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Static cut-points of hypertension and increased arterial stiffness in children and adolescents: The International Childhood Vascular Function Evaluation Consortium

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Abstract

Pediatric elevated blood pressure (BP) and hypertension are usually defined using traditional BP tables at the 90th and 95th percentiles, respectively, based on sex, age, and height, which are cumbersome to use in clinical practice. The authors aimed to assess the performance of the static cut-points (120/80 mm Hg and 130/80 mm Hg for defining elevated BP and hypertension for adolescents, respectively; and 110/70 mm Hg and 120/80 mm Hg for children, respectively) in predicting increased

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arterial stiffness. Using data from five population-based cross-sectional studies conducted in Brazil, China, Korea, and New Zealand, a total of 2546 children and adolescents aged 6-17 years were included. Increased arterial stiffness was defined as pulse wave velocity ≥sex-specific, age-specific, and study population-specific 90th percentile. Compared to youth with normal BP, those with hypertension defined using the 2017 American Academy of Pediatrics guideline (hereafter referred to as "percentile-based cut-points") and the static cut-points were at similar risk of increased arterial stiffness, with odds ratios and 95% confidence intervals of 2.35 (1.74-3.17) and 3.07 (2.20-4.28), respectively. Area under the receiver operating characteristic curve and net reclassification improvement methods confirmed the similar performance of static cut-points and percentile-based cut-points (*P* for difference > .05). In conclusion, the static cut-points performed similarly well when compared with the percentile-based cut-points in predicting childhood increased arterial stiffness. Use of static cut-points to define hypertension in childhood might simplify identification of children with abnormal BP in clinical practice.

1 | INTRODUCTION

Currently, pediatric elevated BP and hypertension are usually defined based on the statistical distribution of BP values in generally healthy pediatric populations.[1-3] In other words, they are defined by systolic BP (SBP)/diastolic BP (DBP) at or above the 90th and 95th percentiles of the reference distribution for sex, age, and height. In 2004, the US National High Blood Pressure Education Program Working Group released the Fourth Report on the diagnosis and treatment of pediatric hypertension.[1] In 2017, the American Academic of Pediatrics (AAP) updated its clinical practice guideline for screening and management of pediatric hypertension based on the same data but excluding overweight or obese children.[2] In 2016, the International Child Blood Pressure References Establishment Consortium established the international references for pediatric hypertension using data from seven countries.[3] However, all these percentile tables above are complex and difficult to use in clinical practice because of several hundreds of BP cut-points. Actually, pediatric hypertension is less frequently diagnosed by physicians,[4,5] which is partially due to the complexity of percentile tables with numerous cut-points.

Subsequently, pediatric researchers proposed several convenient and user-friendly methods for simplifying the definition of pediatric hypertension, including simple tables by sex and age,[6] simple mathematical formulas,[7] BP-to-height ratio index,[8] height-specific BP cut-points,[9] and BP percentile charts.[10] However, all these simplified tools still include many BP cut-points which are not easy to remember in practice. In 2007, the International Diabetes Federation recommended that SBP/DBP ≥ 130/85 mm Hg should be suitable for defining hypertension in children and adolescents aged 10-16 years.[11] In 2017, the AAP proposed static BP cut-points (120/80 mm Hg for elevated BP and 130/80 mm Hg for hypertension) for adolescents aged ≥13 years that corresponded to the American Heart Association and American College of Cardiology adult BP guidelines.[2] Accordingly, we think the static cut-offs as 110/70 mm Hg for elevated BP and 120/80 mm Hg for hypertension may be suitable for children aged 6-12 years. Although the static BP cut-points are easy to remember in practice, it has not been comprehensively determined whether these extremely simplified cut-points above performed similarly well compared with the complex BP percentile tables by sex, age, and height [2] in predicting health-related markers.

Arterial stiffness, assessed by pulse wave velocity (PWV), is a subclinical marker for cardiovascular disease in adults. Previous studies suggested that increased arterial stiffness predicts risk of future cardiovascular disease and mortality.[12,13] It was also reported that high pulse pressure may increase heart load and artery stresses, thereby accelerating cardiovascular degeneration.[14] Indeed, pediatric elevated BP predicts high PWV in both childhood[15] and adulthood.[16]

In the present study, we aimed to evaluate and compare the predictive ability of the static BP cut-points vs 2017 AAP guideline (hereafter referred to as "percentile-based cut-points") on increased arterial stiffness in children and adolescents using international data.

2 | METHODS

Data were from five cross-sectional population-based studies conducted in Brazil, China, Korea, and New Zealand. Detailed information of these studies has been described elsewhere.[17-20] In each center, height, weight, and BP were measured using calibrated devices. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Overweight and obesity were defined using the International Organization Task Force criteria.[21] Each study was approved by the corresponding institutional review boards, and written informed consent was obtained from all the study participants and their parents or guardians.

2.1 | Two studies in Brazil

2.1.1 | Study samples

Two studies were conducted in Vitória, ES, Brazil. The first was performed in 746 children and adolescents aged 6-17 years (130 were whites, 202 were blacks, 396 were brown, and 18 were other race/ethnicity). All attended a community project (*Estação Conhecimento*), and all were regularly enrolled in public schools. This study was conducted from February 2014 to April 2016. [17] The other study was also conducted by the same study group and included a total of 280 children aged 8-14 years (47 were whites, 60 were blacks, 171 were brown, and 2 were other race/ethnicity) from 9 public schools in Vitória from July 2016 to February 2017.

2.1.2 | BP measurements

BP was measured in the sitting position by using an automatic oscillometric device (Omron 705 CP; IntelliSense) which has been clinically validated.[22] Three consecutive readings were recorded for each participant. The mean values of last two BP measurements were used for data analyses.

2.1.3 | PWV measurement

The carotid-femoral PWV (cf-PWV) was measured in the supine position by the same trained technician who was blinded to participant details with a noninvasive and validated device (Complior, SP; Artech Medical).[17] Participants remained in supine position for 5 minutes in a quiet room. Two sensitive pressure transducers were used to detect pulsation of both right common carotid and femoral arteries. The dedicated software measures the time interval between the beginning of carotid wave and the beginning of femoral wave. Fifteen consecutive cf-PWV measurements were registered by the software, and 10 of those with nearest values were considered to determine individual PWV.

2.2 | Childhood CV risk factor study in China

2.2.1 | Study sample

This study was conducted in four public schools (one primary school, two junior high schools, and one senior high school) in Shanghai, China, from September 2014 to May 2015. A total of 537 children and adolescents aged 7-17 years (all were Chinese) with complete data on anthropometric variables and PWV measurements were included for analyses.

2.2.2 | BP measurements

BP was measured in the sitting position by using an oscillometric device (Omron HEM-7012) which has been clinically validated.[23] Three readings were obtained, and mean values of last two readings were used for data analyses.

2.2.3 | PWV measurement

The brachial-ankle PWV (ba-PWV) was measured in the supine position by the same trained examiner using an automatic and validated waveform analyzer (BP-203RPE-I; Colin Medical Technology). The left and right ba-PWV values were averaged for data analyses.[18]

2.3 | Adolescent CV risk factor study in Korea

2.3.1 | Study sample

This study was conducted in one junior public school in Seoul, South Korea, from March 2011 to October 2012.[19] A total of 593 adolescents aged 12-15 years (all were Korean) with complete data on anthropometric variables and PWV measurements were included for analyses.

2.3.2 | BP measurements

BP was measured in the supine position using an automatic oscillometric method (Dinamap Procare 200; GE Medical Systems) which has been clinically validated (SBP passed although DBP could be slightly underestimated).[24] BP was measured three times, and the last two readings were averaged for data analyses.

2.3.3 | PWV measurement

The ba-PWV was measured automatically in the supine position by the same trained examiner who was blinded to participant details with a volume-plethysmographic apparatus (PWV/ABI; Colin Co., Ltd.). The average values of the left and right ba-PWV values in each participant were used as the PWV.[19]

2.4 | Physical activity, exercise, diet and lifestyle study (PEDALS) in New Zealand

The PEDALS was conducted in 17 primary schools in Dunedin, New Zealand, from April to December 2015.[20] A total of 390 children aged 9-11 years (316 were whites and 74 were other race/ethnicity) with complete data on anthropometric variables and PWV measurements were included for analyses.

2.4.1 | BP measurements

BP was measured in the supine position by using an automatic device (SphygmoCor XCEL system; Atcor Medical) which has been clinically validated. Three BP readings were measured, and the last two readings were averaged for data analyses.

TABLE 1 Characteristics of study populations

	Brazil_a			Brazil_b			China		
	Total (n = 746)	Boys (n = 416)	Girls (n = 330)	Total (n = 280)	Boys (n = 127)	Girls (n = 153)	Total (n = 537)	Boys (n = 287)	Girls (n = 250)
Age, y	11.9 (2.7)	11.8 (2.6)	11.9 (2.8)	10.7 (2.0)	10.8 (2.0)	10.6 (1.9)	12.1 (3.3)	12.2 (3.3)	12.1 (3.4)
BMI, kg/m^2	19.3 (3.9)	19.0 (3.7)	19.6 (4.0)	19.5 (4.3)	19.3 (4.2)	19.6 (4.3)	19.5 (4.2)	20.0 (4.5)	19.0 (3.7)
SBP, mm Hg	104.5 (9.0)	105.6 (9.4)	103.2 (8.2)	105.2 (8.0)	106.4 (8.3)	104.2 (7.6)	114.1 (12.8)	117.0 (13.5)	110.8 (11.2)
DBP, mm Hg	62.1 (6.7)	61.6 (7.0)	62.6 (6.3)	64.6 (5.9)	64.4 (5.9)	64.7 (5.9)	68.8 (8.9)	68.7 (9.3)	68.9 (8.4)
Overweight, %	18.0	14.7	22.1	20.4	19.7	20.9	17.0	18.5	15.2
Obese, %	7.1	7.0	7.3	13.2	11.8	14.4	8.2	13.2	2.4
Percentile-based cut-points									
Elevated BP, %	6.4	8.4	3.9	6.8	7.1	6.5	14.5	17.1	11.6
Hypertension, %	5.0	4.8	5.2	7.9	9.5	6.5	29.1	34.8	22.4
Static BP cut-points									
Elevated BP, %	15.3	17.6	12.4	21.1	24.4	18.3	25.7	27.5	23.6
Hypertension, %	3.1	3.6	2.4	3.9	4.7	3.3	22.2	28.2	15.2
PWV, m/s	5.63 (0.91)	5.66 (1.00)	5.59 (0.78)	5.49 (0.74)	5.49 (0.81)	5.49 (0.68)	8.60 (1.26)	8.68 (1.29)	8.50 (1.23)

Notes: Brazil_a, Estação Conhecimento study in Brazil; Brazil_b, Public School study in Brazil.
Continuous variables are expressed as mean (SD) and categorical variables as percentage.
Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; WC, waist circumference.

2.4.2 | PWV measurement

The cf-PWV was measured in the supine position by the same trained examiner who was blinded to participant details using a validated device SphygmoCor XCEL system (Atcor Medical). The cf-PWV was measured in a quiet and private space, with children resting in the supine position for at least 5 minutes to provide hemodynamic stability. A femoral cuff was placed around children's left thigh, and a direct distance (carotid to femoral), corrected for the additional femoral segment between the femoral artery (groin region) and the top edge of the femoral cuff, was measured. The cf-PWV was determined by calculating the ratio of the corrected distance between the pressure waveform measuring sites to the time delay between the carotid and femoral waveforms. All measurements were checked for the quality of waveforms and were repeated if necessary.

2.5 | Definitions of elevated BP and hypertension

2.5.1 | The percentile-based cut-points

Elevated BP and hypertension were defined using the percentile-based cut-points from 2017 AAP guideline: SBP/DBP ≥ the 90th (or ≥120/80 mm Hg) and <the 95th percentile (or <130/80 mm Hg) for sex, age, and height, and SBP/DBP ≥ the 95th percentiles (or ≥130/80 mm Hg) for sex, age, and height, respectively.[2]

2.5.2 | The static cut-points

Elevated BP and hypertension were defined as (a) for children aged 6-12 years: SBP/DBP ≥ 110/70 mm Hg and <120/80 mm Hg, and SBP/DBP ≥ 120/80 mm Hg, respectively[25]; (b) for adolescents aged 13-17 years: SBP/DBP ≥ 120/80 mm Hg and <130/80 mm Hg, and SBP/DBP ≥ 130/80 mm Hg, respectively.[2,25,26]

2.6 | Definitions of increased arterial stiffness

Since there is no consensus on what level defines pediatric increased arterial stiffness, then in each study population, the measured PWV values ≥sex- and age-specific 90th percentile values were used for definition. In sensitivity analyses, we used alternative PWV percentile cut-points (such as P95, P85, and P80) to define increased arterial stiffness, and the results were similar (data not shown).

2.7 | Statistical analysis

The normal distribution of each continuous variable was tested using Kolmogorov-Smirnov method, and all variables were approximately normal distribution. Continuous variables were expressed as mean (SD) and categorical variables as percentage. Logistic regression models were used to examine the association of the static cut-points, as compared to the percentile-based cut-points, with increased arterial stiffness after adjustment for sex, age, race/ethnicity, and BMI. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Analyses were first performed stratified for study population. Thereafter, both data pooling and meta-analyses were used to calculate summary ORs and 95% CIs. If P value based on Q test ≥ .1 or I^2 statistics <50% indicate no or low between-study heterogeneity, and a fixed-effects model was used for meta-analysis; otherwise, a random effects model was used. The receiver operating characteristic curve (ROC) analyses were used to assess

Korea			New Zealand		
Total (n = 593)	Boys (n = 439)	Girls (n = 154)	Total (n = 390)	Boys (n = 191)	Girls (n = 199)
13.7 (0.9)	13.7 (0.9)	13.7 (0.8)	10.2 (0.6)	10.2 (0.6)	10.3 (0.7)
21.4 (3.6)	21.7 (3.8)	20.4 (2.7)	18.0 (3.0)	18.0 (2.9)	18.1 (3.1)
118.4 (13.8)	120.9 (13.7)	111.1 (11.5)	111.1 (9.6)	111.4 (8.9)	110.9 (10.1)
61.6 (7.7)	61.9 (7.9)	60.7 (7.1)	68.3 (6.4)	68.9 (6.5)	67.8 (6.2)
28.3	31.4	19.5	13.9	14.7	13.1
6.4	8.4	0.7	5.9	4.2	7.5
17.4	20.3	9.1	15.1	17.8	12.6
23.1	27.8	9.7	23.3	23.6	23.1
27.3	29.6	20.8	42.6	47.6	37.7
22.4	27.1	9.1	15.9	14.1	17.6
9.42 (1.04)	9.42 (1.04)	9.43 (1.03)	5.77 (0.79)	5.84 (0.78)	5.71 (0.80)

the performance of the static cut-points vs the percentile-based cut-points in predicting increased arterial stiffness. We calculated sensitivity, specificity, positive predictive value and negative predictive value, and area under the curve (AUC) with 95% CI. We calculated net reclassification improvement (NRI)[27,28] to determine the extent to which the static cut-points vs the percentile-based cut-points improve the predictive ability. All statistical analyses were performed with SAS 9.3 software, and a two-sided $P < .05$ was considered to be statistical significance.

3 | RESULTS

3.1 | Participant characteristics

Table 1 shows the characteristics of each study population. A total of 2546 children and adolescents aged 6-17 years from five cohorts were included. The prevalence of pediatric hypertension varied across different definitions and different study populations. According to the percentile-based cut-points, the prevalence of hypertension ranged from 5.0% in Brazil to 29.1% in China; according to the static cut-points, the prevalence of hypertension ranged from 3.1% in Brazil to 22.4% in Korea.

3.2 | Associations of percentile-based cut-points and static cut-points with risk of increased arterial stiffness

3.2.1 | Pooled analyses

Compared to normal BP, elevated BP defined using two definitions was not significantly associated with high odds of increased arterial stiffness, whereas hypertension defined using two definitions was associated with high risk of increased arterial stiffness (percentile-based cut-points: OR = 2.35, 95% CI = 1.74-3.17; static cut-points: OR = 3.07, 95% CI = 2.20-4.28) (Table 2). The similar trends were observed when stratified for sex and age group (Table 2), as well as when stratified for study cohort (Table S1).

3.2.2 | Meta-analyses

Because there was no between-study heterogeneity in each model, a fixed-effects meta-analysis was used to calculate summary OR and 95% CI. The results were similar with those using pooled analyses (Figures S1-S2).

3.3 | Performance of percentile-based cut-points and static cut-points for predicting increased arterial stiffness

The static cut-points performed similarly well as the percentile-based cut-points in predicting increased arterial stiffness in children and adolescents based on area under the ROC curve or NRI ($P > .05$, Table 3). The results were similar across sex (Table 3) and age groups (Table S2).

4 | DISCUSSION

Our study suggests that the static BP cut-points performed similarly in predicting increased arterial stiffness in children and adolescents

TABLE 2 Odds ratio and 95% confidence interval of increased arterial stiffness for percentile-based cut-points and static cut-points in children and adolescents in pooled analysis stratified for sex and age group

	Pooled (n = 2546)	Boys (n = 1460)	Girls (n = 1086)	6-12 y (n = 1485)	13-17 y (n = 1061)
Elevated BP					
Percentile-based cut-points	1.24 (0.84-1.83)	1.25 (0.77-2.04)	1.27 (0.66-2.43)	1.08 (0.62-1.89)	1.75 (0.98-3.11)
Static BP cut-points	1.29 (0.95-1.75)	1.21 (0.81-1.83)	1.44 (0.91-2.27)	1.22 (0.84-1.78)	1.82 (1.03-3.20)
Hypertension					
Percentile-based cut-points	2.35 (1.74-3.17)	2.33 (1.57-3.45)	2.47 (1.54-3.96)	2.07 (1.42-3.01)	3.52 (2.07-5.99)
Static BP cut-points	3.07 (2.20-4.28)	3.07 (1.99-4.74)	3.23 (1.90-5.50)	2.95 (1.91-4.58)	4.10 (2.36-7.11)

Note: Adjusted for sex, age, race/ethnicity, and BMI.

compared with traditional percentile-based cut-points based on sex, age, and height. Our findings have important clinical significance. The static BP cut-points of hypertension (120/80 mm Hg for children and 130/80 mm Hg for adolescents) are easy to remember and convenient to use in clinical practice.

Previously, we used the Bogalusa Heart Study (one longitudinal cohort study) to investigate the predictive utility of static BP cut-points of hypertension (120/80 mm Hg for children aged 6-11 years, and 130/85 mm Hg for adolescents aged 12-17 years) on adult subclinical cardiovascular outcomes (including high PWV, high carotid intima-media thickness, and left ventricular hypertrophy) as compared to the 2004 Fourth Report.[25] The results suggested that these static BP cut-points of hypertension performed similarly well as compared to the 2004 Fourth Report in predicting long-term risk of subclinical cardiovascular outcomes. In the present study, we validated the similar static BP cut-points of hypertension (120/80 mm Hg for children aged 6-12 years, and 130/80 mm Hg for adolescents aged 13-17 years) in predicting short-term risk of high PWV in diverse pediatric populations. Generally, the finding from the present study is similar with that from our previous publication.

The first child BP percentile table used to define hypertension was established in 1977, which was based on sex and age only.[29] Since 1996 Third Report,[30] an additional variable—height—was introduced in consideration of the positive association between height and BP in childhood. The current pediatric BP percentile tables, that is, the 2017 AAP guideline[2] and 2016 international references[3] included several hundreds of BP cut-points, which are difficult to apply in clinical practice. Thus, simplifying these percentile tables and making them easy to use have important clinical and public health implications.

On the other hand, it should be noted that these percentile tables are established based on statistical distributions of BP values in the assumption that the upper limit of BP ranges in general population is abnormal or unhealthy.[31] However, these BP percentile tables seem to be arbitrary to some extent using statistical method as the base. The choices of BP cut-points should be based on the linkage with

TABLE 3 Performance of percentile-based cut-points and static cut-points in predicting increased arterial stiffness in children and adolescents in pooled analysis and stratified by sex

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC (95% CI)	*P* value	NRI, %	*P* value
Total (n = 2546)								
Percentile-based cut-points	43.4	72.4	11.7	90.4	0.589 (0.558-0.620)	Reference		
Static BP cut-points	53.3	63.2	11.7	90.9	0.604 (0.571-0.637)	.076	0.6	.749
Boys (n = 1460)								
Percentile-based cut-points	50.9	66.8	11.1	91.1	0.603 (0.561-0.645)	Reference		
Static BP cut-points	60.2	57.4	10.6	91.6	0.619 (0.575-0.663)	.121	0.0	.990
Girls (n = 1086)								
Percentile-based cut-points	33.8	80.1	13.2	89.7	0.575 (0.531-0.618)	Reference		
Static BP cut-points	44.4	71.0	13.6	90.2	0.589 (0.542-0.637)	.287	−0.5	.833

Abbreviations: AUC, area under the curve; NPV, negative predictive value; NRI, net reclassification improvement; PPV, positive predictive value.

health-related markers, including short-term target organ damage and long-term CVD events, to make them more clinically relevant. In general, it is more feasible to link the short-term outcome than the long-term one because the childhood target organ damage is more easily to collect than adult CVD events which should be followed up for several decades since childhood. In the present study, we linked the percentile-based cut-points and the static BP cut-points to one target organ damage, that is, increased arterial stiffness. The similar performance of static BP cut-points vs. traditional percentile-based cut-points supports the use of these static BP cut-points in clinical practice.

Our study has several strengths. First, we pooled data from five study cohorts and the statistical power is sufficient (n = 2546). Second, the strict quality control and calibrated instruments in each study center make conclusions credible. However, several limitations should be considered. First, BP values were measured only on one occasion in all included surveys, and the definition of pediatric hypertension should be based on BP measurements on at least three different occasions.[1-3] Second, the design of all included five studies was cross-sectional, and the interpretation of findings should be made cautiously. Third, children aged <6 years were not included in the present study. Fourth, the devices used for BP and PWV measurements were different across studies. In addition, two of five studies used supine BP measurements, and two of five studies used brachial-ankle PWV assessment which is not the recommended technique. However, there was no heterogeneity between study cohorts using meta-analyses, supporting the pooled analyses in general. Fifth, the AUCs of hypertension diagnosed by two definitions for predicting increased arterial stiffness were around 0.6, which were fairly moderate. These findings suggested that other important risk factors for increased arterial stiffness should be assessed in future.

The static cut-points performed similarly well as percentile-based cut-points in predicting increased arterial stiffness in children and adolescents. Our findings suggest that the use of the static cut-points of pediatric hypertension in clinical practice would not compromise prediction of those individuals at increased odds of having increased arterial stiffness.

CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

BX, MZ, JGM, WLY, YMH, and PS provided research idea and designed the study; ROA, HSK, PML, YZ, PS, DZ, YJ, PRO, ERF, KM, and DN acquired the data; MZ, BX, JGM, WLY, YMH, PS, LS, AIM-U, AK, and CGM analyzed or interpreted the data; MZ statistically analyzed the data and wrote the first draft; and BX involved in supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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