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Global Prevalence of Hypertension in Children
A Systematic Review and Meta-analysis

Peige Song, PhD; Yan Zhang, MSc; Jinyue Yu, MD; Mingming Zha, MD; Yajie Zhu, PhD; Kazem Rahimi, DM; Igor Rudan, PhD

IMPORTANCE Reliable estimates of the prevalence of childhood hypertension serve as the basis for adequate prevention and treatment. However, the prevalence of childhood hypertension has rarely been synthesized at the global level.

OBJECTIVE To conduct a systematic review and meta-analysis to assess the prevalence of hypertension in the general pediatric population.

DATA SOURCES PubMed, MEDLINE, Embase, Global Health, and Global Health Library were searched from inception until June 2018, using search terms related to hypertension (*hypertension* OR *high blood pressure* OR *elevated blood pressure*), children (*children* OR *adolescents*), and prevalence (*prevalence* OR *epidemiology*).

STUDY SELECTION Studies that were conducted in the general pediatric population and quantified the prevalence of childhood hypertension were eligible. Included studies had blood pressure measurements from at least 3 separate occasions.

DATA EXTRACTION AND SYNTHESIS Two authors independently extracted data. Random-effects meta-analysis was used to derive the pooled prevalence. Variations in the prevalence estimates in different subgroups, including age group, sex, setting, device, investigation period, BMI group, World Health Organization region and World Bank region, were examined by subgroup meta-analysis. Meta-regression was used to establish the age-specific prevalence of childhood hypertension and to assess its secular trend.

MAIN OUTCOMES AND MEASURES Prevalence of childhood hypertension overall and by subgroup.

RESULTS A total of 47 articles were included in the meta-analysis. The pooled prevalence was 4.00% (95% CI, 3.29%-4.78%) for hypertension, 9.67% (95% CI, 7.26%-12.38%) for prehypertension, 4.00% (95% CI, 2.10%-6.48%) for stage 1 hypertension, and 0.95% (95% CI, 0.48%-1.57%) for stage 2 hypertension in children 19 years and younger. In subgroup meta-analyses, the prevalence of childhood hypertension was higher when measured by aneroid sphygmomanometer (7.23% vs 4.59% by mercury sphygmomanometer vs 2.94% by oscillometric sphygmomanometer) and among overweight and obese children (15.27% and 4.99% vs 1.90% among normal-weight children). A trend of increasing prevalence of childhood hypertension was observed during the past 2 decades, with a relative increasing rate of 75% to 79% from 2000 to 2015. In 2015, the prevalence of hypertension ranged from 4.32% (95% CI, 2.79%-6.63%) among children aged 6 years to 3.28% (95% CI, 2.25%-4.77%) among those aged 19 years and peaked at 7.89% (95% CI, 5.75%-10.75%) among those aged 14 years.

CONCLUSIONS AND RELEVANCE This study provides a global estimation of childhood hypertension prevalence based on blood pressure measurements in at least 3 separate visits. More high-quality epidemiologic investigations on childhood hypertension are still needed.

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Editorial
Supplemental content

Author Affiliations: Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, United Kingdom (Song, Rudan); Faculty of Life Science and Medicine, Kings College London, London, United Kingdom (Zhang); UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom (Yu); Medical School Southeast University, Nanjing, Jiangsu, China (Zha); The George Institute for Global Health, University of Oxford, Oxford, United Kingdom (Zhu, Rahimi).

Corresponding Author: Yajie Zhu, PhD, The George Institute for Global Health, University of Oxford, Oxford OX1 2BQ, United Kingdom (yajie.zhu@georgeinstitute.ox.ac.uk).

Hypertension, also known as elevated blood pressure (BP), is a well-recognized risk factor for cardiovascular diseases and chronic kidney disease worldwide.[1-3] Hypertension also substantially contributes to mortality and disability.[3] Globally, more than 1 billion adults were living with hypertension in 2015, among whom most were in low- and middle-income countries.[2,4]

Previous pathophysiologic and epidemiologic evidence has suggested that childhood hypertension is associated with essential hypertension in adulthood and detrimental lifelong cardiovascular events.[5-7] Compared with that of adulthood hypertension, the measurement of childhood hypertension is relatively complicated and unstable.[8,9] The prevalence of elevated BP in children, defined as a systolic BP (SBP) or a diastolic BP (DBP) greater than or equal to the 95th percentile by sex, age, and height, has been suggested to sustainably decrease by 53.7% in the second visit and by 77.7% in the third visit compared with the first visit.[10] Therefore, the fourth report from the National High Blood Pressure Education Program (NHBPEP) Working Group in the United States has suggested that childhood hypertension be confirmed as a high BP on at least 3 separate occasions, and the cutoffs of high BP should simultaneously account for the variations of age, sex, and body size.[9]

From the public health perspective, reliable estimates of the prevalence of childhood hypertension serve as the basis for adequate prevention and treatment, as well as evidence-based health resource allocation and policy making. Despite the existence of a large volume of studies that have assessed the prevalence of hypertension in children and adolescents, to our knowledge, the prevalence estimates of childhood hypertension have rarely been synthesized at the global level.[11-13]

To fill this gap of knowledge, we conducted a systematic review of studies that reported the prevalence of hypertension or elevated BP in children. We aimed to assess the prevalence of childhood hypertension, prehypertension, and stage 1 and stage 2 hypertension at the global level. When possible, the factors potentially associated with childhood hypertension were also explored.

Key Points

Question What is the prevalence of hypertension in the general pediatric population?

Findings In this systematic review and meta-analysis of 47 articles, the prevalence of childhood hypertension increased from 1994 to 2018 and the increase was associated with higher body mass index, with the pooled estimate being 4.00% among individuals 19 years and younger. In 2015, the prevalence of childhood hypertension ranged from 4.32% among children aged 6 years to 3.28% among those aged 19 years and peaked at 7.89% among those aged 14 years.

Meaning The findings suggest that childhood hypertension is becoming more common in the general pediatric population, representing a considerable public health challenge worldwide.

Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[14] The protocol of this study was not preregistered.

From inception to June 2018, 2 researchers (Y. Zhang and J.Y.) independently conducted a literature search in PubMed, MEDLINE, Embase, Global Health, and Global Health Library by using a combination of search terms related to hypertension (*hypertension* or *high blood pressure* or *elevated blood pressure*), children (*children* or *adolescents*), and prevalence (*prevalence* or *epidemiology*). Then a search of reference lists of the included studies in the first step was performed to complement our database searches. No language or time restrictions were applied. The full search strategies for different bibliographic databases are presented in eTable 1 in the Supplement.

To be included in this systematic review, studies needed to be primary investigations based on a generally representative sample of children or adolescents (≤19 years of age) and provide numerical prevalence estimates of hypertension, prehypertension, stage 1 hypertension, stage 2 hypertension, or different phenotypes of hypertension (systolic hypertension, diastolic hypertension, isolated systolic hypertension, isolated diastolic hypertension, or systolic-diastolic hypertension). Only studies that reported the prevalence of systematic hypertension (rather than intracranial or pulmonary hypertension) were included. For studies that were conducted for both adults and children, the prevalence data of hypertension had to be able to be disaggregated for the pediatric group. The adopted methods of measuring BP and definitions of hypertension had to be explicitly described. To avoid an overestimation, only studies that repeated BP measurements on at least 3 separate occasions were eligible.[9] Furthermore, the diagnosis of hypertension should have been performed according to the distribution curves of SBP and DBP, observing the corresponding values at different percentiles.[9] Studies that were confined to a subgroup of children who were not representative of the general pediatric population (eg, obese children, children with specific diseases, and young athletes) were excluded. For multiple articles that used data from the same investigation (duplicates), the one with the most comprehensive results or the largest sample size was kept. However, when different aspects or subgroups of the same investigation were separately reported in different articles, all those articles were kept.

After removing duplicates from different bibliographic databases, 2 researchers (Y. Zhang and J.Y.) independently screened the titles and abstracts of all retrieved records from the literature search. Then the same 2 researchers assessed the eligibility of potentially relevant articles in full text against the selection criteria. Consensus was reached for any disagreements through discussion.

Data Extraction and Quality Assessment

In different articles, the term of elevated BP was not unified. An SBP or DBP of greater than or equal to the 90th percentile

but less than the 95th percentile could be termed as *high-normal* or *prehypertension*; similarly, an SBP or DBP of greater than or equal to the 95th percentile could be *high BP*, *elevated BP*, or *hypertension*.[15-18] To ensure comparability among studies and our ability to synthesize prevalence data, the definition of hypertension in this study was prestandardized in accordance with the fourth report of the NHBPEP (**Table 1**).[9]

Data were independently extracted from the included articles by 2 researchers (Y. Zhang and M.Z.). The collected information included title, author(s), year of publication, year of investigation, study location (country, setting [urban vs rural], and region), study design, sampling strategy, diagnostic criteria, device for BP measurement (aneroid, oscillometric, and mercury), sample size, age range, and the number of participants affected by hypertension. The regions of study location were designated as African Region, Region of the Americas, Southeast Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region according to the World Health Organization (WHO) criteria and as high-income countries and low- and middle-income countries according to the World Bank (WB) criteria. For studies in which the investigation date was not provided, we imputed the year of investigation by subtracting 4 years from the year of publication based on the mean time difference between the year of investigation and publication in which data were provided (eTable 2 in the Supplement).

We rated the quality of included articles according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline in 5 dimensions: sample population, sample size, participation rate, outcome assessment, and analytical methods (eTable 3 in the Supplement).[19] The total score, ranging from 0 to 10, represented the overall bias risk of each article.

Statistical Analysis

Overall Pooled Prevalence of Childhood Hypertension

Before pooling prevalence estimates, the variance of the raw prevalence from each included study was stabilized by using the Freeman-Tukey double arc-sine transformation.[20] All estimates were presented after back transformation. We assessed heterogeneity of prevalence estimates among studies using the Cochran *Q* test and I^2 index.[21,22] For the Cochran *Q* test, $P < .05$ represented significant heterogeneity. For I^2 index, values of 25% or lower corresponded to low degrees of heterogeneity, 26% to 50% to moderate degrees of heterogeneity, and greater than 50% to high degrees of heterogeneity.[21-23] Because of high heterogeneity (as expected and observed), a random-effects (DerSimonian and Laird method) meta-analysis was used to calculate the overall pooled prevalence of hypertension with 95% CIs throughout this study.[23,24] To examine whether single studies had a disproportionally excessive influence, we applied a leave-1-out sensitivity analysis for each meta-analysis.[25] Publication bias in the meta-analysis was detected qualitatively by visual inspection of funnel plots and quantitatively by the Egger linear regression test and the Begg rank correlation test when more than 10 estimates were available in a single analysis.[26-28]

Table 1. Standardized Definition of Childhood Hypertension in This Systematic Review

Hypertension Type	Definition
Prehypertension	An SBP and/or DBP ≥90th percentile but <95th percentile (for age, sex, and height) or ≥120/80 mm Hg
Hypertension	An SBP and/or DBP≥95th percentile (for age, sex, and height) on ≥3 separate occasions
SH	An SBP≥95th percentile (for age, sex, and height) on ≥3 separate occasions
DH	A DBP≥95th percentile (for age, sex, and height) on ≥3 separate occasions
ISH	An SBP≥95th percentile (for age, sex, and height) but a DBP<95th percentile (for age, sex, and height) on ≥3 separate occasions
IDH	A DBP≥95th percentile (for age, sex, and height) but an SBP<95th percentile (for age, sex, and height) on ≥3 separate occasions
SDH	An SBP and DBP≥95th percentile (for age, sex, and height) on ≥3 separate occasions
Stage 1 hypertension	An SBP and/or DBP≥95th percentile (for age, sex, and height) but ≤99th percentile plus 5 mm Hg (for age, sex, and height) on ≥3 separate occasions
Stage 2 hypertension	An SBP and/or DBP>99th percentile plus 5 mm Hg (for age, sex, and height) on ≥3 separate occasions

Abbreviations: DBP, diastolic blood pressure; DH, diastolic hypertension; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; SBP, systolic blood pressure; SDH, systolic-diastolic hypertension; SH, systolic hypertension.

Subgroup Meta-analysis of Childhood Hypertension Prevalence

For childhood hypertension, prehypertension, and stage 1 and stage 2 hypertension, we conducted subgroup meta-analyses to determine the potential sources of heterogeneity. As a rule, at least 3 studies should be available per subgroup.

Meta-regression of Childhood Hypertension Prevalence

For childhood hypertension, multiple data points (age- or sex-specific prevalence) were generally reported in a single study. To assess the associations of various sample characteristics and the prevalence of childhood hypertension, we first conducted a univariable meta-regression, followed by a multivariable meta-regression.[29,30] As a rule, at least 10 data points should be available for each variable in univariable meta-regression and 20 in multivariable meta-regression (the eMethods in the Supplement gives more details).[23,31] Data were analyzed using Stata, version 14.0 (StataCorp) and R, version 3.3.0 (R Foundation for Statistical Computing).

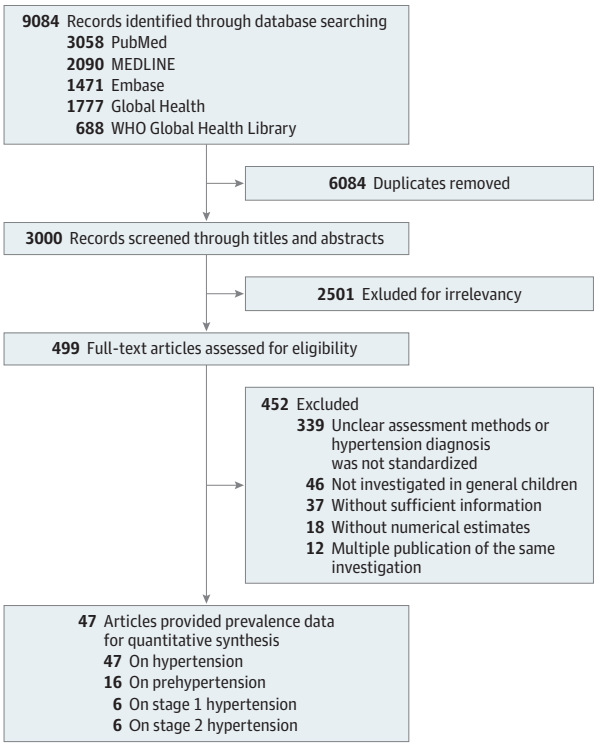
Results

Study Selection and Characteristics

As outlined in **Figure 1**, our initial literature search identified a total of 9084 records. After applying the eligibility criteria, 47 articles were included in our quantitative synthesis, of which 47 articles provided prevalence data on hypertension, 16 on prehypertension, 6 on stage 1 hypertension, and 6 on stage 2 hypertension. The list of the 47 included articles is given in eTable 4 in the Supplement.

The detailed characteristics of the included articles can be found in eTable 4 in the Supplement. All the included articles

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Diagram of Literature Search and Study Selection



WHO indicates World Health Organization.

were based on cross-sectional investigations and defined childhood hypertension in the prespecified standardized manner. A total of 32 of the 47 articles (68%) were published from 2010 onwards, and 22 (47%) were conducted in urban-rural mixed settings. In addition, 29 (62%) of the included articles reported the prevalence data for both boys and girls and 28 (60%) with a sample size greater than 2000. The most commonly used device for measuring BP was mercury sphygmomanometer (19 [40.4%]), followed by oscillometric sphygmomanometer (16 [34.0%]). Moreover, 13 of the 47 articles (28%) were conducted in the Region of the Americas (13 [28%]) or the European Region (13 [28%]) and in low- and middle-income countries (26 [55.3%]). All the included articles had a quality score of at least 6. The detailed quality assessments are presented in eTable 5 in the Supplement.

Pooled and Stratified Prevalence of Childhood Hypertension

Table 2 gives the results of overall and subgroup meta-analyses. For childhood hypertension, the pooled prevalence was 4.00% (95% CI, 3.29%-4.78%) by using random-effects meta-analysis (eFigure 1 in the Supplement). The sensitivity analysis showed that the pooled prevalence of hypertension among children varied from 3.85% (95% CI, 3.17%-4.60%) to 4.10% (95% CI, 3.39%-4.88%) after removing a single study at 1 time (eFigure 2 in the Supplement), but no single study had an excessive influence on the pooled prevalence. No publication bias was found based on the funnel plot, Egger test, and Begg test (eFigure 3 in the Supplement). The pooled prevalence of different hypertension phenotypes was also estimated using random-effects models: 2.99% (95% CI, 1.92%-4.29%) for systolic hypertension, 1.87% (95% CI, 1.06%-2.91%) for diastolic hypertension, 1.50% (95% CI, 0.83%-2.36%) for isolated systolic hypertension, 0.73% (95% CI, 0.34%-1.24%) for isolated diastolic hypertension, and 1.25% (95% CI, 0.72%-1.92%) for systolic-diastolic hypertension. Table 2 also gives the prevalence of childhood hypertension according to sex, urban or rural setting, device, investigation period, body mass index (BMI), WHO region, and WB region. The prevalence of childhood hypertension did not differ significantly when stratified by sex, urban or rural setting, WHO region, and WB region. The prevalence of childhood hypertension was the highest when taken by an aneroid sphygmomanometer (7.23%; 95% CI, 3.83%-11.59%) compared with mercury (4.59%; 95% CI, 3.24%-6.15%) or oscillometric (2.94%; 95% CI, 2.37%-3.57%) sphygmomanometers. An upward secular trend in the prevalence of childhood hypertension was detected, by which the prevalence was the highest in the latest period of 2010 to 2014 (6.02%; 95% CI, 4.38%-7.91%) than during the 2000s (3.30%; 95% CI, 2.69%-3.97%) and 1990s (1.26%; 95% CI, 0.79%-1.84%). A difference in childhood prevalence was also noted in different BMI groups, by which obese (15.27%; 95% CI, 7.31%-25.38%) and overweight (4.99%; 95% CI, 2.18%-8.81%) children had substantially higher prevalence estimates than children with normal weight (1.90%; 95% CI, 1.06%-2.97%).

Regarding prehypertension in children, the pooled prevalence was estimated to be 9.67% (95% CI, 7.26%-12.38%) based on a random-effects meta-analysis (Table 2 and eFigure 4 in the Supplement). According to the leave-1-out sensitivity analysis (eFigure 5 in the Supplement), the pooled prevalence of childhood prehypertension ranged from 9.10% (95% CI, 6.80%-11.70%) to 10.46% (95% CI, 8.24%-12.90%) when removing 1 study at a time from the pooled analysis. No study disproportionately affected the overall result. The funnel plot, Egger test, and Begg test suggested no publication bias (eFigure 6 in the Supplement). The subgroup meta-analyses indicated no statistically significant difference in prehypertension prevalence among children by age group (6-9 years vs 10-19 years), sex (male vs female), setting (urban vs rural), BP measurement method (oscillometric vs mercury), investigation period (2004-2009 vs 2010-2014), BMI group (underweight vs normal weight vs overweight vs obese), WHO region (Region of the Americas vs European Region), or WB region (high-income countries vs low- and middle-income countries).

The pooled prevalence was 4.00% (95% CI, 2.10%-6.48%) for stage 1 childhood hypertension and 0.95% (95% CI, 0.48%-1.57%) for stage 2 childhood hypertension from random effects meta-analyses (Table 2 and eFigure 7 and eFigure 8 in the Supplement). Subgroup meta-analyses were only performed by sex and device type because of the availability of data sources. No statistically significant difference of prevalence rates was found between sexes, whereas studies that used mercury sphygmomanometers showed higher prevalence

Table 2. Global Prevalence of Childhood Hypertension Using Random-Effects Meta-analysis and Subgroup Meta-analysis

Variable	No. of Articles	No. of Participants	No. of Cases	Prevalence (95% CI)	I^2, %	*P* Value			
						Q test	Egger Test	Begg Test	Subgroup Difference
Global Analysis for Hypertension									
Hypertension	47	186 630	7203	4.00 (3.29-4.78)	98.5	<.001	.20	.14	NA
SH	17	68 345	1910	2.99 (1.92-4.29)	98.8	<.001	.11	.15	NA
DH	17	68 345	1206	1.87 (1.06-2.91)	98.7	<.001	.10	.11	NA
ISH	16	65 545	1094	1.50 (0.83-2.36)	98.4	<.001	.44	.50	NA
IDH	16	65 545	438	0.73 (0.34-1.24)	97.7	<.001	.06	.03	NA
SDH	16	65 545	746	1.25 (0.72-1.92)	97.8	<.001	.08	.10	NA
Subgroup Analysis for Hypertension									
Sex									
Overall	58	121 237	5350	4.56 (3.90-5.26)	96.7	<.001	.18	.28	
Male	29	59 764	2740	4.65 (3.80-5.58)	95.8	<.001	.51	.35	.79
Female	29	61 473	2610	4.46 (3.46-5.58)	97.3	<.001	.25	.42	
Setting									
Overall	23	86 009	3576	4.26 (3.33-5.30)	97.7	<.001	.53	NA	
Urban	16	78 208	3247	4.32 (3.21-5.60)	98.3	<.001	.54	.53	.88
Rural	7	7801	329	4.11 (2.45-6.15)	93.5	<.001	NA	NA	
Device									
Overall	40	167 812	6370	4.03 (3.29-4.85)	98.4	<.001	.20	.09	
Aneroid	4	4938	472	7.23 (3.83-11.59)	95.8	<.001	NA	NA	.01
Oscillometric	17	83 310	2440	2.94 (2.37-3.57)	95.9	<.001	.62	.18	
Mercury	19	79 564	3458	4.59 (3.24-6.15)	98.8	<.001	.47	.85	
Investigation period									
Overall	47	186 630	7203	4.00 (3.29-4.78)	98.5	<.001	.20	.14	
1990-1999	3	17 853	190	1.26 (0.79-1.84)	76.4	.01	NA	NA	<.001
2000-2009	28	127 070	4342	3.30 (2.69-3.97)	97.4	<.001	.97	.15	
2010-2014	16	41 707	2671	6.02 (4.38-7.91)	98.2	<.001	.87	.59	
BMI group									
Overall	35	36 614	1126	5.47 (3.95-7.20)	97.6	<.001	<.001	.002	
Underweight	3	1400	53	4.00 (1.96-6.70)	78.6	.01	NA	NA	
Normal	12	25 034	495	1.90 (1.06-2.97)	96.5	<.001	.50	.48	<.001
Overweight	9	5326	179	4.99 (2.18-8.81)	96.3	<.001	NA	NA	
Obese	11	4854	399	15.27 (7.31-25.38)	98.5	<.001	.03	.79	
WHO region									
Overall	47	186 630	7203	4.00 (3.29-4.78)	98.5	<.001	.20	.14	
AFR	3	4654	379	6.94 (2.56-13.20)	97.5	<.001	NA	NA	
AMR	13	57 293	1460	3.02 (2.24-3.90)	96.3	<.001	.22	.81	
EMR	5	14 447	712	5.26 (1.45-11.22)	99.4	<.001	NA	NA	.32
EUR	13	71 851	3011	4.09 (2.96-5.39)	98.4	<.001	.94	.26	
SEAR	6	10 454	307	3.10 (1.47-5.28)	96.7	<.001	NA	NA	
WPR	7	27 931	1334	4.64 (2.52-7.36)	98.9	<.001	NA	NA	
WB region									
Overall	47	186 630	7203	4.00 (3.29-4.78)	98.5	<.001	.20	.14	
HIC	21	123 914	4203	3.52 (2.74-4.39)	98.3	<.001	.56	.25	.24
LMIC	26	62 716	3000	4.43 (3.16-5.90)	98.5	<.001	.60	.85	
Global Analysis for Prehypertension									
Prehypertension	16	55 625	6859	9.67 (7.26-12.38)	98.8	<.001	.33	.42	NA

(continued)

Table 2. Global Prevalence of Childhood Hypertension Using Random-Effects Meta-analysis and Subgroup Meta-analysis (continued)

Variable	No. of Articles	No. of Participants	No. of Cases	Prevalence (95% CI)	I^2, %	*P* Value			
						Q test	Egger Test	Begg Test	Subgroup Difference
Subgroup Analysis for Prehypertension									
Age group, y									
Overall	7	29 003	2921	7.04 (3.61-11.49)	98.9	<.001	NA	NA	
6-9	3	2438	100	4.06 (2.52-5.92)	67.3	.05	NA	NA	.08
10-19	4	26 565	2821	9.12 (4.11-15.84)	99.3	<.001	NA	NA	
Sex									
Overall	22	45 490	5781	11.15 (9.19-13.27)	97.5	<.001	.69	.80	
Male	11	22 583	2961	12.35 (9.09-16.02)	97.8	<.001	.90	.82	.31
Female	11	22 907	2820	9.98 (7.22-13.12)	97.5	<.001	.48	.94	
Setting									
Overall	8	36 965	4444	9.25 (6.40-12.56)	98.3	<.001	NA	NA	
Urban	4	34 401	4220	11.24 (6.80-16.62)	99.2	<.001	NA	NA	.19
Rural	4	2564	224	7.49 (4.97-10.47)	84.0	<.001	NA	NA	
Device									
Overall	12	47 438	5766	9.14 (6.30-12.44)	99.0	<.001	.39	.41	
Oscillometric	4	10 776	1423	8.07 (1.36-19.61)	99.6	<.001	NA	NA	.73
Mercury	8	36 662	4343	9.82 (7.17-12.84)	97.9	<.001	NA	NA	
Investigation period									
Overall	16	55 625	6859	9.67 (7.26-12.38)	98.8	<.001	.33	.42	
2004-2009	7	40 106	5132	11.92 (8.55-15.75)	98.8	<.001	NA	NA	.18
2010-2014	9	15 519	1727	8.02 (4.30-12.74)	98.9	<.001	NA	NA	
BMI group									
Overall	19	17 948	2731	14.53 (11.09-18.34)	97.6	<.001	.88	.86	.50
Underweight	3	1400	154	10.96 (9.37-12.66)	0.0	.56	NA	NA	
Normal	6	11 010	1634	12.41 (8.82-16.51)	97.0	<.001	NA	NA	
Overweight	5	2970	498	16.81 (6.39-30.81)	98.6	<.001	NA	NA	
Obese	5	2568	445	18.02 (5.75-34.91)	98.6	<.001	NA	NA	
WHO region									
Overall	10	44 536	5309	9.41 (6.29-13.08)	99.10	<.001	.45	.79	
AMR	5	10 383	1463	9.79 (2.91-20.05)	99.4	<.001	NA	NA	.88
EUR	5	34 153	3846	9.08 (5.84-12.95)	98.6	<.001	NA	NA	
WB region									
Overall	16	55 625	6859	9.67 (7.26-12.38)	98.8	<.001	.33	.42	
HIC	7	38 508	4386	8.30 (4.60-12.95)	99.3	<.001	NA	NA	.34
LMIC	9	17 117	2473	10.88 (7.94-14.21)	97.5	<.001	NA	NA	
Global Analysis for Stage 1 Hypertension									
Stage 1 hypertension	6	20 703	778	4.00 (2.10-6.48)	98.4	<.001	NA	NA	NA
Subgroup Analysis for Stage 1 Hypertension									
Sex									
Overall	6	9798	475	5.69 (2.71-9.65)	98.0	<.001	NA	NA	
Male	3	4823	229	5.59 (1.25-12.67)	98.4	<.001	NA	NA	.95
Female	3	4975	246	5.87 (1.34-13.21)	98.5	<.001	NA	NA	
Device									
Overall	6	20 703	778	4.00 (2.10-6.48)	98.4	<.001	NA	NA	
Oscillometric	3	13 418	295	2.04 (1.37-2.85)	88.5	<.001	NA	NA	.004
Mercury	3	7285	483	6.73 (3.41-11.06)	97.1	<.001	NA	NA	

(continued)

Table 2. Global Prevalence of Childhood Hypertension Using Random-Effects Meta-analysis and Subgroup Meta-analysis (continued)

Variable	No. of Articles	No. of Participants	No. of Cases	Prevalence (95% CI)	I^2, %	*P* Value			
						Q test	Egger Test	Begg Test	Subgroup Difference
Global Analysis for Stage 2 Hypertension									
Stage 2 hypertension	6	20 703	179	0.95 (0.48-1.57)	93.3	<.001	NA	NA	NA
Subgroup Analysis for Stage 2 Hypertension									
Sex									
Overall	6	9798	89	1.11 (0.54-1.87)	87.1	<.001	NA	NA	
Male	3	4823	46	1.16 (0.38-2.29)	85.0	.001	NA	NA	.99
Female	3	4975	43	1.16 (0.22-2.74)	91.9	<.001	NA	NA	
Device									
Overall	6	20 703	179	0.95 (0.48-1.57)	93.3	<.001	NA	NA	
Oscillometric	3	13 418	65	0.42 (0.22-0.68)	74.1	.02	NA	NA	<.001
Mercury	3	7285	114	1.74 (1.11-2.51)	74.2	.02	NA	NA	

Abbreviations: AFR, African Region; AMR, Region of the Americas; BMI, body mass index; DH, diastolic hypertension; EUR, European Region; EMR, Eastern Mediterranean Region; HIC, high-income countries; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LMIC, low- and middle-income countries; NA, not applicable; SDH, systolic-diastolic hypertension; SH, systolic hypertension; SEAR, Southeast Asia Region; WB, World Bank; WHO, World Health Organization; WPR, Western Pacific Region.

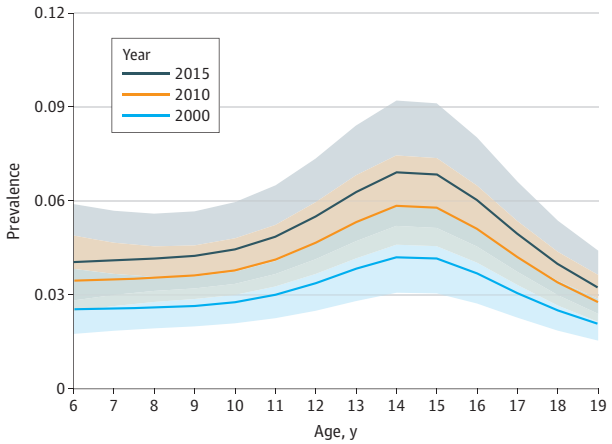
rates among children (stage 1 hypertension: 6.73%; 95% CI, 3.41%-11.06%; stage 2 hypertension: 1.74%; 95% CI, 1.11%-2.51%) than those using oscillometric sphygmomanometers (stage 1 hypertension: 2.04%; 95% CI, 1.37%-2.85%; stage 2 hypertension: 0.42%; 95% CI, 0.22%-0.68%).

Age-Specific Prevalence of Childhood Hypertension From 2000 to 2015

For childhood hypertension, we conducted a multilevel mixed-effects meta-regression because of the availability of a substantial number of age- and sex-specific data points. To control for the association of different devices with prevalence estimates (as detected in the above subgroup meta-analyses), we chose only studies that used mercury sphygmomanometer for measuring BP, which had the largest data set (96 data points) compared with those that used an aneroid sphygmomanometer (9 data points) or oscillometric sphygmomanometer (29 data points). The association between age and hypertension prevalence among children is shown in eFigure 9 in the Supplement. Five variables with more than 10 data points (age, sex, investigation year, WHO region, and WB region), were first assessed in univariable meta-regression analyses (eTable 6 in the Supplement). The results of univariable meta-regression analyses demonstrated that age and investigation year were significantly associated with the prevalence of childhood hypertension. The final model for estimating the age-specific prevalence of hypertension in children aged 6 to 19 years for the years 2000, 2010, and 2015 is detailed in the eMethods in the Supplement.

As shown in **Figure 2** and **Table 3**, the prevalence of hypertension (measured by mercury sphygmomanometer) increased from 4.32% (95% CI, 2.79%-6.63%) among children aged 6 years to 7.89% (95% CI, 5.75%-10.75%) among those aged 14 years and then decreased to 3.28% (95% CI, 2.25%-4.77%) among those aged 19 years in 2015. During the 15 years from 2000 to 2015, the increasing rates of childhood hypertension prevalence were similar across the whole age range (6-19 years), fluctuating at 75% to 79%.

Figure 2. Age-Specific Prevalence of Childhood Hypertension in 2000, 2010, and 2015



Childhood hypertension was based on blood pressure measured by mercury sphygmomanometer. Shaded areas indicate 95% CIs.

Discussion

This systematic review and meta-analysis comprehensively describes the prevalence of hypertension in children based on available data published from 1994 to 2018. The prevalence of hypertension among children varied significantly when measured by different devices. A positive secular trend of childhood hypertension prevalence was observed during the last 2 decades of the analysis. Overweight and obese children were more likely to have hypertension than their underweight or

Table 3. Age-Specific Prevalence of Childhood Hypertension (Measured by Mercury Sphygmomanometer) in 2000, 2010, and 2015 and the Rate of Change From 2000 to 2015 by Age Group

Age, y	Prevalence of Hypertension, % (95% CI)			Relative Rate of Change (1990-2015), %
	2000	2010	2015	
6	2.42 (1.44-4.04)	3.57 (2.35-5.37)	4.32 (2.79-6.63)	78.10
7	2.46 (1.57-3.84)	3.62 (2.56-5.10)	4.38 (3.00-6.36)	78.04
8	2.50 (1.67-3.73)	3.68 (2.73-4.94)	4.45 (3.16-6.23)	77.99
9	2.56 (1.75-3.74)	3.77 (2.84-4.98)	4.56 (3.27-6.34)	77.89
10	2.71 (1.86-3.93)	3.98 (3.00-5.26)	4.82 (3.44-6.71)	77.69
11	3.00 (2.07-4.35)	4.41 (3.34-5.80)	5.33 (3.83-7.37)	77.27
12	3.47 (2.36-5.08)	5.08 (3.84-6.70)	6.13 (4.42-8.45)	76.61
13	4.05 (2.75-5.93)	5.91 (4.46-7.78)	7.12 (5.14-9.76)	75.81
14	4.51 (3.09-6.53)	6.56 (5.00-8.57)	7.89 (5.75-10.75)	75.17
15	4.45 (3.06-6.44)	6.49 (4.94-8.47)	7.80 (5.67-10.65)	75.25
16	3.85 (2.64-5.60)	5.63 (4.28-7.37)	6.79 (4.92-9.29)	76.08
17	3.07 (2.08-4.51)	4.51 (3.40-5.96)	5.44 (3.92-7.52)	77.17
18	2.38 (1.57-3.57)	3.50 (2.58-4.73)	4.23 (2.99-5.96)	78.16
19	1.83 (1.18-2.85)	2.70 (1.92-3.80)	3.28 (2.25-4.77)	78.94

normal weight counterparts. On the basis of studies that measured BP by mercury sphygmomanometer, the age-specific prevalence of childhood hypertension from 2000 to 2015 was established. Between 2000 and 2015, the prevalence of childhood hypertension increased by 75% to 79% among children aged 6 to 19 years, among whom the prevalence continued to increase before the onset of puberty and during puberty, reached the peak level at the end of puberty, and steadily decreased until the beginning of adulthood.

Previous systematic reviews[11,32-34] have synthesized the prevalence of childhood hypertension in Africa, Nigeria, Brazil, and worldwide. However, none of those studies adopted the standardized BP measurement in children recommended by the NHBPEP, which states that the diagnosis of childhood hypertension should be confirmed on at least 3 occasions to avoid false-positive cases.[9] To our knowledge, this study was the first systematic review and meta-analysis to explore the global prevalence of childhood hypertension based on BP measurements on at least 3 separate occasions.

In line with previous systematic reviews and individual investigations,[11,17,35,36] a positive association between the prevalence of childhood hypertension and BMI was observed in our study. This finding supports previous results showing that obesity may be a risk factor for hypertension and underlines the importance of weight control for hypertension management in the pediatric population.[36] Another key finding of this study is the pattern of hypertension prevalence according to age, by which the prevalence of childhood hypertension started to increase rapidly from the onset of puberty and reached the peak level at the end of puberty. In previous studies,[37,38] a higher level of BP during puberty than before or after it has been well documented, which might be associated with hormone change and rapid growth spurts.

Studies[39,40] in the United States have observed an increase in BP in children during the past decade, partially caused by an increase in childhood obesity, especially abdominal obesity. In this study, a significant temporal trend of increasing prevalence of childhood hypertension during the past 2 decades was also found at the global level, as revealed in subgroup meta-analysis and meta-regression. However, such a secular trend was not observed in Africa during the past 2 decades, as previously reported.[11] With the potential forthcoming epidemic of childhood obesity in developing countries, an increase in the prevalence of childhood hypertension may also transpire in these countries. In 2017, the new clinical practice guideline for screening and management of high BP in children and adolescents updated the normative pediatric BP table in the fourth report by NHBPEP by excluding data for overweight and obese children, according to which the global prevalence of childhood hypertension might be even higher.[41] Considering the unfavorable health consequences of childhood hypertension, this finding highlights the need for global actions to prevent and manage childhood hypertension.[7,36]

Strengths and Limitations

Strengths of this study include the comprehensive search strategies, a double review process, and stringent selection criteria. In our systematic review, we included only studies that were conducted in the general pediatric population so that the generalizability of our results could be well guaranteed. Moreover, the standardized definitions of hypertension and its subtypes reduced heterogeneity largely because of methodologic variability and made the synthesis of prevalence possible. Also, we were able to pool the prevalence of hypertension and its phenotypes, prehypertension, and stage 1 and stage 2 hypertension in children based on the available evidence, which allowed our systematic review and meta-analysis to provide a broad scope of the prevalence of childhood hypertension. For the first time, to our knowledge, in a systematic review and meta-analysis, we constructed age-specific prevalence of childhood hypertension and explored its secular trend after eliminating the effects of BP measurement devices.

Several intrinsic limitations of this study should also be recognized. First, although we unified the definitions of child-

hood hypertension and its subtypes before pooling the prevalence estimates, substantial heterogeneity was detected. Second, the limited number of included studies for prehypertension, stage 1 hypertension, and stage 2 hypertension in children increased the uncertainty of our pooled prevalence estimates, and the sources of heterogeneity could only be explored by subgroup meta-analysis in a limited set of groups. Third, we could not estimate the prevalence of childhood prehypertension, stage 1 hypertension, and stage 2 hypertension at the regional level. Even for childhood hypertension, for which the contributing data points successfully covered all the 6 WHO regions, the prevalence estimation at the regional level was not optimal given that more than half of the included studies were concentrated in only 2 regions (Region of the Americas and European Region).

Our overall pooled prevalence of childhood hypertension was lower than that in a previous systematic review of the worldwide prevalence (4.0% vs 11.2%).[42] The large disparity might be explained mainly by the different numbers of visits for BP measurements in these 2 systematic reviews. In their study, the pooled prevalence of childhood hypertension was based on individual studies that had measured BP on a single occasion or on 2 occasions or more, which could lead to a higher prevalence estimate given that the prevalence of childhood hypertension could decrease with the increase of visit numbers.[10]

Conclusions

This study suggests that childhood hypertension represents a considerable public health challenge worldwide. Childhood hypertension was generally more common in adolescents undergoing puberty and children who were overweight or obese. An upward trend of hypertension prevalence in children during the past 2 decades was observed and may persist in the future. More high-quality epidemiologic investigations on childhood hypertension (ideally in accordance with the recommendations by NHBPEP) appear to be needed, especially for different subgroups of hypertension (prehypertension, stage 1 hypertension, and stage 2 hypertension) and within the Region of the Americas, Eastern Mediterranean Region, Southeast Asia Region, and Western Pacific Region.

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Concept and design: Song, Zhu, Rahimi, Rudan.
Acquisition, analysis, or interpretation of data: Song, Zhang, Yu, Zha, Zhu.
Drafting of the manuscript: Song.
Critical revision of the manuscript for important intellectual content: Zhang, Yu, Zha, Zhu, Rahimi, Rudan.
Statistical analysis: Song, Zhu.
Administrative, technical, or material support: Zhang, Yu, Zha, Rudan.
Supervision: Song, Zhu, Rudan.

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REFERENCES

1. Danaei G, Lu Y, Singh G, et al; Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes Endocrinol*. 2014;2(8):634-647. doi:10.1016/S2213-8587(14)70102-0

2. Zhou B, Bentham J, Di Cesare M, et al; NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. *Lancet*. 2017; 389(10064):37-55. doi:10.1016/S0140-6736(16)31919-5

3. World Health Organization. *A GLOBAL BRIEF on Hypertension: Silent Killer, Global Public Health Crisis: World Health Day 2013*. Geneva, Switzerland: World Health Organization; 2013.

4. Mills KT, Bundy JD, Kelly TN, et al. Global disparities of hypertension prevalence and control clinical perspective: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134(6):441-450. doi:10.1161/CIRCULATIONAHA.115.018912

5. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. *Am J Hypertens*. 1995;8(7):657-665. doi:10.1016/0895-7061(95)00116-7

6. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA*. 2003;290(17):2277-2283. doi:10.1001/jama.290.17.2277

7. Beckett LA, Rosner B, Roche AF, Guo S. Serial changes in blood pressure from adolescence into adulthood. *Am J Epidemiol*. 1992;135(10):1166-1177. doi:10.1093/oxfordjournals.aje.a116217

8. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 2007;298(8):874-879. doi:10.1001/jama.298.8.874

9. Falkner B, Daniels SR, Flynn JT, et al; 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(2)(Suppl 4th Report):555-576. doi:10.1542/peds.114.2.S2.555

10. Sun J, Steffen LM, Ma C, Liang Y, Xi B. Definition of pediatric hypertension: are blood pressure measurements on three separate occasions necessary? *Hypertens Res*. 2017;40(5):496-503. doi:10.1038/hr.2016.179

11. Noubiap JJ, Essouma M, Bigna JJ, Jingi AM, Aminde LN, Nansseu JR. Prevalence of elevated blood pressure in children and adolescents in Africa: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2(8):e375-e386. doi:10.1016/S2468-2667(17)30123-8

12. Akbari M, Moosazadeh M, Ghahramani S, et al. High prevalence of hypertension among Iranian children and adolescents: a systematic review and meta-analysis. *J Hypertens*. 2017;35(6):1155-1163. doi:10.1097/HJH.0000000000001261

13. McCrindle BW. Assessment and management of hypertension in children and adolescents. *Nat Rev Cardiol*. 2010;7(3):155-163. doi:10.1038/nrcardio.2009.231

14. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64. doi:10.7326/0003-4819-151-4-200908180-00135

15. Cinteza E, Balgradean M. Hypertension in Romanian children and adolescents: a cross-sectional survey. *Maedica (Buchar)*. 2013;8(1):5-10.

16. de Oliveira LMFT, da Silva AO, Diniz PRB, et al. The number of visits and blood pressure measurements influence the prevalence of high blood pressure in adolescents. *J Am Soc Hypertens*. 2017;11(6):343-349. doi:10.1016/j.jash.2017.04.002

17. Acosta AA, Samuels JA, Portman RJ, Redwine KM. Prevalence of persistent prehypertension in adolescents. *J Pediatr*. 2012;160(5):757-761. doi:10.1016/j.jpeds.2011.10.033

18. Moore WE, Eichner JE, Cohn EM, Thompson DM, Kobza CE, Abbott KE. Blood pressure screening of school children in a multiracial school district: the Healthy Kids Project. *Am J Hypertens*. 2009;22(4):351-356. doi:10.1038/ajh.2009.13

19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577. doi:10.7326/0003-4819-147-8-200710160-00010

20. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11):974-978. doi:10.1136/jech-2013-203104

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

22. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

23. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol 5. New York, NY: Wiley Online Library; 2008, . doi:10.1002/9780470712184

24. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*. 2013;67(11):974-978. doi:10.1136/jech-2013-203104

25. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol*. 2009;9(1):80. doi:10.1186/1471-2288-9-80

26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101. doi:10.2307/2533446

28. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676-680. doi:10.1001/jama.295.6.676

29. Hox JJ, Moerbeek M, van de Schoot R. *Multilevel Analysis: Techniques and Applications*. Abingdon, UK: Routledge; 2010, . doi:10.4324/9780203852279

30. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36(3):1-48. doi:10.18637/jss.v036.i03

31. Baranyi G, Scholl C, Fazel S, Patel V, Priebe S, Mundt AP. Severe mental illness and substance use disorders in prisoners in low-income and middle-income countries: a systematic review and meta-analysis of prevalence studies. *Lancet Glob Health*. 2019;7(4):e461-e471. doi:10.1016/S2214-109X(18)30539-4

32. Ejike CECC. Prevalence of hypertension in Nigerian children and adolescents: a systematic review and trend analysis of data from the past four decades. *J Trop Pediatr*. 2017;63(3):229-241. doi:10.1093/tropej/fmw087

33. Magliano ES, Guedes LG, Coutinho ESF, Bloch KV. Prevalence of arterial hypertension among Brazilian adolescents: systematic review and meta-analysis. *BMC Public Health*. 2013;13(1):833. doi:10.1186/1471-2458-13-833

34. McCarron P, Smith GD, Okasha M. Secular changes in blood pressure in childhood, adolescence and young adulthood: systematic review of trends from 1948 to 1998. *J Hum Hypertens*. 2002;16(10):677-689. doi:10.1038/sj.jhh.1001471

35. Okpokowuruk FS, Akpan MU, Ikpeme EE. Prevalence of hypertension and prehypertension among children and adolescents in a semi-urban area of Uyo Metropolis, Nigeria. *Pan Afr Med J*. 2017;28(1):303. doi:10.11604/pamj.2017.28.303.14396

36. Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. *Hypertension*. 2002;40(4):441-447. doi:10.1161/01.HYP.0000032940.33466.12

37. Shankar RR, Eckert GJ, Saha C, Tu W, Pratt JH. The change in blood pressure during pubertal growth. *J Clin Endocrinol Metab*. 2005;90(1):163-167. doi:10.1210/jc.2004-0926

38. Ewald DR, Haldeman PhD LA. Risk factors in adolescent hypertension. *Glob Pediatr Health*. 2016;3:X15625159.

39. Din-Dzietham R, Liu Y, Bielo M-V, Shamsa F. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation*. 2007;116(13):1488-1496. doi:10.1161/CIRCULATIONAHA.106.683243

40. Muntner P, He J, Cutler JA, Wildman RP, Whelton PK. Trends in blood pressure among children and adolescents. *JAMA*. 2004;291(17):2107-2113. doi:10.1001/jama.291.17.2107

41. Flynn JT, Kaelber DC, Baker-Smith CM, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140(3):e20171904. doi:10.1542/peds.2017-1904

42. de Moraes ACF, Lacerda MB, Moreno LA, Horta BL, Carvalho HB. Prevalence of high blood pressure in 122,053 adolescents: a systematic review and meta-regression. *Medicine (Baltimore)*. 2014;93(27):e232. doi:10.1097/MD.0000000000000232