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Trends and Status of the Prevalence of Elevated Blood Pressure in Children and Adolescents in China: a Systematic Review and Meta-analysis

Lulin Wang[1] · Lulu Song[1] · Bingqing Liu[1] · Lina Zhang[1] · Mingyang Wu[1] · Zhongqiang Cao[2] · Youjie Wang[1]

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Abstract

Purpose of Review To evaluate the status of elevated blood pressure in Chinese children and adolescents, and identify potential influence factors.

Recent Findings We searched PubMed, the Web of science, the WanFang, the VIP, and the CNKI to identify articles that were published from Jan 1, 1997, to May 30, 2019. We used random effects models to estimate the pooled prevalence of elevated blood pressure, and heterogeneity among the studies was assessed with Cochran's Q statistic. The potential source of heterogeneity was explored by meta-regression and subgroup comparisons using Q test based on ANOVA. Fifty-nine studies were included in the qualitative synthesis and the prevalence of elevated blood pressure ranged from 2.2 to 26.4%. The meta-analysis included 25 studies (341,281 participants), and the pooled prevalence of elevated blood pressure was 9.8% (95% CI 7.9, 11.9). The prevalence of elevated blood pressure in the obese children (34.1%, 95% CI 26.9, 41.7) and overweight children (15.5%, 95% CI 10.1, 21.7) was much higher than that in the normal or underweight children (5.0%, 95% CI 2.4, 8.4). Fluctuating trends in the prevalence of elevated blood pressure both in the total sample of Chinese children and adolescents and in each subgroup were observed from 2007 to 2014.

Summary Our study showed that prevalence of elevated blood pressure in children and adolescents in China was in the medium level in the world. Primary prevention for childhood hypertension should be implemented and focus on weight control and healthy lifestyle habits.

Keywords Elevated blood pressure · Children · Adolescents · Meta-analysis

Introduction

Hypertension is a global public health issue that contributes to the burden of cardiovascular disease, stroke, and premature mortality. Approximately 17.7 million deaths are attributed to cardiovascular disease worldwide every year, and hypertension accounts for 9.4 million of these deaths [1, 2]. From 1975 to 2015, the prevalence of hypertension in adults increased due to population growth and aging at the global level. Favorable trends have been seen in high-income countries while the majority of the increase in the past four decades occurred in low- and middle-income countries [3, 4]. China has been in a fast and stable development state in recent years. A national survey conducted from October 2012 to December 2015 revealed that estimated 244.5 million Chinese people aged 18 or older had hypertension, which indicates that hypertension is a severe public health issue in China [5, 6].

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✉ Zhongqiang Cao
bestfriends985@163.com

✉ Youjie Wang
wangyoujie@mails.tjmu.edu.cn

[1] Department of Maternal and Child Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

[2] Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China

The evidence suggesting that hypertension tracks from childhood to adulthood and the high prevalence of hypertension among children and adolescents make childhood hypertension a major concern [7]. Elevated blood pressure (EBP) in childhood impacts long-term outcomes of cardiovascular complications, such as arterial stiffness, left ventricular hypertrophy, and early blood vessel endothelial damage. Children with sustained hypertension have a greater chance of developing cognitive impairment and retinal changes [8, 9]. Furthermore, in recent years, blood pressure in children and adolescents has showed an uptrend and prevalence rates of EBP have also increased over time in Chinese children and adolescents [10–14]. Thus, preventing and controlling hypertension during childhood is of far-reaching significance.

Because hypertension is less common in children and adolescents, most studies on hypertension have focused on adults. Evidence for trends in the prevalence of hypertension and its causes in children and adolescents in China is limited. In this study, we performed a systematic review and meta-analysis to estimate the trend in the prevalence of EBP in children and adolescents in China and to explore the relationship between EBP and obesity.

Methods

Search Strategy and Study Eligibility

We did a comprehensive search of PubMed, the Web of science, the WanFang database (China Online Journals), the VIP database (Chinese Scientific Journals Database), and the CNKI (China Academic Journals Full-text Database). All relevant articles on EBP among Chinese children and adolescents, which were published in English or Chinese from Jan 1, 1997, to May 30, 2019, were identified online. We prelimited articles to recent two decades to avoid outmoded estimates. The search strategy we applied contained three aspects. Terms we used for EBP were "hypertension," "high blood pressure," "systolic hypertension," and "diastolic hypertension." Children and adolescents were identified with the terms "children," "child," "childhood," "adolescent," "pediatric," "teens," "teen," "teenager," "youth," and "infant." Except for "China," names of each province/municipality/AR (Autonomous Region)/SAR (Special Administration Region) in China were also implemented to locate our target population, such as "Zhejiang" and "Jiangsu." All the queries used in PubMed were presented in Online Resource 1. We recomposed the search strategies and utilized them on other databases. All the articles we got were collected to the next step.

The studies included in this systematic review met the following inclusion criteria: observational studies of populations without a specific disease or profile (overweight, obese, female, or minority) and studies focusing on children and adolescents aged 1 to 20 years residing in China. We excluded studies on non-systematic hypertension (pulmonary hypertension, portal hypertension), clinical trials, or case-control studies in which participants were selected based on their blood pressure level, and studies conducted among populations that included adults older than 20 years and studies that included fewer than 581 subjects. The minimum sample size was calculated by the following formula: $n = \frac{z^2_{1-\alpha/2}p(1-p)}{d^2} \approx 581$, where the expected prevalence ($p = 6.47\%$) of EBP in children and adolescents was obtained from a national survey in China [13]; the significant level was 95% ($z_{1-0.05/2} \approx 1.96$), and the allowable error was 2% ($d = 0.02$). Reviews, letters, comments, responses, news, conference proceedings and articles without prevalence of hypertension, primary data, expatiation of the methods (blood pressure testing protocol, diagnostic criterion, or sampling method), or an acceptable definition of EBP (e.g., blood pressure greater than the mean ± SD, applied unacceptable diagnostic criteria derived from their own sample population, ≥ 130/85 mmHg, ≥ 140/90 mmHg) were also excluded. If studies were published in more than one report, we deemed the report with the largest sample size as the most representative.

In our systematic review, studies were screened independently by two investigators based on titles and abstracts. The split between two reviewers was resolved by consensus through discussion.

Data Extraction and Quality Assessment

We extracted information about first author, time of publication and recruitment, characteristics of population, method of blood pressure assessment, and numbers diagnosed with EBP (systolic or diastolic blood pressure greater than or equal to the 95th percentile) and slightly EBP (systolic or diastolic blood pressure greater or equal to 90th percentile but lower than 95th percentile), elevated diastolic and systolic blood pressure respectively. Two regions (southern, northern), which were mainly based on differences in geographical location, physical geography, and human geography, were assigned to every study according to the location of the majority of the recruitment areas. We retrieved the gross domestic products per capita (GDP) in the Chinese currency yuan for each year and each province from the National Bureau of Statistics of China. We considered the GDP of the first year of recruitment if the period of recruitment covered more than 1 year. For studies that included more than one province, mean GDP of the provinces was calculated.

The tool developed by Hoy and Brooks in the year 2012 [15] was applied to assess the risk of bias of the included studies. There are ten items included in this tool, and each particular item is scored as follows: the answer "no (high risk)" counts as a score of 0 or and the answer "yes (low risk)"

counts as a score of 1. The methodological quality of each study was assessed based on the overall scores ranging from 0 to 10, and we divided the studies into three groups: low (≥ 8), moderate (6–7), and high (≤ 5) risk of bias studies.

Data Analysis

The studies with low risk of bias, random selection, and prospective data collection were included in meta-analysis. Data were analyzed using Stata software, version 12.0. The prevalence estimates were calculated with the double arcsine transformed prevalence of each study to stabilize variances [16]. We summarized the study-specific estimates using a random effects model to obtain a pooled estimate because of the high heterogeneity among the studies. The heterogeneity was estimated with Cochran's Q statistic based on χ^2 and I^2 statistics (values of 25%, 50%, and 75% represent low, moderate, and high degrees of heterogeneity, respectively). To further investigate potential sources of heterogeneity, we performed subgroup analyses and meta-regression analysis. Subgroups were determined by the following relevant characteristics: geographical region (southern, northern), setting (urban, rural), age group (4–12 years old, 13–20 years old), gender, measurement device (aneroid, digital, mercury), definition of diastolic blood pressure (Korotkoff fourth sound or fifth sound), number of blood pressure measurements (average of two, average of three), BMI (underweight or normal, overweight, obese), sample size (< 6399, ≥ 6399; the median of sample size), and diagnostic criteria (Chinese, American). Subgroup comparisons applied a Q test based on the analysis of variance, and a p value less than 0.05 was considered to be significant. A meta-regression was used to analyze the association between the prevalence of EBP and GDP. Due to the correlations between obesity and GDP, we adjusted for the proportional of overweight and obese children in the original study population (the mean of BMI from the original studies was limited). As for the time trends of the prevalence of EBP, we pooled the prevalence for each recruitment year and showed the trends with time line charts. The proportions of the overweight and obese individuals were also summarized for each year to explore the correlations between EBP and overweight and obesity.

Results

Our systematic analysis included 59 studies from 58 articles [12, 17–74], of which 25 studies were considered in the meta-analysis. The flow diagram of studies screening was showed in Fig. 1. Online Resource 1 shows the characteristics of original studies. Table 1 presents the summarization of methodological quality and characteristics of included studies. All 25 studies [17–39, 69, 70] included in meta-analysis had randomly selected participants, prospectively collected data, and low risk of bias in methodology.

The prevalence rate of EBP from 59 studies varied from 2.2 to 26.4% and prevalence of slightly EBP was between 3.9 and 29.9% from 15 studies. There were 10 studies reported the prevalence rates of elevated systolic blood pressure (from 1.8 to 14.1%) and diastolic EBP (from 1.8 to 10.8%). Prevalence of EBP was between 1.3 and 15.3% among populations with normal weight or underweight, 5.0% and 32.2% among the overweight, 9.6% and 70.4% among the obese, and 2.0% in the underweight mentioned in only one studies. Prevalence of EBP was between 1.5 and 32.2% in female, and 2.4 and 23.8% in male. Prevalence also widely varied by age group for 1.3–23.0% in children aged 2–12 years and 3.3–18.0% in teenagers aged 13–20 years.

A total of 341,281 participants from 25 studies were included in this meta-analysis. The pooled prevalence of EBP was 9.8% (95% CI 7.9, 11.9). The prevalence of slightly EBP was 7.7% (95% CI 6.2, 9.3). The rate of elevated diastolic blood pressure (6.2%, 95% CI 4.4, 8.4) was lower than that of elevated systolic blood pressure (9.7%, 95% CI 6.4, 13.4). The prevalence of EBP was 9.2% (95% CI 6.3, 12.6) in the northern region, which was similar to the prevalence in the southern region (10.1%, 95% CI 7.6, 12.9) (Fig. 2). The prevalence of EBP was higher in urban areas. All pooled prevalence rates of EBP were showed in Fig. 3. With respect to BMI, the prevalence of EBP in the obese and overweight children was significantly higher than that in the normal weight or underweight children (Fig. 4). The prevalence of EBP differed between subgroups stratified by age, gender, and sample size. The prevalence was higher among boys and children aged 12 and younger, and in studies with a sample size greater than the median. Method of blood pressure assessment also altered the prevalence rates of EBP. The prevalence rates were higher when blood pressure was measured by a digital sphygmomanometer, and when the diastolic blood pressure was defined as the disappearance of the fifth korotkoff sound. We also found that the prevalence of EBP measured with three readings was lower than that measured with two readings, and the prevalence of EBP determined according to the American diagnostic criteria was higher than that determined according to the Chinese criteria. All differences between subgroups were significant (all p value < 0.0001) (Fig. 3, Online Resource 2).

As shown in Fig. 5, from 2007 to 2014, the prevalence of EBP among Chinese children and adolescents fluctuated over time from 6.14% in 2011 to 18.14% in 2007. Generally, the prevalence showed a U-shaped curve from 2007 to 2014 with a fluctuation in 2010 and a decline observed after 2013. Similar trends were found for both sexes and for both age groups. The trends of prevalence in the three subgroups divided by BMI were all similar, and the differences among the three subgroups were notable, which was consistent with the results of the

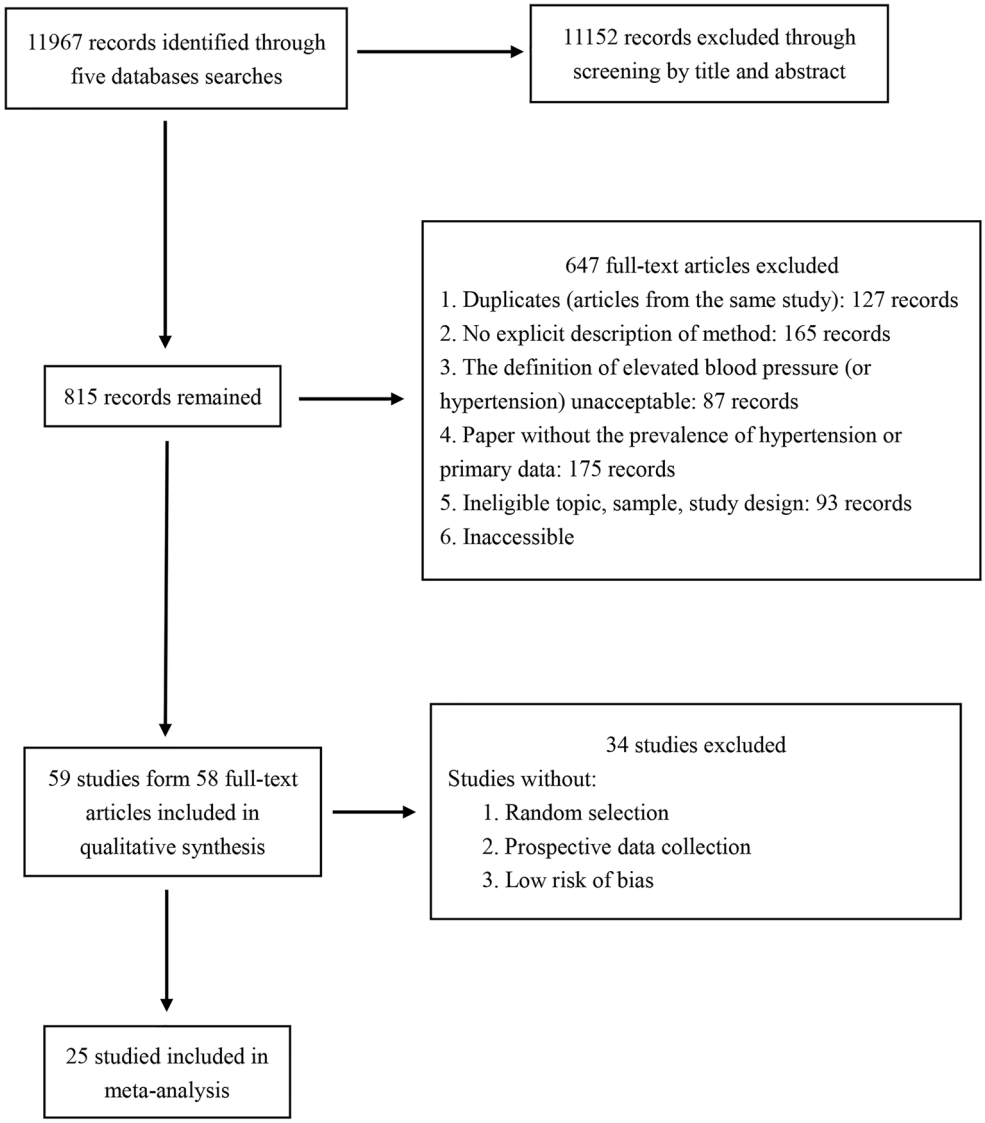

Fig. 1 Study selection

subgroup analysis. The prevalence of EBP in the northern region fluctuated more than that in the southern region.

Meta-regression analysis did not show significant association between prevalence of EBP and gross domestic product per capita (regression coefficient 8.40e−7; 95% CI − 3.46e−6, 5.14e−6; $p = 0.687$; from 21 studies) until we adjusted for the $\log_{10}$-transformed proportion of overweight and obesity population in each study (adjusted regression coefficient 7.30e−6; 95% CI 6.05e−8, 1.45e−5; $p = 0.049$; from 9 studies). Provinces with higher GDP had higher prevalence of EBP in children and adolescents (Online Resource 2).

Discussion

Our systematic review identified 59 studies, and the meta-analysis summarized the prevalence data from 25 studies that included a total of 341,281 individuals. The pooled prevalence of elevated blood pressure among children and adolescents was 9.8%, and the pooled prevalence of slightly elevated blood pressure was 7.7% in China. High BMI was a main risk factor for elevated blood pressure. The prevalence of elevated blood pressure in obese children and adolescents was more than six times higher than that in the normal and underweight children and adolescents.

A systematic review of the prevalence of high blood pressure in adolescents worldwide published in 2014 provided an estimated high blood pressure prevalence of 12.4% in Asians. Africa had the highest prevalence of 25.5%, and the lowest prevalence of 5.3% was found in the Middle East [75]. Our estimate of the prevalence among Chinese children and adolescents is similar to the prevalence in the Asian population and is in the medium level worldwide. The prevalence revealed in this study is comparable to that in Korea from

Table 1 Characteristics of included studies

Methodological quality	All studies ($n = 59$)	Studies included in meta-analysis ($n = 25$)
Timing of data collection	Prospective ($n = 50$); retrospective ($n = 9$)	Prospective ($n = 25$)
Risk of bias	Low risk ($n = 29$); moderate risk ($n = 30$)	Low risk ($n = 25$)
Selection of participants	Random ($n = 52$); not random ($n = 7$)	Random ($n = 25$)
Characteristics		
Time of publication	2009–2018	2010–2018
Patient recruitment period	2000–2018 (from 50 studies)	2007–2015 (from 22 studies)
Provinces*	Anhui (3), Beijing (6), Heilongjiang (4), Chongqing (9), Gansu (2), Guangdong (7), Guangxi (4), Guizhou (3), Hainan (3), Hebei (3), Henan (3), Hong Kong (1), Hubei (2), Hunan (7), Inner Mongolia (2), Sichuan (2), Jiangsu (7), Jiangxi (3), Liaoning (6), Tianjin (4), Ningxia (6), Shandong (8), shanghai (8), Shanxi (2), Taiwan (1), Xinjiang (2), Yunnan (2), Zhejiang (4), Jilin (2)	Anhui (2), Beijing (1), Chongqing (4), Guangdong (1), Guangxi (1), Hebei (2), Henan (1), Hunan (3), Jiangsu (3), Liaoning (2), Ningxia (1), Shandong (1), Shanghai (2), Taiwan (1), Zhejiang (1), Tianjin (1)
Blood pressure values considered	One reading ($n = 1$); average of two readings ($n = 33$); average of three readings ($n = 17$); missing data ($n = 8$)	One reading ($n = 0$); average of two readings ($n = 12$); average of three readings ($n = 9$); missing data ($n = 4$)
Types of device for blood pressure measurement	Aneroid sphygmomanometer ($n = 1$); digital sphygmomanometer ($n = 10$); mercury sphygmomanometer ($n = 41$); missing data ($n = 7$)	Aneroid sphygmomanometer ($n = 1$); digital sphygmomanometer ($n = 3$); mercury sphygmomanometer ($n = 20$); missing data ($n = 1$)
Definition of elevated blood pressure	Acceptable definition‡ ($n = 59$)	Acceptable definition‡ ($n = 25$)
DBP was defined by the fourth/fifth Korotkoff sound	Fourth ($n = 18$); fifth ($n = 19$); missing data ($n = 22$)	Fourth ($n = 8$); fifth ($n = 6$); missing data ($n = 11$)
Diagnostic criteria†	Chinese ($n = 40$); American ($n = 21$); International ($n = 1$); Japanese ($n = 1$)	Chinese ($n = 16$); American ($n = 10$)
Mean age (years)	4.8–14.7 (from 21 studies)	9.3–14.5 (from 9 studies)
Age range (years)	2, 20	4, 20
Mean BMI (kg/m^2)	16.10–20.10 (from 14 studies)	19.6 (from 1 studies)
Overweight and obesity participants	3.98–43.66% (from 30 studies)	13.28–39.02% (from 11 studies)
Male participants	44.19–68.16%	48.38–56.15%
Gross domestic product per capita, median (IQR)	CNY§41,378 (21,864–62,121) (from 44 studies)	CNY§42,355 (28,792–56,649) (from 21 studies)

*Some studies covered more than one province; †some studies applied more than one criterion; ‡acceptable definition: systolic or diastolic blood pressure ≥ 95th percentile; §CNY: China Yuan

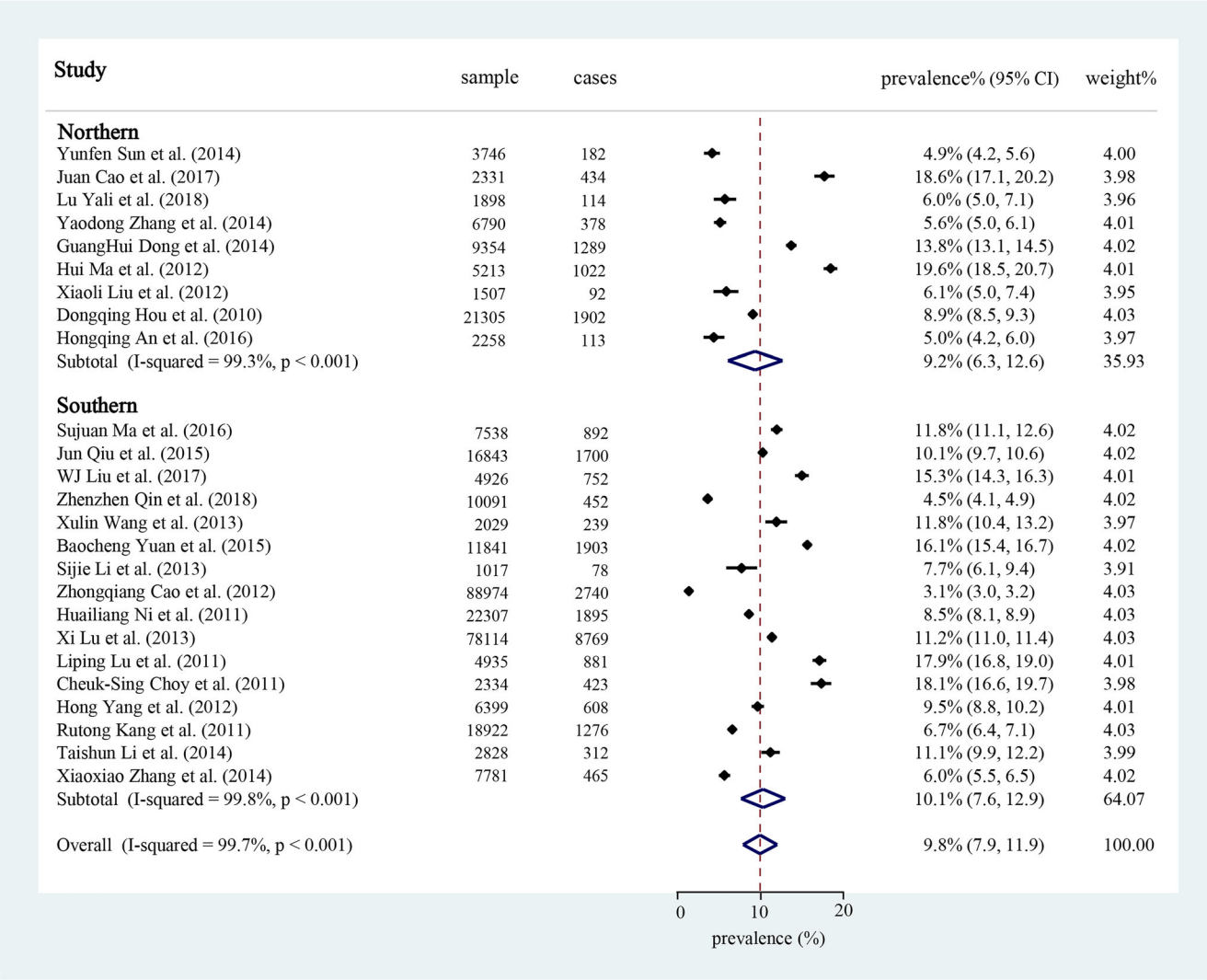

Fig. 2 Prevalence rates of elevated blood pressure among children and adolescents in China. DBP, diastolic blood pressure; K4/5, korotkoff fourth/fifth sound; BP, blood pressure

1997 to 2013, but is much higher than the prevalence in Korea in recent years [76], indicating the importance and urgency of addressing EBP in Chinese children and adolescents.

In the present study, we found that the prevalence of EBP in children and adolescents fluctuated over time and did not show any long-term increasing or decreasing trend. Four original studies reported time trends in the prevalence of EBP in Chinese children and adolescents. Two studies demonstrated an upward trend from 1993 to 2009 and from 2000 to 2010 [11, 12]. The other two studies observed U-type fluctuation trends during the periods of 1985 to 2010 and 1995 to 2014, with the lowest prevalence observed in 2005 [13, 14]. However, these four studies analyzed data that was collected every 5 years or at only two time points, trends in prevalence could not be fully described. We also explored the trends in the prevalence of EBP in different subgroups. Except for the large difference between the subgroups that were divided by region, we observed similar trends in the subgroups that were stratified by gender, BMI, and age. The trend in the southern region subgroup was flatter than that in the northern region, which might be due to the larger geographic area of the northern region leading to more diverse lifestyle habits and human characteristics.

Our findings suggested that overweight and obesity were major risk factors for hypertension, consistent with those of previous studies in different countries [77, 78]. The mechanisms underlying had been widely discussed before, and the increased systemic circulation volume induced by excess body fat and increased sodium reabsorption in overweight and obese children was largely responsible [79]. However, in this study, we did not find parallelism between trends in the proportion of overweight and obesity among the study participants and the prevalence of hypertension, consistent with results from many previous studies [80]. This discordant result indicates that some other factors may influence the prevalence of EBP, such as healthy dietary habits, salt intake, or physical activity.

	Number of studies	Number of participants	Number of cases	Prevalence (95%*CI*)	I^2	*P* values	
						Heterogeneity	Subgroup difference
Global analysis							
Overall elevated blood pressure	25	341281	28911	9.8% (7.9,11.9)	99.7%	<0.0001	-
Elevated systolic blood pressure	4	86391	7815	9.7% (6.4,13.4)	98.7%	<0.0001	-
Elevated diastolic blood pressure	4	86391	4975	6.2% (4.4,8.4)	97.2%	<0.0001	-
Slightly elevated blood pressure	6	133357	9613	7.7% (6.2,9.3)	98.6%	<0.0001	-
Subgroup analysis							
Geographical region							
Overall	25	341281	28911	9.8% (7.9,11.9)	99.7%	<0.0001	<0.0001
Northern	9	54402	5526	9.2% (6.3,12.6)	99.3%	<0.0001	-
Southern	16	286879	23385	10.1% (7.6,12.9)	99.8%	<0.0001	-
Setting							
Overall	11	156521	9683	9.0% (5.7,13.0)	99.8%	<0.0001	<0.0001
Urban	8	147153	8544	9.2% (5.5,13.7)	99.8%	<0.0001	-
Rural	3	9368	1139	8.6% (1.8,19.9)	99.6%	<0.0001	-
Age group							
Overall	22	205323	13406	8.5% (6.6,10.6)	99.6%	<0.0001	<0.0001
4~12years	12	69166	5754	8.8% (5.9,12.2)	99.5%	<0.0001	-
13~20years	10	136157	7652	8.1% (5.7,11.0)	99.5%	<0.0001	-
Gender							
Overall	42	253667	18768	9.4% (7.7,11.2)	99.5%	<0.0001	<0.0001
Male	21	129543	11453	10.6% (8.5,12.8)	99.3%	<0.0001	-
Female	21	124124	7315	8.3% (5.9,11.0)	99.6%	<0.0001	-
Device							
Overall	24	340264	28833	9.9% (7.9,12.1)	99.7%	<0.0001	<0.0001
Aneroid	1	2828	312	11.1% (9.9,12.2)	-	-	-
Digital	3	14795	2078	15.1% (11.6,19.0)	97.3%	<0.0001	-
Mercury	20	322641	26443	9.1% (7.1,11.5)	99.8%	<0.0001	-
Definition of DBP(K4/K5)							
Overall	14	265372	21690	10.1% (7.3,13.2)	99.8%	<0.0001	<0.0001
K4	8	211097	15984	9.4% (5.7,14.0)	99.9%	<0.0001	-
K5	6	54275	5706	11.0% (7.7,14.8)	99.4%	<0.0001	-
Number of BP measurement							
Overall	21	234418	17274	9.7% (7.4,12.2)	99.7%	<0.0001	<0.0001
Average of two	12	77031	8182	10.6% (7.9,13.7)	99.4%	<0.0001	-
Average of three	9	157387	9092	8.5% (5.4,12.1)	99.8%	<0.0001	-
Sample size							
Overall	25	341281	28911	9.8% (7.9,11.9)	99.7%	<0.0001	<0.0001
<6399	12	35022	4642	11.2% (8.1,14.8)	99.0%	<0.0001	-
⩾6399	13	306259	24269	8.6% (6.2,11.2)	99.8%	<0.0001	-
Diagnostic criteria							
Overall	25	341281	28911	9.8% (7.9,11.9)	99.7%	<0.0001	<0.0001
American	9	58332	6133	10.8% (8.1,13.9)	99.1%	<0.0001	-
Chinese	16	282949	22778	9.2% (6.8,12.0)	99.8%	<0.0001	-

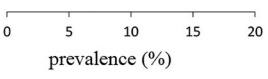

Fig. 3 Prevalence rates of elevated blood pressure in children and adolescents in southern and northern regions of China

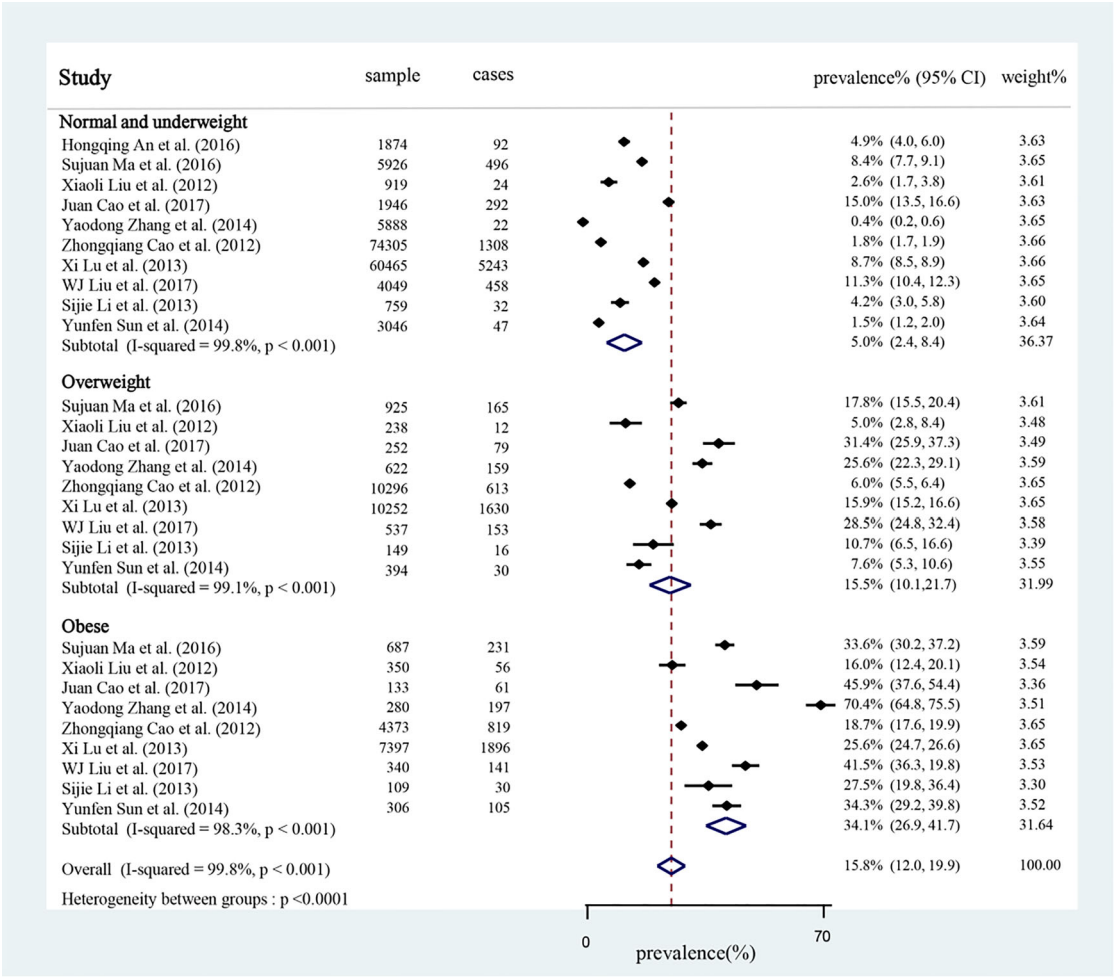

Fig. 4 Prevalence rates of elevated blood pressure among Chinese children and adolescents in subgroups stratified by body mass index

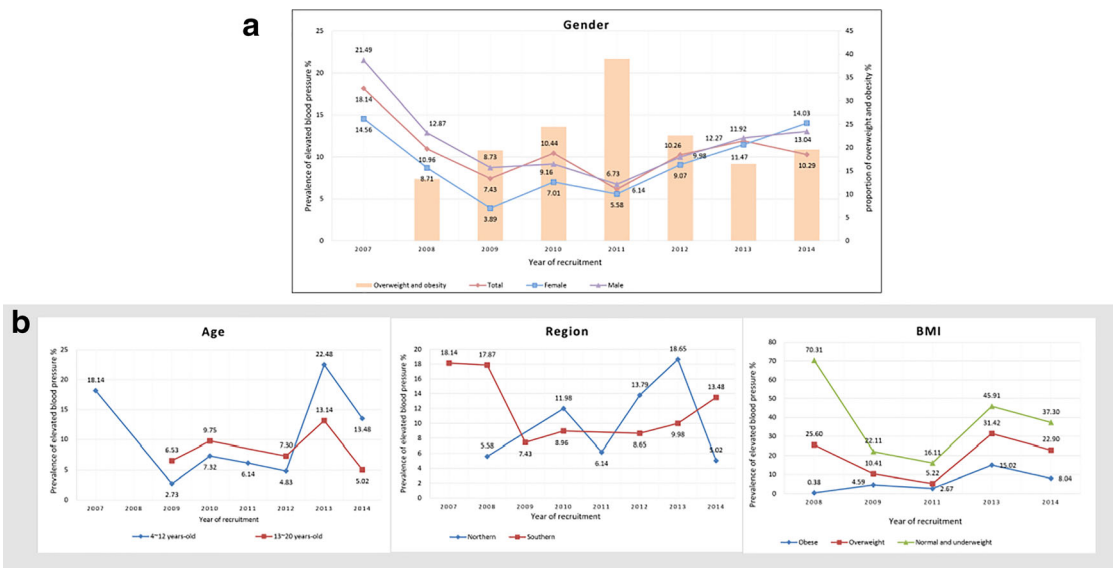

Fig. 5 **a** Trends in prevalence of elevated blood pressure in Chinese children and adolescents, in Chinese boys and girls from 2007 to 2014. **b** Trends in prevalence of elevated blood pressure in subgroups stratified by age, region, and body mass index among Chinese children and adolescents. BMI, body mass index

Previous studies showed that compared to urban areas, rural areas had a significantly lower prevalence of hypertension [81, 82]. The same pattern was also found in this study. Urbanization was thought to be strongly associated with an increased prevalence of hypertension [83], and increased blood pressure has even been observed in migrants from rural to urban areas [84]. The large differences between urban and rural lifestyles might account for the higher prevalence of hypertension in urban populations. Greater accessibility to highly processed and fast foods with more fats, oil, and carbohydrates in urban areas results in increased energy intake. In addition, the widespread use of motorized transportation, convenient daily life, and reduced manual labor decrease the energy expenditure of inhabitants of urban areas.

EBP in children and adolescents is a heavy burden on the health of children and adolescents in China and might be largely driven by high BMI. EBP in children and adolescents not only affects childhood health but also increases the risk of hypertension and cardiovascular disease in adulthood [7, 8]. Although the awareness, treatment, and control rates of hypertension among adults in China have significantly improved in the past decades, the prevalence of hypertension, compared to some developed countries, is still suboptimal [5, 85, 86]. Additionally, the prevalence in children and adolescents has been neglected. To our knowledge, this systematic review and meta-analysis was the first to summarize the prevalence of EBP among Chinese children and adolescents and show the trends of prevalence of EBP in recent years.

Nonetheless, some limitations of this study should be taken into consideration. First, the studies included in our review applied different diagnostic criteria, which were derived from populations from different countries, including China, America, Japan, and a combination of seven countries (China, India, America, Tunisia, Japan, Iran, Korea, and Poland). Second, there was high heterogeneity between the studies included in our review. We performed subgroup analyses and determined wide variation in the methods used for blood pressure measurement. These differences in measurement methods could partly explain the heterogeneity among the studies. Third, the limited information and data in our study did not allow to describe the age and region distribution of hypertension prevalence. Fourth, the exploration of the trends in prevalence was restricted to between 2007 and 2014 and did not adjust for confounders.

Conclusions

This study described the prevalence of EBP among Chinese children and adolescents and noted that overweight and obesity might be important risk factors. The prevalence of EBP fluctuated over time and did not show a unidirectional long-term trend from 2007 to 2014. More detailed studies with uniform and reliable diagnostic methods are needed to obtain a better estimate of the prevalence of EBP and its drivers in children and adolescents in China.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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