Impact of the 2017 American Academy of Pediatrics' Clinical Practice Guideline on the Identification and Risk Stratification of Youth at Increased Cardiovascular Disease Risk

Tammy M. Brady, MD, PhD[1], Kathleen Altemose, MD, MHS[2], Elaine M. Urbina, MD, MS[3]

[1]Johns Hopkins University School of Medicine, Division of Pediatric Nephrology

[2]Penn State College of Medicine, Division of Pediatric Nephrology and Hypertension

[3]Cincinnati Children's Hospital Medical Center, Division of Cardiology

Abstract

The updated clinical practice guideline (CPG) published by the American Academy of Pediatrics in 2017 introduced significant changes to the diagnostic and evaluative approach towards children with elevated blood pressure. The goals of this review were to summarize the current evidence regarding the impact of the new CPG on the identification and risk stratification of children at increased cardiovascular disease risk. Universally, the new CPG definitions of abnormal blood pressure led to more children classified as having a hypertensive blood pressure when compared to alternative definitions. Youth who moved to a higher blood pressure stage with the CPG typically had worse cardiometabolic profiles and more co-morbidites. The association of CPG-defined hypertension and concurrent intermediate cardiovascular disease outcomes such as left ventricular hypertrophy and increased pulse wave velocity remains unclear; however, longitudinal data suggests an improved identification of those at greatest risk for adult cardiovascular disease with the CPG definitions. The majority of studies reviewed used blood pressure from one encounter, not replicate blood pressures from multiple visits, to define an abnormal or hypertensive blood pressure. Therefore, future studies investigating the prevalence of confirmed hypertension and the association between confirmed hypertension and outcomes are needed to optimally characterize the performance of the new CPG on identifying children at cardiovascular disease risk.

Keywords

cardiovascular disease; hypertension; blood pressure; left ventricular hypertrophy; risk factors; target organ damage; atherosclerosis

In 2017 the American Academy of Pediatrics (AAP) published an updated Clinical Practice Guideline (CPG) regarding the "Evaluation and Management of Elevated Blood Pressure and Hypertension in Children".[1] This guideline, encompassing 30 key action statements and 27 expert recommendations, was developed based on the comprehensive review of almost

Corresponding author: Tammy M. Brady MD, PhD, Johns Hopkins School of Medicine, The David M. Rubenstein Child Health Building, 200 North Wolfe Street, Room 3062, Baltimore, MD 21287, tbrady8@jhmi.edu Office: 410-955-2467, Fax: 410-614-3680.

15,000 articles published since the prevailing guideline at the time, the National Heart Lung and Blood Institute's "Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (4th Report),[2] had been published in January 2004. This new guideline included significant changes to the nomenclature, the normative blood pressure (BP) tables, and the diagnostic and evaluative approach towards children with elevated BP.

One of the more striking updates in the CPG was the revised approach to staging BP in children, including extensive changes to the normative BP tables. Whereas the 4th Report normative BP tables included data from over 60,000 healthy children in the United States (US) across the continuum of body size, the CPG normative tables were reconstructed after excluding data from children with overweight or obesity. This removal of ~12,000 children with body mass index (BMI) percentiles 85% led to an overall downshifting of the 50th, 90th, 95th and the new 95th +12 mmHg category BPs across age, sex, and height stratum. In addition, the CPG simplified the diagnosis of abnormal BP for children 13 years of age and above by recommending static cutpoints for this group in lieu of the age-sex-height specific percentile based definitions recommended previously. These adolescent BP thresholds align with those in the latest American College of Cardiology (ACC)/American Heart Association (AHA) adult hypertension guidelines.[3] These new adult guidelines recommend thresholds that are notably lower than those endorsed by the Joint National Committee VII.[4] Specifically, for all individuals 13 years of age and older, elevated BP (formerly pre-hypertension) is now defined as 120-129/<80, Stage 1 hypertension is now defined as BP 130-139/80-89, and Stage 2 hypertension is defined as BP 140/90.[1,3]

The clinical impact of these changes varies by sex across the pediatric age range. As nicely detailed in Antolini et al's 2019 publication[5], for younger, shorter boys, the new CPG percentiles resulted in BP norms that were 1-4 mmHg lower than in the 4th report, but for school age boys the norms were 3-5 mmHg higher. Younger girls overall have BP norms that are 1-3 mmHg lower in the CPG, while those 7-12 years of age have norms that are 1-3 mmHg higher. Perhaps most striking is the impact on BP classification for adolescents. Starting at age 14 years, the 4th Report 95th percentile SBP was 130 mmHg for taller boys and the 95th percentile DBP was 80 mmHg or greater for all boys. So, for many males, the new 130/80 definition of hypertension would lead to more adolescents identified as hypertensive than those classified using 4th Report percentiles. Conversely, shorter male adolescents are more likely to be downclassified as normotensive because their 4th report percentile based SBP norms had been well below 130mmHg. This change to a static cutpoint is most impactful for adolescent females: almost all girls 13 years of age and above had 4th report SBP norms <130mmHg. The new CPG hypertension definitions will therefore lead to a lower prevalence of hypertension among teen girls.

This CPG also expanded its definition of left ventricular hypertrophy (LVH). LVH is now considered present when the left ventricular mass index (LVMI) exceeds either $51g/m^{2.7}$ for children 8 years of age and above or when left ventricular mass exceeds 115g/[body surface area (BSA)] for girls and 95g/BSA for boys. It was expected that these significant updates would lead to a change in the landscape of disease burden, the strength of association between hypertension and co-morbid cardiovascular disease (CVD) risk factors, and the

association of abnormal childhood BP with adult CVD. Therefore, the goals of this review were to summarize the current evidence regarding the impact of the new CPG on the identification and risk stratification of children at increased CVD risk.

Prevalence of Hypertension and Abnormal Blood Pressure

At the time of the CPG publication in 2017, the estimated prevalence of pediatric hypertension overall in the United States was 3.5%. This burden was more pronounced in high-risk populations such as children with overweight/obesity (3.9-25%), prematurity (7.3%), kidney disease (50-80%), and sleep disorders (3.6-14%).[1] Since then, several investigators have described the prevalence of hypertensive BP in various groups using the new CPG definitions (Table 1). It should be noted that no published study to date reports on the prevalence of confirmed hypertension, but instead describes the prevalence of abnormal BP. Most studies provide these estimates from measurements taken at one visit. Several provide estimates from measurements taken over multiple visits, but notably lack confirmation according to recommended guidelines. Adherence to the guideline recommended replicate measurements via manual auscultation over multiple visits with ultimate confirmation by 24-hour ambulatory blood pressure monitoring would likely lead to prevalence estimates 30-50% lower than the reported estimates, particularly those obtained from single visits.[6]

Sharma et al was one of the first to publish data regarding the impact of the new CPG definitions on abnormal BP prevalence.[7] In their large study that included data from over 15,000 healthy, low-risk children aged 5-18 years who participated in the US National Health and Nutrition Examination Surveys (NHANES), the new CPG thresholds and definitions led to a substantial increase in high BP prevalence (defined as a BP in the elevated, stage 1 *or* stage 2 hypertension range): 12.8% had high BP using 4th Report thresholds and percentiles while 15% had high BP using CPG thresholds and percentiles. In addition, almost 6% were classified as being in a higher stage of BP with the new CPG, with the overall prevalence of both Stage 1 and Stage 2 hypertensive BP being greater with CPG definitions.

Other investigators investigated for temporal trends in prevalence when applying the different thresholds by comparing the burden of abnormal BP among children 8-17 years of age in earlier and later NHANES cycles.[8] While this analysis did reveal an overall lower burden of elevated and hypertensive BP in the later cycles, consistent with the results in the Sharma at al study they also found an increase in hypertensive BP prevalence with use of the CPG definitions regardless of cycle era. A possible explanation for the greater proportion of youth with higher BP in earlier years is that the median age of children with a hypertensive BP was higher in the 2005-2008 cohort (12 years) than those in the 2013-2016 cohort (10-11 years). Notably, approximately 2.5% of youth in 2005-2008 and 1.5% of youth in 2013-2016 were reclassified as hypertensive when using the CPG.

Other studies in US children revealed similar increases in hypertension prevalence with the new CPG guidelines. In a secondary analysis of data collected for a study investigating the association of obesity and type 2 diabetes mellitus (T2DM) on cardiovascular measures,

Khoury et al found the proportion of hypertensive BPs increased from 8% with the 4th Report to 13% with the CPG (p=0.007).[9] One quarter of participants with a BP in the elevated range per the 4th Report were reclassified to the stage 1 hypertension range with the CPG; all of these reclassified children were 13 years of age or greater. Using data from 2600 pediatric well child visits extracted from the electronic medical record, Condren et al found that the prevalence of a hypertensive BP increased from 9.5% to 17.85% when using the CPG, with 12% of blood pressures overall being "up-classified" from normal to abnormal.[10] Contrary to results found by Khoury et al, children younger than 13 years of age were more likely to be reclassified to a higher BP category than children who were 13 years of age and older [Odds Ratio (OR) 1.6, 95% confidence interval (CI): 1.25, 2.05]. A possible explanation for this difference is related to how BP measures were obtained: the BPs in the Khoury study were all obtained according to a rigorous, standardized research protocol via manual auscultation whereas the BPs in the Condren study were obtained during routine clinical care via oscillometry.

In contrast to the above studies that evaluated the impact of the CPG on BP obtained at one visit, Bell et al studied the effect of the CPG definitions using replicate measurements done in a standardized fashion during three separate visits.[11] Of the 22,224 children who were predominantly between 11-15 years of age evaluated in this School Based Screening Program in the southern US, 2.3% had confirmed hypertension based on measurements obtained at 3 separate screening sessions when using CPG guidelines, compared to 2.7% when using the 4th Report guidelines. Age, sex and height were the greatest drivers of re-classification of "confirmed hypertension" with the CPG, with younger, shorter boys more likely to have BPs persistently in the hypertensive range across the three screening periods. It should be noted that all BP measurements in this study were obtained with an automated device; none of the elevations were confirmed via manual auscultation as recommended by the CPG. When considering only the BPs obtained during the initial screen, the difference in prevalence of elevated BP and hypertensive BP using the 4th Report vs. CPG was 14.7% vs. 16.3% and 7.8% vs. 6.9%, respectively. Notably, the increase in elevated BP prevalence with the CPG was due to down-classification of children from the Stage 1 hypertension range to this lower elevated BP range.

In a Bogalusa Heart Study cohort of 3940 children who were followed longitudinally into adulthood, the CPG reclassified 329 children into a higher BP stage: 2.7% were up-classified to elevated BP and 5.6% were up-classified to hypertension.[12] A small percentage (1%) were reclassified downward. Notably, the children who were classified upward had greater BMIs and more CVD risk factors overall. Finally, Kharbanda et al demonstrated that a greater number of children with elevated BP progressed to hypertension when using the CPG guidelines compared to the 4th Report guidelines (5.9% vs. 1.1%) and that progression was most common in older children and children with obesity.[13] In fact, among youth with obesity, progression to hypertension was almost twice as common than among those with overweight or normal weight.

Internationally, the new CPG recommendations perform similarly. In a large cohort (>47,000) of children 6-17 years of age who participated in national surveys in Europe and Asia, fewer children had an elevated BP with the CPG definition than with the 4th Report

(8.6% vs 14.9%), but this decreased prevalence was explained by a more than doubling of hypertensive BP prevalence for both stage 1 and stage 2 hypertension with the CPG: BP in the Stage 1 range increased from 6.6% to 14.5%, and BP in the Stage 2 range increased from 0.4% to 1.7%.[14] As with US studies, males, adolescents and youth with overweight/obesity were most likely to be up-classified with the CPG than their comparators. Similar reclassification percentages were observed in a large, population based cross-sectional study in China, with hypertensive BP increasing from 10.8% to 16.7% among children 6-12 years of age and from 6.3% to 7.9% among children 13-17 years of age when using the CPG (vs. the 4th Report).[15]

In a school based study of Thai children aged 8-13 years, hypertensive BP was determined based on the presence of persistently elevated replicate BPs on 2 separate occasions separated by 4-6 months.[16] In this cohort, 10.8% had hypertensive BP using CPG vs. 6.9% using the 4th Report definitions; however, it should be noted that these authors solely utilized percentile based definitions of hypertension for children and adolescents. Another group of investigators used a similar approach to BP classification when studying a cohort of Italian youth. Using the mean of triplicate automated BPs, the prevalence of elevated and hypertensive BP increased by 6% and 7% respectively in their study population when using the percentile based thresholds for all children (including those 13 years of age and older).[5] Notably, some children were reclassified into a lower BP category with the CPG: 1.4% moved to either normotensive or elevated BP stages. Among the 177 children in this cohort who were 13 years of age and older, 30% were reclassified when the static CPG cutpoints were employed: roughly 15% overall to a worse BP category and 15% to a better BP category.

CPG Performance in Risk Stratification

One of the main motivators for updating the normative data and diagnostic thresholds in the CPG was to improve risk stratification of children at risk for concurrent and future CVD. Some of the above studies and others explored the impact of the CPG updates on identifying children at greatest CVD risk.

Pediatric Obesity, Diabetes and Dyslipidemia

Consistent with the studies described previously, many of which included a substantial number of children with overweight and obesity, implementation of the CPG resulted in an increased proportion hypertensive BP among children with Type 1 Diabetes Mellitus (T1DM).[17] Specifically, among a group of European children 5-20 years of age with T1DM, the prevalence of hypertensive BP increased from 26.5% when using the 4th Report to 44.1% when using the CPG. This difference was maintained across all age groups, with the difference most pronounced among the older adolescents.

In addition to identifying more hypertensive BP among youth in at-risk groups, there is evidence that children and adolescents in the general population who are reclassified as having a hypertensive BP may also have more co-morbidities. Across studies in the US and international settings, youth who were reclassified as hypertensive by CPG were more likely to have a greater BMI,[7,12,16] dyslipidemia[7,12,14] and evidence of impaired glucose

tolerance[7,14] when compared to children who were classified as normotensive. For instance, youth who were reclassified as hypertensive by the CPG in NHANES were more likely to be overweight or obese (55.9% vs 35.0%, P<0.001), with higher lipid levels (% with high low density lipoprotein-c level: 12.2% vs 3.9%, p=0.002) and abnormal hemoglobin A1c values (% with high hemoglobin A1c: 3.4% vs. 0.6%, p=0.02) when compared to age-, sex-, and height matched normotensive controls.[7] Du et al reported a greater BMI (18 vs. 17 kg/m^2, p=0.028) and total cholesterol level (168 vs. 162 mg/dL, p=0.03) among children who were reclassified into a higher BP category with the CPG than propensity-score matched normotensive children.[12] An international cohort of pediatric patients had similar findings, with those reclassified into a higher BP category more likely to have increased BMI (20.4 vs 16.5 kg/m^2; p<0.001) and greater overweight/obesity (26.8% vs. 1.4%; p<0.001), dyslipidemia (all components, all p<0.001) and abnormal fasting glucose (87 vs. 85.7 mg/dL, p<0.001) compared to age-, sex-, height percentile-, and country-matched normotensive controls.[14] In fact, 6.3% of children reclassified to a higher BP category in this study had 3 or more CVD risk factors compared to 0.1% of the normotensive group (p<0.001).

Cardiac Target Organ Damage

Multiple investigators have sought to determine the ability of the CPG BP definitions to identify children at elevated CVD risk due to the presence of LVH. These studies have had mixed results.

Despite finding a greater prevalence of CPG-defined hypertensive BP (vs. 4th report-defined hypertensive BP) among children with an LVMI 38.6 g/m$^{2.7}$ (31% vs. 20%, p<0.001), US investigators did not find either definition of hypertensive BP to be significantly associated with the presence of LVH.[9] An Italian study came to a similar conclusion when basing the definition of abnormal BP solely on percentiles for all children[5]: the CPG did not perform any better than the 4th Report in identifying patients with LVH (defined as LVMI 95th percentile[18]).

Atherosclerosis/Vascular Markers

As seen with cardiac target organ damage in the US study mentioned above, a greater proportion of youth with elevated carotid intima media thickness (cIMT) and increased pulse wave velocity (PWV) had hypertensive BP when using CPG than when using 4th Report BP thresholds.[9] However, the odds of having one of these surrogate markers of atherosclerosis was no different among children with hypertensive BP when using either guideline thresholds.

The CPG definitions were also no better at discriminating children with abnormal cIMT or PWV than strategies using universal static BP cutpoints across childhood (hypertensive BP defined as 120/80 for children 6-12 years and as 130/80 for children 13 years),[19,20] or different reference BP values derived from the population-based German KiGGS study (Children and Adolescents Health Survey)[21] to classify youth.

CPG performance in identifying youth at increased risk for adult CVD

The overarching goal of pediatric hypertension care is to promote the CV health of youth and to prevent CV events and the resultant morbidity and mortality in adulthood. Several studies have attempted to investigate the impact of the updated guidelines on identifying children and adolescents at risk for CVD. Du et al specifically aimed to determine how well the CPG performed in identifying adult hypertension, metabolic syndrome and cardiac target organ damage in the form of LVH when compared to the 4th Report.[12] Using data from the Bogalusa Heart Study, which included 36-years of data since childhood, they determined that 7% and 11% of the cohort had pediatric hypertension per the 4th Report and CPG respectively. The relative risk for developing adult hypertension, metabolic syndrome or LVH was similar when using either definition of childhood prehypertension/elevated BP and childhood hypertension. However, the children who were reclassified into a higher stage of BP (either to elevated BP or stage 1 or 2 hypertension) with the CPG had greater LVMI as adults and had a greater prevalence of hypertension, metabolic syndrome and LVH as adults than their normotensive counterparts, even after adjusting for pediatric BMI and total cholesterol levels. Children who were reclassified downward did not have increased risk for any of the adult outcomes studied.

Another study using data from the Bogalusa Heart Study investigated whether static cutpoints to define pre-hypertension and hypertension in childhood could better predict intermediate outcomes such as adult hypertension, subclinical atherosclerosis (increased cIMT), arterial stiffness (increased PWV) and left ventricular hypertrophy (elevated LVMI) in adulthood than the percentile based definitions in the 4th Report.[22] This study, published prior to the CPG, used 110/70 and 120/80 as cutoffs for pre-hypertension and hypertension in children 6-11 years of age, respectively and 120/80 and 130/85 for pre-hypertension and hypertension cutoffs for children 12- 17 years of age, respectively. The risk for development of these intermediate outcomes in adulthood was similar when using either definition: the hazard ratio for any cardiovascular (CV) outcome was 3.21 (95% CI 2.07-4.96) with static cutpoints and 2.2 (95% CI 1.47-3.3) with 4th Report percentile based cutpoints. In fact, the net reclassification improvement analysis (2.17% improvement with static cutpoints, p=0.17) and the receiver operating characteristic curve analysis [area under the curve with static cutpoints 0.55 (0.53-0.58) vs. 0.54 (0.52-0.57) with 4th Report percentiles, p=0.115], both employed to determine if the simplified classification schema better identified intermediate outcomes, were non-significant and confirmed no significant difference between the two definitions.

Young adults have also seen a benefit to the lower hypertension thresholds endorsed by the ACC/AHA in terms of predicting their future CV risk. While not directly comparing the risk for CV events (such as coronary heart disease, heart failure, stroke, transient ischemic attack, and peripheral artery disease) when using these new adult BP thresholds to the older thresholds, Yano et al described a 1.75 greater hazard (95% CI 1.22-2.53) of future CV events with a Stage 1 BP in young adulthood (18-40 years) and a 3.49 (95% CI 2.42-5.05) greater hazard with a stage 2 BP when compared to normal BP (<120/80) even after adjusting for known confounders.[23]

Comparison with European Society of Hypertension guidelines

The European Society of Hypertension (ESH) published updated guidelines regarding the management of high BP in youth[24] one year before the AAP published the CPG. While there are several notable differences between the guidelines,[25] they both recommend static cutpoints for hypertension diagnosis during adolescence (starting at age 13 years in the US and at age 16 years in Europe; Table 2). However, the ESH guidelines continue to endorse the use of the 4th Report normative BP tables. They also recommend percentile based definitions of LVH (LVMI >95th percentile) and define elevated relative wall thickness (RWT) as >0.38. In contrast, the CPG not only recommends static left ventricular mass cutpoints for LVH but also recommends a higher threshold for defining elevated RWT (defined as >0.42).

As was found with the 4th Report, a greater proportion of children had a hypertensive BP when using the CPG definitions than when using the ESH definitions. Among a population of white, Italian children with overweight/obesity, not only was a greater proportion categorized as having a hypertensive BP with the CPG (38.4% vs. 30.7% with ESH)[26], but 11% of ESH-normotensive children were reclassified as having a hypertensive BP with the CPG.[27] And, as seen in the US studies, children reclassified as hypertensive were older with poorer cardiometabolic profiles (higher BMI, greater insulin resistance, more dyslipidemia, and greater measures of target organ damage) than those with persistently normal BP by CPG thresholds.[27] This difference in abnormal BP prevalence by CPG criteria also extended to children with BMI across the spectrum (healthy weight, overweight and obesity): the prevalence of elevated BP, stage 1 and stage 2 hypertensive BP using CPG definitions was 10.5, 9.1 and 1.5%, compared to 6.6, 6.0 and 0.6% when using ESH definitions.[28] Children ≥ 13 years were particularly prone to reclassification with the CPG. As an example, in the study of Italian youth with increased adiposity, there was a 43% increase in prevalence of hypertensive BP among adolescents compared to a more modest increase of 11% among children <13 years when using the CPG.[26]

Notably, each guideline performed similarly in regards to cardiac target organ damage. A similar proportion of children with hypertensive BP by ESH and CPG had LVH both when defined by LVMI-percentile criteria (61% for both) and when defined by static LVMI cutpoints (17% by ESH and 16% by CPG). They also had a similar ability to predict concentric LVH when defined using LVMI-percentile based criteria: ESH-hypertensive BP was associated with a 2.53 greater odds (95% CI: 1.43-4.47) of LVH and CPG-hypertensive BP was associated with a 2.95 greater odds (95% CI: 1.70-5.14) of LVH when compared to children with a normal BP. Interestingly, neither definition of hypertensive BP was associated with LVH when defined using the static left ventricular mass cutpoints endorsed by the CPG.[26]

24-hour Ambulatory Blood Pressure Monitoring

Ambulatory BP phenotype is based on the combination of a resting, clinic BP and the mean of repeated out-of-office measurements obtained by an ambulatory BP monitor. It follows that ambulatory BP phenotype is therefore influenced by the thresholds used in interpreting these clinic BP measurements. When clinic BP classification changes, ABPM interpretation

is affected. Unsurprisingly, significant differences in the prevalence of white coat hypertension (high clinic BP with normal ambulatory BP) and masked hypertension (normal clinic BP with ambulatory hypertension) have been described when using the CPG or the ESH guidelines for clinic BP interpretation. Lurbe et al found more white coat hypertension with the CPG definitions and more masked hypertension with ESH definitions. No differences were observed in sustained normotension (83.3% ESH and 81.0% CPG) or sustained hypertension (3.1 ESH and 3.9% CPG).[28] Recognizing that the CPG uses a lower static threshold to define hypertension in youth at a younger age than the ESH guidelines (130/80 at age 13 years vs 140/90 at age 16 years) these findings are not surprising. Another notable difference between ESH and CPG ABPM interpretation is the fact that the ESH guidelines recommend using the adult cutpoint of 135/85 when the sex-height-based ABPM percentile values exceed this threshold. The CPG follows the AHA recommendations[29], which support the use of percentile-based cutoffs for all youth; as a result, some taller children have higher thresholds than endorsed by the adult US ABPM guidelines. These differences suggest that more work is needed to identify the optimal ambulatory BP thresholds for youth.

Conclusions

The updated Clinical Practice Guideline by the American Academy of Pediatrics introduced several key changes regarding the approach to the diagnosis and evaluation of elevated BP in youth. Updating the normative BP database to be more "normal" through the exclusion of data from children with overweight and obesity and endorsing adult static cutpoints for hypertension diagnosis starting in adolescence has changed contemporary estimates regarding the burden of pediatric CVD. Specifically, these new CPG hypertension definitions have led to a global increase in hypertensive BP prevalence. In addition, studies published in the 3 years since publication of the CPG suggest the key action statements endorsed by the guideline allow for an improved ability to identify at-risk youth. Many studies showed that the children who were "up-classified" with the CPG – meaning, those who had BP measurements categorized into a higher BP stage when using the CPG definitions than when using another definition - had worse cardiometabolic profiles in childhood and greater CVD risk factors in adulthood than those who were not. These findings suggest the CPG staging schema may more optimally identify children at greatest risk.

While the research reviewed makes a compelling case for use of the CPG over other guidelines, one needs to be mindful of the fact that there was significant heterogeneity in the (1) study population (general vs. at increased risk; age range); (2) BP measurement technique (standardized research vs. typical clinical care; automated vs. manual; single vs. replicate); (3) BP categorization (as a "hypertensive" BP from one visit vs. as "hypertension" based on replicate measures over time); and (4) target organ damage definitions between studies. In fact, almost all studies reviewed (8 out of 11) used BP from one point in time to report changes in prevalence. This is important to keep in mind as hypertension is defined as the sustained elevation in BP when replicate BPs are obtained over several visits. Additionally, HTN should also only be diagnosed in children when elevations are confirmed with an auscultatory measurement and then later with 24-hour

ABPM. Of the studies reporting prevalence, only 6 used auscultatory measures. None of the longitudinal studies reviewed used auscultatory measures for confirmation. It therefore remains unknown what the prevalence of pediatric hypertension in the US and across the world will be with widespread adoption of the new CPG. However, based on the cross-sectional results above, an increase in prevalence is likely. Further, while not addressed in this review, the removal of the cumbersome age-, sex-, and height-based definitions starting in adolescence paves the way for even greater recognition of BP elevations. With pediatric studies showing improved recognition of BP elevations when the systolic BP is greater than 120 mmHg,[30,31] it is likely that the CPG-recommended static cutpoints in adolescence will enhance provider diagnosis of hypertension leading to downstream increased prevalence estimates.

What remains unclear is the ability of the new CPG to identify cardiac target organ damage or proxy measures of atherosclerosis. While the burden of hypertensive BP is greater among children with these markers, hypertensive BP by the CPG does not appear to better predict these outcomes than other definitions. A notable limitation of the studies reviewed is that they all explored the association of a hypertensive BP from one point in time with outcomes, not a hypertension diagnosis based on the sustained elevation of BP over several weeks to months or with ABPM confirmation. Future studies should investigate the association of confirmed HTN with these intermediate outcomes to better determine how well the CPG performs in this regard.

With ongoing results from the SHIP AHOY study in the US expected to provide more data regarding clinically meaningful diagnostic thresholds in children[32] and the International Childhood Cardiovascular Cohort working to provide more data regarding the long-term cardiovascular implications of abnormal BP in childhood,[33] it is likely that the landscape of pediatric cardiovascular health promotion will change even further in the coming years. While guidelines may change, regular screening of BP for abnormalities will remain a cornerstone of CVD prevention.

Acknowledgements:

Abbreviations:

ACC	American College of Cardiology
AHA	American Heart Association
AAP	American Academy of Pediatrics
BMI	body mass index
BP	blood pressure

BSA	body surface area
CI	confidence interval
cIMT	carotid intima media thickness
CPG	Clinical Practice Guidelines
CV	cardiovascular
CVD	cardiovascular disease
ESH	European Society of Hypertension
HTN	hypertension
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
NHANES	National Health and Nutrition Examination Surveys
OR	odds ratio
PWV	pulse wave velocity
RWT	relative wall thickness
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
US	United States

References:

1. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 2017;140.

2. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555–76. [PubMed: 15286277]

3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:e13–e115. [PubMed: 29133356]

4. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52. [PubMed: 14656957]

5. Antolini L, Giussani M, Orlando A, et al. Nomograms to identify elevated blood pressure values and left ventricular hypertrophy in a paediatric population: American Academy of Pediatrics Clinical Practice vs. Fourth Report/European Society of Hypertension Guidelines. J Hypertens 2019;37:1213–22. [PubMed: 31022109]

6. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics 2004;113:475–82. [PubMed: 14993537]

7. Sharma AK, Metzger DL, Rodd CJ. Prevalence and Severity of High Blood Pressure Among Children Based on the 2017 American Academy of Pediatrics Guidelines. JAMA Pediatr 2018;172:557–65. [PubMed: 29710187]

8. Al Kibria GM, Swasey K, Sharmeen A, Day B. Estimated Change in Prevalence and Trends of Childhood Blood Pressure Levels in the United States After Application of the 2017 AAP Guideline. Prev Chronic Dis 2019;16:E12. [PubMed: 30702999]

9. Khoury M, Khoury PR, Dolan LM, Kimball TR, Urbina EM. Clinical Implications of the Revised AAP Pediatric Hypertension Guidelines. Pediatrics 2018;142.

10. Condren M, Carter J, Mushtaq N, et al. The impact of new guidelines on the prevalence of hypertension in children: A cross-sectional evaluation. J Clin Hypertens (Greenwich) 2019;21:510–5. [PubMed: 30847994]

11. Bell CS, Samuel JP, Samuels JA. Prevalence of Hypertension in Children. Hypertension 2019;73:148–52. [PubMed: 30571555]

12. Du T, Fernandez C, Barshop R, Chen W, Urbina EM, Bazzano LA. 2017 Pediatric Hypertension Guidelines Improve Prediction of Adult Cardiovascular Outcomes. Hypertension 2019;73:1217–23. [PubMed: 31006329]

13. Kharbanda EO, Asche SE, Dehmer SP, et al. Impact of updated pediatric hypertension guidelines on progression from elevated blood pressure to hypertension in a community-based primary care population. J Clin Hypertens (Greenwich) 2019;21:560–5. [PubMed: 30980615]

14. Yang L, Kelishadi R, Hong YM, et al. Impact of the 2017 American Academy of Pediatrics Guideline on Hypertension Prevalence Compared With the Fourth Report in an International Cohort. Hypertension 2019;74:1343–8. [PubMed: 31630571]

15. Dong Y, Song Y, Zou Z, Ma J, Dong B, Prochaska JJ. Updates to pediatric hypertension guidelines: influence on classification of high blood pressure in children and adolescents. J Hypertens 2019;37:297–306. [PubMed: 30044314]

16. Pirojsakul K, Paksi W, Sirijunpen S, Nuntnarumit P. Increased prevalence of hypertensive-level blood pressure using the American Academy of Pediatrics 2017 guidelines: a cross-sectional study in a primary school in Thailand. Paediatr Int Child Health 2019;39:279–84. [PubMed: 31038015]

17. Dost A, Bechtold S, Fink K, et al. 2017 American Academy of Pediatrics Clinical Practice Guideline: Impact on Prevalence of Arterial Hypertension in Children and Adolescents With Type 1 Diabetes. Diabetes Care 2020;43:1311–8.

18. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 2009;22:709–14. [PubMed: 19423289]

19. Zhao M, Mill JG, Yan WL, et al. Static cut-points of hypertension and increased arterial stiffness in children and adolescents: The International Childhood Vascular Function Evaluation Consortium. J Clin Hypertens (Greenwich) 2019;21:1335–42. [PubMed: 31389662]

20. Yang L, Whincup PH, López-Bermejo A, et al. Use of Static Cutoffs of Hypertension to Determine High cIMT in Children and Adolescents: An International Collaboration Study. Can J Cardiol 2020;36:1467–73. [PubMed: 32492399]

21. Köchli S, Endes K, Steiner R, et al. Obesity, High Blood Pressure, and Physical Activity Determine Vascular Phenotype in Young Children. Hypertension 2019;73:153–61. [PubMed: 30571553]

22. Xi B, Zhang T, Li S, et al. Can Pediatric Hypertension Criteria Be Simplified? A Prediction Analysis of Subclinical Cardiovascular Outcomes From the Bogalusa Heart Study. Hypertension 2017;69:691–6. [PubMed: 28223474]

23. Yano Y, Reis JP, Colangelo LA, et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. JAMA 2018;320:1774–82. [PubMed: 30398601]

24. Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016;34:1887–920. [PubMed: 27467768]

25. Brady TM, Stefani-Glücksberg A, Simonetti GD. Management of high blood pressure in children: similarities and differences between US and European guidelines. Pediatr Nephrol 2018;34:405–12. [PubMed: 29594504]

26. Di Bonito P, Valerio G, Pacifico L, et al. Impact of the 2017 Blood Pressure Guidelines by the American Academy of Pediatrics in overweight/obese youth. J Hypertens 2019;37:732–8. [PubMed: 30817454]

27. Bonito PD, Licenziati MR, Baroni MG, et al. The American Academy of Pediatrics hypertension guidelines identify obese youth at high cardiovascular risk among individuals non-hypertensive by the European Society of Hypertension guidelines. Eur J Prev Cardiol 2019;27:8–15. [PubMed: 31387383]

28. Lurbe E, Torro I, Alvarez J, et al. Impact of ESH and AAP hypertension guidelines for children and adolescents on office and ambulatory blood pressure-based classifications. J Hypertens 2019;37:2414–21. [PubMed: 31688292]

29. Flynn JT, Daniels SR, Hayman LL, et al. Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association. Hypertension 2014;63:1116–35. [PubMed: 24591341]

30. Brady TM, Neu AM, Miller ER 3rd, Appel LJ, Siberry GK, Solomon BS. Real-time electronic medical record alerts increase high blood pressure recognition in children. Clin Pediatr (Phila) 2015;54:667–75. [PubMed: 25416626]

31. Brady TM, Solomon BS, Neu AM, Siberry GK, Parekh RS. Patient-, provider-, and clinic-level predictors of unrecognized elevated blood pressure in children. Pediatrics 2010;125:e1286–93. [PubMed: 20439598]

32. Mendizabal B, Urbina EM, Becker R, et al. SHIP-AHOY (Study of High Blood Pressure in Pediatrics: Adult Hypertension Onset in Youth). Hypertension 2018;72:625–31. [PubMed: 29987102]

33. Sinaiko AR, Jacobs DR, Woo JG, et al. The International Childhood Cardiovascular Cohort (i3C) consortium outcomes study of childhood cardiovascular risk factors and adult cardiovascular morbidity and mortality: Design and recruitment. Contemp Clin Trials 2018;69:55–64. [PubMed: 29684544]

Table 1.

Changes in hypertensive blood pressure prevalence when applying the American Academy of Pediatrics Clinical Practice Guideline Definitions

Study Location	Study Authors	Study design and Participant Pool	Population	Overweight and/or Obesity Prevalence	Blood Pressure determination and staging	4th report Pre-HTN	CPG Elevated BP	4th report HTN	CPG HTN	Agreement between categories
US Studies	Sharma et al, 2018	Cross-sectional 8 NHANES cycles	5–18 years NHANES cycles A to H (1999-2014) N= 15,647	Obesity: 10%	Auscultation Standardized research measurements Mean of last 2-3 BPs One visit	9.1 %	8.7%	Stage 1: 2.6% Stage 2: 0.06%	Stage 1: 5.1% Stage 2: 0.4%	κ = 0.73 (95% CI 0.71-0.75 P< .001)
	Al Kibria, et al, 2019	Cross-sectional 2 groups of NHANES cycles, considered separately	8 to 17 years NHANES: 2005-2008 cycles N=3,633 2013-2016 cycles N=3,471	Overweight/Obesity: 41% (2005-2008) 42% (2013-2016)	Auscultation Standardized research measurements Mean of first 1-3 BPs One visit	2005-2008: 10.3% 2013-2016: 7.5%	2005-2008: 9.5% 2013-2016: 7.1%	2005-2008: 3.1% 2013-2016: 1.9%	2005-2008: 5.7% 2013-2016: 3.5%	
	Khoury et al, 2018	Cross-sectional Secondary analysis of data from established research cohort (ref)	10-18 years N=364	Obesity: 47%	Auscultation Standardized research measurements Mean of 3 BPs One visit	21%	16%	8%	13%	
	Condren et al, 2018	Cross-sectional Electronic health record data	3-18 years 73% < 13 yrs Well child visits 4 primary care clinics Oklahoma July-December 2017 N=2600	Overweight/obesity: 44%	Automated Clinical care measurement One BP One visit	16.1%	16.3%	9.5%	17.9%	κ = 0.71 (95% CI 0.69, 0.7 Bowker' test of symmetr p<0.000)
	Bell et al., 2019	Cross-sectional with repeated measures School-based screening study	10 to 17 years Majority 11-15 yrs Houston, TX 2000-2017 N= 22,224	Overweight/obesity: 37%	Automated - ABPM device - Office device If BP normal: one BP, one visit If BP elevated: mean of 2nd and 3rd BP, 2-3 visits Standardized research measurements Used BPs from up to 3 visits to classify hypertension stage	Based on mean BP at initial screen: 14.7%	Based on mean BP at initial screen: 16.3%	Based on mean BP at initial screen: 7.8% Based on mean BPs at 3 screenings: 2.7%	Based on mean BP at initial screen: 6.9% Based on mean BPs at 3 screenings: 2.3%	κ = 0.86 Overall agreemen = 93.4%
	Du et al, 2019	Cross-sectional Bogalusa Heart Study	3-18 years 1973-2016 N=3940	Not reported	Auscultation Standardized research measurements Mean of 6 BPs Highest mean BP from any one study visit	19%	17%	6.5%	11%	κ = 0.83 (95% CI 0.82-0.85

Study Location	Study Authors	Study design and Participant Pool	Population	Overweight and/or Obesity Prevalence	Blood Pressure determination and staging	4th report Pre-HTN	CPG Elevated BP	4th report HTN	CPG HTN	Agreement between categories
	Kharbanda et al, 2019	Retrospective cohort study Electronic health record data	10-17 years PCP visits 21 PCP sites in upper Midwest 4/15/14-4/14/16 N= 2025 with pre-HTN/ elevated BP at study entry and with 3 subsequent BPs available over 2 years	Overweight/ obesity: 48.9%	Automated Standardized clinical care measurements Mean of 1-2 BPs/visit 60% with only 1 BP per visit 3 visits	Had pre-HTN at study entry	Had elevated BP at study entry	Overall: 1.1% Among youth with obesity: 1.9%	Overall: 5.9% Among youth with obesity: 10.2%	Not reported
International Studies	Yang, et al, 2019	Cross-sectional 6 national surveys	6-17 years 6 countries: China, India, Iran, Korea, Poland, Tunisia N = 47,200	Overweight/ obesity: 19.9%	Auscultation Standardized research measurements Mean of last 2 BPs One visit	14.9%	8.6%	7%	16.2%	Not reported
	Pirojsakul, et al, 2019	Cross-sectional with repeated measures School-based screening study	8-13 years Bangkok, Thailand August 2017 to February 2018 N=536	Overweight/ obesity: 36%	Automated Standardized research measurements Mean of last 2 BPs 2 visits	Not reported	Not reported	6.9%	10.8%	Not reported
	Antolini, et al, 2019	Cross-sectional Patients from an obesity and elevated BP clinic	4-17 years - 81% < 13 yrs Milan, Italy January 2009 to August 2018 N=951	Overweight/ obesity: 76%	Automated Standardized measurements Mean of 3 BPs One visit Hypertensive BP for the entire cohort was determined using percentile based thresholds for all, using separate normograms for 4th report and CPG estimates. Reclassification of children 13 years of age and older when using static cutpoints was determined separately	16%	Percentile based cutpoints for all ages (N=951): 14.8% Static-cutpoints for 13 years only (N=177): 38%	34.9%	Percentile based cutpoints for all ages (N=951): 40.9% Static-cutpoints for 13 years only (n=177): 33.9%	Not reported
	Dong et al, 2019	Cross sectional Baseline data from RCT	6-17 years 7 provinces in China 2013 N = 50,336	Overweight/ obesity: 22.4%	Auscultation Standardized research measurements Mean of 3 BPs One visit	Not reported	Not reported	Children 6-12 years: 10.8% Adolescents 13-17 years: 6.3%	Children 6-12 years: 16.7% Adolescents 13-17 years: 7.9%	

Abbreviations: BP – blood pressure; HTN – hypertension; NHANES – National Health and Nutrition Examination Study; PCP – primary care provider; RCT – randomized clinical trial

Table 2.

Differences in Blood Pressure Categorization and Definition of Cardiac Target Organ Damage by Different Pediatric Guidelines

Cardiovascular Disease Risk Factor	Fourth Report (2004)	AAP Clinical Practice Guideline (2017)		ESH Guidelines (2016)	
	All Children	<13 years	13 years	<16 years	16 years
Normotension	<90th %ile	<90th %ile [*]	<120/80	<90th %ile	<130/85
Prehypertension/ Elevated Blood Pressure	90th %ile [*] to <95th %ile	90th %ile [*] to <95th %ile	120-129/<80	90th %ile [*] to <95th %ile	130-139/85-90
Stage 1 Hypertension	95th to 99th + 5 mmHg	95th to < 95th + 12 mmHg [¥]	130-139/80-89	95th to 99th + 5 mmHg	140-159/90-99
Stage 2 Hypertension	>99th + 5 mmHg	95th + 12 mmHg [€]	140/90	>99th + 5 mmHg	160-179/100-109
Left Ventricular Hypertrophy	LVMI > 51 g/m$^{2.7}$ [£]	LVMI > 51 g/m$^{2.7}$ [β] or LVM > 115 g/BSA for boys and LV mass >95 g/BSA for girls		LVMI > age-sex specific 95th %ile	
Increased Relative Wall Thickness	Not defined	>0.42		>0.38	

[*] Or 120/80, whichever lower;

[¥] Or 130/80-139-89, whichever lower;

[€] Or 140/90, whichever lower

[£] "conservative cutpoint"

[β] For children >8 years

AAP: American Academy of Pediatrics; BSA: body surface area; ESH: European Society of Hypertension; LVM: left ventricular mass; LVMI: left ventricular mass index

Fourth Report: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114:555-76