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ORIGINAL ARTICLE

Definition of pediatric hypertension: are blood pressure measurements on three separate occasions necessary?

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The US Fourth Report (2004) recommended that elevated blood pressure (BP) on at least three occasions should be used to define hypertension in children and adolescents. However, there is no sufficient evidence to support this decision. This study aimed to assess the change in the prevalence of elevated BP obtained on three separate visits in children and adolescents worldwide using a meta-analysis. The PubMed database was searched for eligible studies published in English until 20 April 2016. Included studies were population based and reported on the prevalence of elevated BP measured on two or three separate occasions in pediatric populations. A meta-analysis was performed to calculate a summary prevalence of elevated BP over three different visits. A total of 21 studies with 179 561 participants aged 3–20 years were included in the present meta-analysis. The summary prevalence of elevated BP decreased across visits, from 12.1% (95% confidence interval (CI) = 10.1–14.0%) during the first visit to 5.6% (95% CI = 4.3–7.0%) during the second visit and to 2.7% (95% CI = 2.1–3.3%) during the third visit. These findings were independent of sex, age group, ethnicity/race and the definition of elevated BP. When compared with visit 1, the prevalence of elevated BP decreased by 53.7% during visit 2 and by 77.7% during visit 3. Our study suggested that the prevalence of elevated BP decreased substantially from the first visit to the subsequent visits. Worldwide, the true prevalence of hypertension in children and adolescents is ~3% over three different visits.
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Keywords: children; definition; epidemiology; hypertension; prevalence

INTRODUCTION

Elevated blood pressure (BP) in children and adolescents is a serious public health issue worldwide.[1] Evidence suggests that elevated BP is associated with the risk of target organ damage.[2,3] In addition, modest tracking of elevated BP from childhood to adulthood[4] increases the long-term risk of cardiovascular diseases and premature death in adulthood.[5] Therefore, early accurate detection and effective control of high BP in children and adolescents are crucial to reduce the risk of target organ damage in children and the long-term risk of cardiovascular diseases in adults.

As recommended by several medical guidelines, the definition of hypertension in adults should be based on multiple BP measurements on each of at least two different visits owing to the significant variability of BP within and between days.[6–8] Similarly, hypertension in children is defined as elevated BP (systolic BP/diastolic BP (SBP/DBP) $\geqslant$ 95th percentile by sex, age and height) on at least three separate occasions.[9–12] There are many factors that can influence the stability of BP values, including within-person variability (for example, accommodation, nervous status, stress and so on), the 'white-coat' effect[13] and regression to the mean.[14] The BP measurements on a single occasion can result in an overestimated prevalence of true hypertension.[14–16] Therefore, repeated readings on several occasions may be necessary for the diagnosis of true hypertension.

However, in most epidemiological studies, the diagnosis of 'hypertension' mainly relies on one to three readings during a single screening visit for both adults[17] and children,[1] and true hypertension is undoubtedly overestimated. Accuracy when estimating the prevalence of hypertension is important for making decisions on intervention measures and evaluating the effect of these measures. In 2004, the US Fourth Report by the National High Blood Pressure Education Program Working Group (NHBPEP) recommended that elevated BP on at least three occasions should be used to define hypertension in children and adolescents. However, to our knowledge, there is no sufficient evidence to support this decision. Fortunately, several publications thus far have investigated and reported the number of visits on BP measurements in children and adolescents.[18–38] This provides us with the opportunity to assess the accuracy of the hypertension definition according to the US Fourth Report by NHBPEP. In this study, we performed the first meta-analysis to assess the variability of elevated BP prevalence estimated from two or three separate visits and provided the scientific evidence for accurate measurements of BP in children and adolescents.

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METHODS

Search strategy

This review was performed based on the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (http://www.prisma-statement.org/). The PubMed database was searched to retrieve eligible studies conducted until 20 April 2016. Search terms were as follows: (children OR adolescents OR pediatric OR school age OR puberty OR youths) and (blood pressure OR high blood pressure OR elevated blood pressure OR hypertension OR sustained elevated BP OR persistent elevated BP OR sustained hypertension OR persistent hypertension) and (three occasions OR three visits OR two occasions OR two visits OR multiple occasions OR multiple visits OR repeated measurements OR repeated visits OR multiple measurements). The search strategy is given in detail in Supplementary Table S1. The publication language was restricted to English only. In addition, related reference lists in the eligible papers were also searched. Two trained authors (Jiahong Sun and Chuanwei Ma) performed the search and extracted the data independently. If the opinions of the two authors were different, a third author (Bo Xi) was consulted to reach an agreement.

For all the included studies, children or adolescents with an 'elevated BP' based on measured BP readings during the first visit had a second set of BP readings taken during a separate visit several weeks later. Children or adolescents who still had an 'elevated BP' based on BP readings during that second visit had a third set of BP readings taken another several weeks later.

Inclusion criteria and data extraction

To be eligible for inclusion in this review, studies had to meet the following criteria: (1) provide the prevalence or incidence of elevated BP (definitions are presented in Table 1) or sufficient data for calculation during two or three visits; (2) population- or school-based studies; and (3) population included children and/or adolescents. The information extracted included: (1) name of authors; (2) year of publication; (3) origin of country; (4) sample size; (5) age of participants; (6) proportion of boys; (7) definition of elevated BP; (8) BP measurement device; (9) interval of each visit; and (10) survey year.

Data analysis

A meta-analysis was performed to calculate the summary prevalence of elevated BP during each of the three visits. Cochran's *Q* test was used to test the between-study heterogeneity. A random-effect model was used to calculate pooled prevalence because of the strong heterogeneity between the studies (All $I^2 > 90\%$). Publication bias was assessed by Begg's test and Egger's test ($P < 0.05$ was considered statistically significant). Meta-regression analysis was performed to examine the source of heterogeneity using potential variables, including sex, age, race, the definition of elevated BP and BP measurement devices. Data were analyzed using Stata version 11.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of included studies

A flowchart of study inclusion/exclusion is presented in Figure 1. A total of 21 studies (179 561 participants) that met the inclusion criteria were included in this review.[18–38] All included studies were population-based and cross-sectional in design. The sample size ranged from 552 to 85 780 participants. The definitions of elevated BP included the definitions from the US NHBPEP released in the years 1977, 1987, 1996 and 2004 as well as the established BP references from China (2010), Hong Kong (2008) and Hungary (2003). Detailed characteristics are displayed in Table 1.

Prevalence of elevated BP and the change over three separate visits

The prevalence of elevated BP and the change in the prevalence of elevated BP over two or three separate visits for each study are presented in Supplementary Table S2. For elevated BP, 14 studies had available data during three visits and 6 studies during two visits. For elevated SBP and DBP, there were four studies with available data during three visits and three studies with available data during two visits. The summary of the prevalence of elevated BP and 95% confidence interval (CI) was 12.1% (10.1–14.0%) during visit 1 (Figure 2), 5.6% (4.3–7.0%) during visit 2 (Figure 3) and 2.7% (2.1–3.3%) during visit 3 (Figure 4). There was no significant difference in the prevalence of elevated BP during each of the three visits between sexes, age groups, child BP definitions or ethnicity/races (Table 2). When compared with visit 1, the prevalence of elevated BP decreased by 53.7% during visit 2 and by 77.7% during visit 3.

The summary prevalence of elevated SBP over three separate occasions was 8.3% (4.6–12.0%), 3.5% (1.8–5.1%) and 1.7% (0.8–2.7%), respectively, and the summary prevalence of elevated DBP over three separate occasions was 5.9% (3.3–8.5%), 2.1% (0.8–3.3%) and 0.7% (0.4–1.1%), respectively (Table 2).

There was significant heterogeneity between studies for the prevalence of elevated BP in each of the three visits. Meta-regression analysis was performed to examine the source of the heterogeneity using potential variables, including sex, age, race, definition of elevated BP and BP measurement devices. However, these variables cannot explain the source of the heterogeneity. There was no publication bias according to Begg's test (first visit prevalence: $P = 0.417$; second visit prevalence: $P = 0.753$; third visit prevalence: $P = 1.000$) and Egger's test (first visit prevalence: $P = 0.151$; third visit prevalence: $P = 0.542$). However, there was marginal publication bias according to Egger's test for the prevalence during the second visit ($P = 0.037$). We used the trim and fill method to address this publication bias, and the pooled prevalence was slightly changed to 5.0% (95% CI = 3.6–6.9%). Additionally, we performed a sensitivity analysis using the studies where BP measurements were performed on three different occasions, and the results from the meta-analysis were similar with those when all studies were included.

DISCUSSION

To our knowledge, this is the first review to assess the changes in elevated BP prevalence across three separate visits. Our report illustrated that the prevalence of elevated BP decreased substantially (by 77.7%) from the first to the third screening. As expected, the prevalence of elevated SBP and DBP also showed significant decreasing trends from the first to the third visit (decreased by 79.5% for elevated SBP and decreased by 88.1% for elevated DBP). The true prevalence of hypertension in children and adolescents is ~3% over three different visits. The present meta-analysis underlines the necessity of measuring BP on at least three separate occasions to identify a hypertensive child in clinical practice or to accurately estimate the true prevalence of hypertension in a pediatric population.

One previous meta-analysis demonstrated that the prevalence of elevated BP in all children, in boys only and in girls only was 11.2, 13, and 9.6%, respectively.[1] However, it should be noted that the prevalence in that meta-analysis was based on BP measurements during only one visit, and the true prevalence of hypertension most likely was overestimated. In the studies included in our meta-analysis, the prevalence of elevated BP during the first visit was 12.1%, but it decreased substantially to 5.6% during the second visit and then to 2.7% during the third visit. However, there was significant heterogeneity between the studies on the prevalence of elevated BP during each of the three visits. The between-study heterogeneity might be due to differences in the study year, race/ethnicity and age distribution of the target population, definitions for elevated BP or devices used to measure BP, but our meta-regression analysis did not indicate any of these differences. In epidemiological studies, BP is usually measured two or three times during only one visit because of cost and

Table 1 Characteristics of the eligible studies included in the review

Study	*Country*	*Ethnicity*	*Sample size*	*Boys (%)*	*Age, years*	*BMI (kg m^{-2}) or prevalence of obesity (%)*	*Visit interval*	*Survey year*	*BP measurement device*	*Definition (cutoff)*
Marcovecchio *et al.*[18]	Italy	Caucasian	564	55.1	8.8±1.4	18.8±3.8	1 week	—	Mercury	NHBPEP2004(⩾P95)
Patil and Garg[19]	Indian	Asian	958	48.4	6–16	—	<4 weeks	2010–2012	Mercury	NHBPEP2004(⩾P95)
Kidy *et al.*[20]	Uganda	Africa	552	46.4	7–18	Overweight and obesity: 13.6%	3 months	2010	Oscillometric	NHBPEP2004(⩾P95)
Lu *et al.*[21]	China	Asian	1352	50.2	7–12	Boys: 19.1 (10.7–40.9); girls: 17.4 (12.4–32.8)	—	2011	Mercury	NHBPEP2004(⩾P95)
Lo, [22]	USA	Mixed	85 780	50.5	3–17	Overweight: 15.3%; obesity: 16.2%	3.5 years	2007–2009	Mercury	NHBPEP2004(⩾P95)
Meng *et al.*[23]	China	Asian	6692	49.7	10.7±5.0	19.1± 4.5	2 weeks	2010	Mercury	China2010 (⩾P95)
Steinthorsdottir *et al.*[24]	Iceland	Caucasian	970	49.6	9.6±0.3	Boys:17.4±2.5; girls:17.8±3.0	2 weeks	2009	Mercury	NHBPEP2004(⩾P95)
Leung *et al.*[25]	China (Hong Kong)	Asian	6193	49.6	15.2±1.9	0.20±1.00 (BMI *z*-score)	2 weeks	2006	Oscillometric	HongKong2008 (⩾P95)
Katona *et al.*[26]	Hungary	Caucasian	10 194	50.6	16.6 ±1.0	20.8±3.0	—	1999	Oscillometric	Hungary2003 (first and second visits: ⩾P90, third visit: ⩾P95)
McNiece *et al.*[27]	USA	Mixed	6790	51.0	12.7±1.2	Overweight: 18.0%; obesity: 18.1% using US CDC criteria	—	2003–2005	Oscillometric	NHBPEP2004(⩾P95)
Chiolero *et al.*[28]	Switzerland	Caucasian	5207	50.3	12.3±0.5	18.7±3.0	1–2 weeks	2005–2006	Oscillometric	NHBPEP2004(⩾P95)
Kardas *et al.*[29]	Poland	Caucasian	637	54.8	9–14	—	⩾1week	—	Mercury	NHBPEP1996(⩾P95)
Genovesi *et al.*[30]	Italy	Caucasian	2416	49.9	6–11	Overweight: 27.1% using IOTF criteria		2003–2004	Mercury	NHBPEP1996(⩾P95)
Sorof *et al.*[31]	USA	Mixed	5102	49.0	13.3±1.6	22.3±5.2	1–2 weeks	2002	Oscillometric	NHBPEP1996(⩾P95)
Antal *et al.*[32]	Poland	Caucasian	6345	48.4	15–18	Boys: 21.5±3.8; girls: 21.4±3.7	⩾2 weeks	1997–2000	Oscillometric	SBP/DBP⩾135/85 mm Hg for 15 years group and SBP/DBP⩾140/90 for 16–18 years group
Sorof *et al.*[33]	USA	Mixed	2460	47.0	15.1±1.2	24.3±6.0	1–2 weeks	2000–2001	Oscillometric	NHBPEP1996 (First visit: ⩾P90, second and third visits: ⩾P95)
Sinaiko *et al.*[34]	USA	Mixed	14 686	50.8	12.7±0.01	Boys: 19.9±0.1; Girls: 20.5±0.1	<3 weeks	1986–1987	Mercury	NHBPEP1987(⩾P95)
Fixler *et al.*[35]	USA	Mixed	10 641	53.3	14.0±0.01	—	4 weeks	1976–1977	Mercury	NHBPEP1977 (⩾P95)
Rames *et al.*[36]	USA	Caucasian (96.4%)	6622	49.7	5–18	—	4–12 months	1971–1972; 1973–1974	Mercury	SBP/DBP⩾P95 or 140/90 mm Hg
Reichman, [37]	USA	Mixed	1863	9.6	12–20	—	⩾1week	1972–1973	Mercury	SBP/DBP⩾140/90 mm Hg
Kilcoyne and Richter[38]	USA	Mixed	3537	42.8	14–19	—	7–10 days	1970	Mercury	SBP/DBP⩾140/90 mm Hg

Abbreviations: BMI, body mass index; BP, blood pressure; CDC, Centers for Disease Control; DBP, diastolic blood pressure; IOTF, International Obesity TaskForce; NHBPEP, National High Blood Pressure Education Program; SBP, systolic blood pressure.
'—' indicates that the data are not available.

inconvenience. However, the present meta-analysis indicated that childhood BP should be measured on three different visits to avoid overestimating the prevalence of elevated BP during one or two screening occasions.

The National Heart, Lung, and Blood Institute (NHLBI, 2011), based on the Fourth Report, recommended that, for children with BP readings between the 95th percentile and the 99th percentile plus 5 mm Hg on a single visit, additional BP measurements should be taken on two more occasions. If hypertension is confirmed, evaluations should be conducted, including the evaluation of lifestyle factors (diet habits, smoking, drinking alcohol, physical examination and so on), substance use and sleep disorders that might cause hypertension, metabolic abnormalities and target organ damage (for eample, left ventricular hypertrophy and microalbuminuria). However, for children with BP readings >the 99th percentile plus 5 mm Hg on a single visit, a prompt referral should be made for evaluation and treatment.[39]

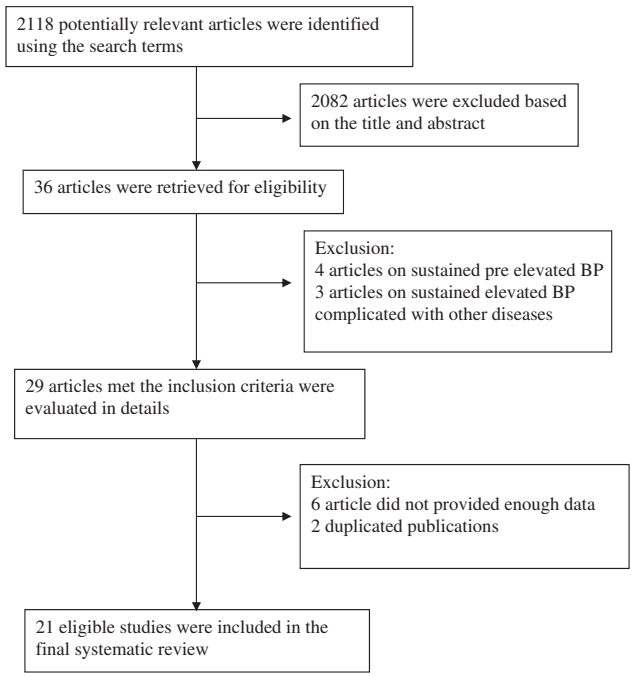

Figure 1 Flowchart of study inclusion and exclusion.

As for the minimum number of BP measurements during each of the three visits, this is beyond the scope of our review. But three readings during each visit and the mean of the second and third readings would reduce the false positive cases of elevated BP when compared with one or two readings on each visit.[15] However, a previous meta-analysis using one BP measurement on one visit as the reference group demonstrated that more than three measurements did not seem superior to two measurements for childhood BP tracking into adulthood.[4] On the other hand, to reduce the white-coat effect, successive measurements of BP with the first office reading discarded may improve the possibility of knowing the actual BP.[40]

In our opinion, it is important to standardize the procedure to assess the actual BP and therefore the actual hypertensive status among children and adolescents in clinical or epidemiological practice. However, adverse effects of elevated BP in childhood on related morbidity and mortality are mainly based on one or two readings during a single visit.[5,41] Two studies, one from the Swedish Military Conscription Registry and the other from the Harvard Alumni Health Study, with a follow-up median duration of ~20 years, showed that hypertension in late adolescence or early adulthood defined using BP readings during a single visit predicted the risk of cardiovascular

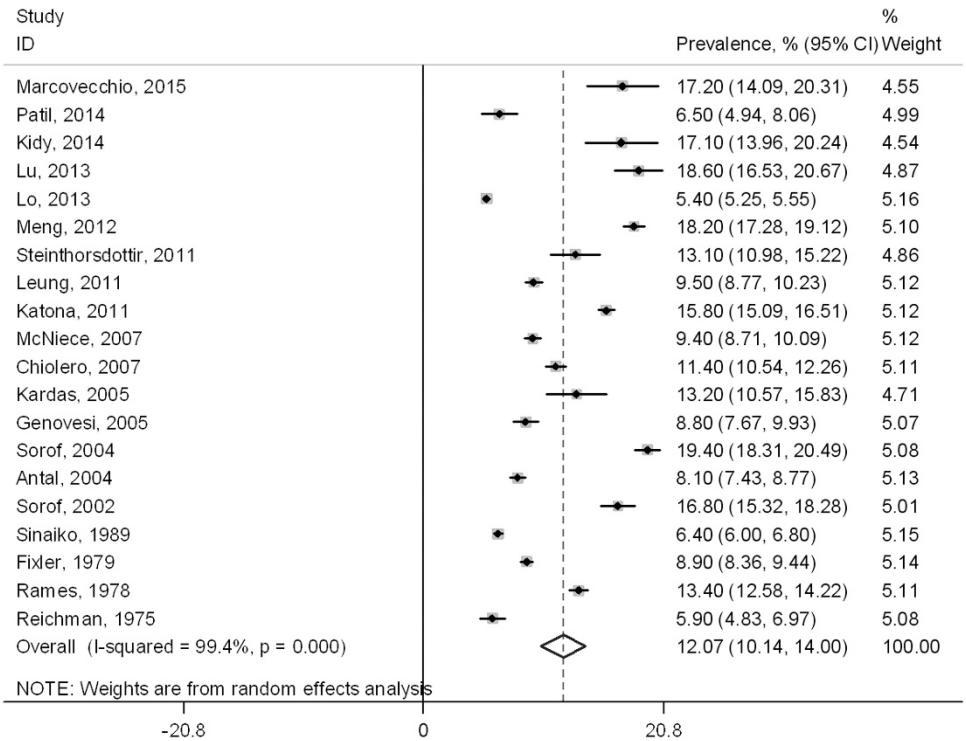

Figure 2 Meta-analysis of the prevalence of elevated BP during the first visit. A full color version of this figure is available at the *Hypertension Research* journal online.

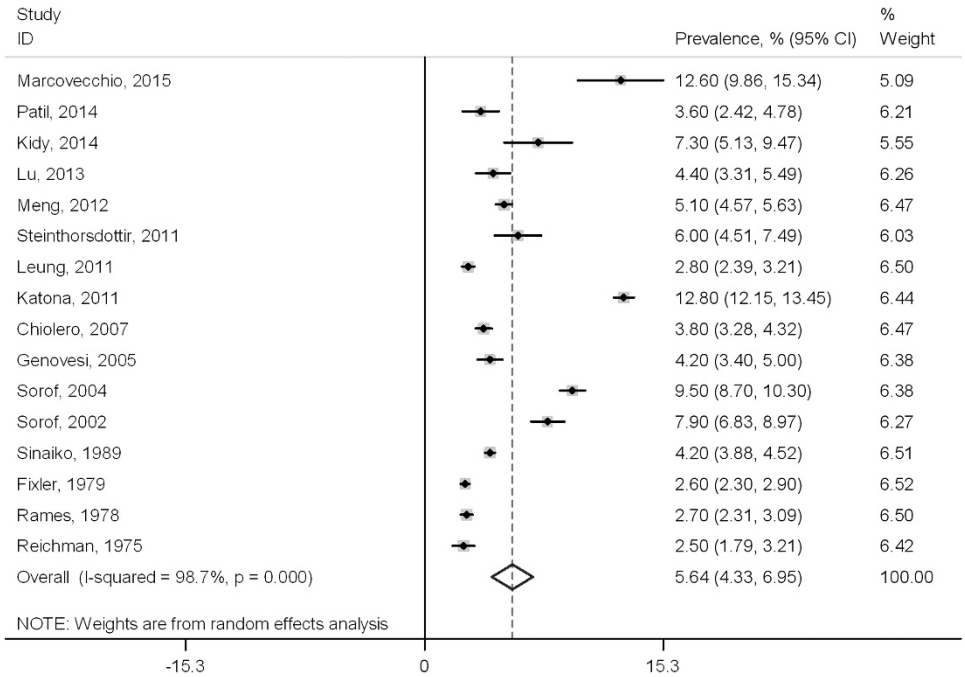

Figure 3 Meta-analysis of the prevalence of elevated BP during the second visit. A full color version of this figure is available at the *Hypertension Research* journal online.

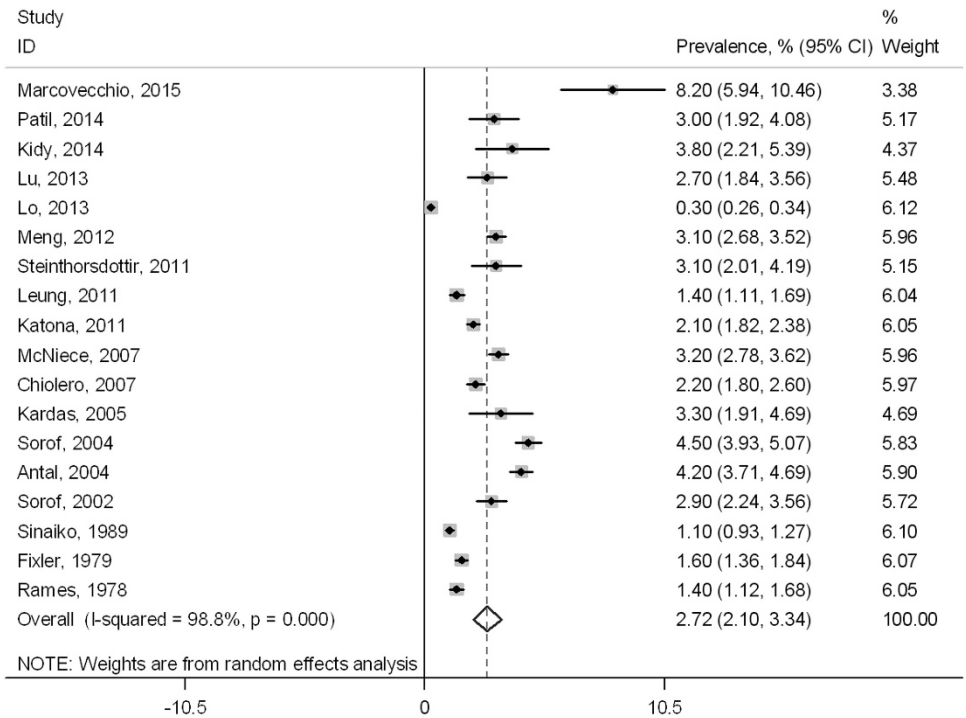

Figure 4 Meta-analysis of the prevalence of elevated BP during the third visit. A full color version of this figure is available at the *Hypertension Research* journal online.

disease mortality.[42,43] It should be noted that BP measurements during a single visit may result in many false positive cases, and the findings on the risk of high BP in childhood may be inaccurate. Further, findings from the Fels Longitudinal Study suggested that several repeated body mass index values rather than repeated BP values were associated with adult left ventricular hypertrophy.[44] In addition, data from the Bogalusa Heart Study indicated that both body mass index and BP values measured at least four times during childhood statistically as the area under the curve predicted a risk of left ventricular hypertrophy, with body mass index having a larger effect than BP.[45] Although these two cohort studies used more than one BP value during different visits to predict adult health outcomes, it is still

Table 2 Meta-analyses of prevalence of elevated BP over three separate visits

	No. of studies (participants)	*Prevalence (95% CI)*	$P_{z\text{-}test}$	I^2 *(%)*	$P_{heterogeneity}$
Elevated BP					
First visit					
Total	20 (176 024)	12.1 (10.1–14.0)	<0.001	99.4	<0.001
Sex					
Boys	7 (53 986)	14.2 (8.4–20.1)	<0.001	99.4	<0.001
Girls	7 (56 860)	10.0 (6.7–13.2)	<0.001	99.2	<0.001
Age group, years					
3–11	6 (61 977)	12.3 (8.5–16.1)	<0.001	98.8	<0.001
12–20	9 (92 393)	10.6 (7.9–13.3)	<0.001	99.5	<0.001
Definition					
US references	12 (134 685)	11.7 (9.6–13.7)	<0.001	99.1	<0.001
Others	8 (41 339)	12.6 (9.5–15.6)	<0.001	98.9	<0.001
Race					
Caucasian	8 (32 955)	12.5(10.1–14.9)	<0.001	97.6	<0.001
Asian	4 (15 195)	13.3 (7.6–18.9)	<0.001	99.0	<0.001
Others	8 (127 874)	10.9 (8.5–13.4)	<0.001	99.4	<0.001
Second visit					
Total	16 (76 472)	5.6 (4.3–6.9)	<0.001	98.7	<0.001
Sex					
Boys	2 (5948)	4.8 (3.2–6.4)	0.004	88.1	<0.001
Girls	2 (5951)	4.2 (3.3–5.0)	0.082	66.9	<0.001
Age group, years					
3–11	5 (10 509)	5.6 (4.1–7.1)	<0.001	90.9	<0.001
12–20	6 (44 946)	6.6 (3.9–9.2)	<0.001	99.6	<0.001
Definition					
US references	9 (41 478)	5.5 (4.1–6.8)	<0.001	97.4	<0.001
Others	7 (34 944)	5.7 (3.0–8.4)	<0.001	99.3	<0.001
Race					
Caucasian	6 (25 973)	6.9 (3.4–10.4)	<0.001	99.3	<0.001
Asian	4 (15 195)	4.0 (2.6–5.3)	<0.001	93.6	<0.001
Others	6 (35 304)	5.5 (3.6–7.4)	<0.001	98.5	<0.001
Third visit					
Total	18 (171 701)	2.7 (2.0–3.3)	<0.001	98.8	<0.001
Sex					
Boys	7 (54 271)	3.5 (1.5–5.6)	<0.001	98.8	<0.001
Girls	7 (55 670)	2.3 (1.2–3.3)	<0.001	97.4	<0.001
Age group, years					
3–11	5 (59 561)	3.0 (1.4–4.5)	<0.001	97.8	<0.001
12–20	8 (90 530)	2.5 (1.6–3.4)	<0.001	99.2	<0.001
Definition					
US references	12 (134 685)	2.7 (1.9–3.5)	<0.001	98.7	<0.001
Others	6 (37 016)	2.6 (1.8–3.3)	<0.001	95.9	<0.001
Race					
Caucasian	8 (32 955)	3.1 (2.2–4.0)	<0.001	95.2	<0.001
Asian	4 (15 195)	2.5 (1.4–3.6)	<0.001	93.8	<0.001
Others	6 (123 551)	2.3 (1.4–3.1)	<0.001	99.0	<0.001
Elevated SBP					
First visit	6 (43 223)	8.3 (4.6–12.0)	<0.001	99.7	<0.001
Second visit	5 (32 582)	3.5 (1.8–5.1)	<0.001	98.9	<0.001
Third visit	5 (39 686)	1.7 (0.8–2.7)	<0.001	98.6	<0.001
Elevated DBP					
First visit	6 (43 223)	5.9 (3.3–8.5)	<0.001	99.4	<0.001
Second visit	5 (32 582)	2.1 (0.8–3.3)	<0.001	98.6	<0.001
Third visit	5 (39 686)	0.7 (0.4–1.1)	<0.001	94.0	<0.001

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

unclear whether or not persistent childhood elevated BP during three separate visits would be better for predicting target organ damage in childhood and the long-term cardiovascular disease burden in adulthood using a prospective study design before the appropriate recommendations can be made. Most recently, the Cardiovascular Risk in Young Finns Study showed that persistent elevated BP on two occasions is superior to elevated BP measured during a single visit for predicting adult hypertension.[46]

There are two strengths in our study. First, this is the first meta-analysis comprehensively assessing changes in the prevalence of elevated BP on three separate visits in children and adolescents. Second, the included studies included a total of 179 561 participants, which provides sufficient statistical power to draw creditable conclusions. However, several limitations should be noted. First, because there was significant between-study heterogeneity during each of the three visits, the results should be interpreted with caution. We performed a meta-regression analysis to examine the source of heterogeneity using potential variables, including sex, age, race, definition of elevated BP and BP measurement devices, but we failed to find the source of the heterogeneity. Second, several included studies did not consider loss to follow-up during the second or third visit, which may have potentially resulted in slight underestimation of the true hypertension prevalence. Third, within-person BP changes may be more important than repeated population measures; however, all the included studies treated the participants as a group, not as individuals. Fourth, the included studies were mainly conducted in Caucasian children; therefore, the generalizability of our results to other populations should be cautious.

In conclusion, the true prevalence of hypertension in children and adolescents is ~3% over three different visits. In addition, the present meta-analysis provides evidence-based results in support of the recommendation of the US Fourth Report by NHBPEP in 2004 that the definition of pediatric hypertension should be based on BP measurements on at least three occasions in clinical practice or epidemiological studies to avoid false positive cases. Further prospective studies should determine whether this procedure is better than BP measurements during only one visit in predicting future BP-related morbidity and mortality in both childhood and adulthood.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Author contributions: Dr BX conceptualized and designed the study, reviewed and revised the manuscript and approved the final manuscript as submitted. Dr JS and Dr BX drafted the initial manuscript and approved the final manuscript as submitted. Dr JS, Dr CM and Dr YL designed the data collection instruments, coordinated and supervised data collection and approved the final manuscript as submitted. Dr LMS reviewed and revised the manuscript and approved the final manuscript as submitted.

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