whether current definitions of hypertension in children and adolescents should be reevaluated.

Renal System Hypertension is the second leading cause of chronic kidney disease after diabetes, with higher blood pressure above ideal levels increasing the risk of end-stage renal disease. Numerous studies demonstrate that eGFR and proteinuria are important predictors of cardiovascular morbidity and mortality.

An Italian study examined renal function and urinary protein excretion in 186 children with high-normal blood pressure (mean age 10 years) defined according to the Fourth Report criteria. Compared to 120 normotensive children, those with high-normal blood pressure had lower creatinine clearance and estimated glomerular filtration rate and higher urinary protein excretion rates. A recent study of 306 South African children aged 6–9 years [37] classified blood pressure according to the 2017 American Academy of Pediatrics guideline, showing hypertension prevalence of 10.5% (32/306) and high-normal blood pressure prevalence of 42.8% (131/306). Even within the high-normal range, microalbuminuria (defined as urinary albumin/creatinine ratio 3–30 mg/mmol) was present, with a linear correlation between systolic blood pressure level and urinary albumin/creatinine ratio (R^2=0.003).

Leiba et al. [38] used data from 2.2 million Israeli military recruits to examine the relationship between adolescent blood pressure levels (ages 16–19 years) and future end-stage renal disease risk. They found that adolescents in the high-normal blood pressure range had higher odds of developing end-stage renal disease after a mean follow-up of approximately 17 years compared to normoten-

sive individuals, with even greater risk in those at Stage 1 hypertension levels and lowest risk at systolic blood pressure of 94 mmHg.

Cerebral System Hypertension is associated with cerebrovascular structural changes that may lead to cognitive alterations over time. Like the kidneys, hypertension' s impact on cognition tends to develop gradually, becoming more apparent in older individuals than in younger hypertensive patients. Transient ischemic attacks or stroke are common manifestations of hypertensive brain damage. Hypertension can cause cerebral microvascular disease, with early subclinical changes most sensitively detected by magnetic resonance imaging, appearing as lacunar infarcts, asymptomatic vascular lesions, and white matter hyperintensities. White matter hyperintensities are associated with cognitive decline, mood disorders, gait disturbances, and increased disability and mortality [39].

Lande et al. [40] studied a sample of 5,100 youth aged 6–16 years, finding that 217 individuals with systolic blood pressure ≥P90 (approximately half between P90–P95) performed worse on several cognitive assessments including digit span, block design, and mathematics compared to normotensive peers. Significantly reduced digit span test scores were independently associated with systolic blood pressure ≥P90, suggesting cognitive changes begin at levels below currently defined hypertension.

A longitudinal, observational cohort study conducted at 46 pediatric nephrology centers in North America [41] examined children with mild-to-moderate chronic kidney disease, finding that subjects with elevated systolic and diastolic blood pressure (>P90 based on age-, gender-, and height-specific standards) had worse performance IQ scores on the Wechsler Abbreviated Scale of Intelligence compared to normotensive subjects. Another longitudinal study [42] found that subjects with systolic blood pressure in the high-normal range performed significantly worse on spatial learning and memory tasks than those with lower systolic blood pressure. Additionally, subjects with parental hypertension history and systolic blood pressure in the high-normal range showed lower performance in verbal learning, indicating that neurocognitive test performance may decline even within the high-normal blood pressure range.

Retinal System Hypertensive retinopathy results from retinal vascular damage due to elevated blood pressure. Over recent decades, several studies have examined retinal vascular diameter as a microvascular biomarker of cardiovascular risk [43]. Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) can predict long-term cardiovascular outcomes in adults and are associated with increased stroke, hypertension, and adult cardiovascular mortality and morbidity [44,45].

In the aforementioned Swiss study of 1,171 children (mean age 7 years) [21], CRAE and CRVE diameters, PWV, BMI, blood pressure, and cardiorespiratory fitness were assessed. Children with high-normal blood pressure had nar-

rower CRAE diameter (202.5 [200.0–205.0] μm) and hypertensive children had narrower CRAE diameter (198.8 [196.7–201.0] μm) compared to normotensive children (203.7 [202.9–204.6] μm), P<0.001. Moreover, CRAE diameter showed very high similarity between high-normal and hypertensive ranges.

Conclusion

Currently, pediatric hypertension guidelines worldwide define hypertension as blood pressure values consistently at or above P95. High-normal blood pressure (P90–P95) represents a substantial proportion of children and adolescents, who have greater probability of developing hypertension compared to normotensive peers. Numerous studies demonstrate that hypertension-related target organ changes can occur at high-normal blood pressure levels, and hypertension-mediated target organ damage is crucial for risk stratification and prognosis in hypertensive patients. Therefore, current definitions of hypertension in children and adolescents may be set too high. To prevent progression to sustained hypertension and mitigate target organ damage, we should pay greater attention to blood pressure at P90 in children and adolescents. Additionally, the potential roles of pharmacological treatment and lifestyle modifications in preventing hypertension development among adolescents with high-normal blood pressure should be explored.

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Note: Figure translations are in progress. See original paper for figures.