

# The prevalence of hypertension in Chinese adolescents aged 15–17 years: A comparison of different criteria

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## Abstract

This study intended to compare the prevalence of hypertension in adolescents aged 15–17 years in China according to different criteria defined by various guidelines. We included 28 715 adolescents aged 15–17 years from the China Hypertension Survey study (CHS) 2012–2015, and the 2017 American Association of Pediatrics (AAP) Clinical Practice Guideline and 2018 Chinese guidelines for children and adults were used to define hypertension. The prevalence of hypertension among Chinese adolescents aged 15–17 years was 24.4% according to the 2018 Chinese guidelines for children; the corresponding values were 18.6% according to the 2017 AAP Guidelines, and 3.5% according to 2018 Chinese guidelines for adults. The age-specific prevalence of hypertension in the age of 15, 16, and 17 years in the same population was 26.2%, 24.4%, and 23.3% according to 2018 Chinese guidelines for children; 18.8%, 17.9%, and 19.2% as per the 2017 AAP Guidelines; 3.4%, 3.4%, and 3.6% as per the 2018 Chinese guidelines for adults. A highest prevalence of hypertension was observed according to 2018 Chinese guidelines for children than the other two guidelines. Compared with the 2018 Chinese guidelines for children, a higher 95<sup>th</sup> percentile BP (systolic and diastolic) was also observed in the present study in each gender-age-height-specific group. And the height, which was key factor to influence blood pressure, was similar between adolescents aged 15–17 and adults, and a paralleled result was seen in the present study. Therefore, the 2018 Chinese guidelines for adults may also be appropriate for adolescents aged 15–17 years.

## KEYWORDS

adolescents, China, cross-sectional study, hypertension, prevalence

## 1 | INTRODUCTION

Cardiovascular diseases are a serious global health issue, and hypertension (HTN) is one of the most important risk factors of cardiovascular disease.<sup>1</sup> HTN in children can find its way into adulthood, and childhood HTN is an independent risk factor of adult HTN.<sup>2–4</sup> In addition, HTN during childhood and adolescence is associated with the risk of damage to various organs and other clinical manifestations,<sup>5</sup> including an increase of carotid intima media thickness,<sup>6</sup> left ventricular hypertrophy,<sup>7</sup> and increased arterial stiffness.<sup>8</sup> These manifestations increase the risk of adverse cardiovascular outcomes in the future. Meanwhile, BP levels and prevalence of HTN among children in China have increased significantly in recent decades.<sup>9,10</sup> According to the latest study, 22.1% of children and adolescents in China of age 13–17 years had HTN.<sup>10</sup> Therefore, timely identification and treatment of HTN are critical.

However, no criterion is currently available to define an accurate BP level in children and adolescents that would result in cardiovascular diseases in adulthood. BP changes substantially during normal growth and development during childhood and during pubertal development in adolescents. Sex, age, and height are all important influencing factors of BP level.<sup>11</sup> Therefore, all criteria, including China, take into account the percentile rank based on age, sex, and height when defining HTN among children and adolescents.<sup>12</sup> The 2017 American Association of Pediatrics Clinical Practice Guideline (CPG) adopted the 2017 American Heart Association and American College of Cardiology adult Hypertension guidelines for adolescents  $\geq 13$  years of age.<sup>13</sup> However, the 2018 Chinese Hypertension Prevention and Treatment Guideline for children and adolescents aged 3–17 years (CGC) still used a percentile-based definition,<sup>14</sup> although the heights of Chinese adolescents aged 15–17 years are similar to those of Chinese adults.<sup>15</sup> It remains unclear whether the Chinese guidelines for adults (CGA) can be used for adolescents aged 15–17 years. In this study, we aim to compare the prevalence of HTN in adolescents aged 15–17 years based on the China Hypertension Survey study (CHS) 2012–2015 data estimated by three HTN criteria, namely 2017 CPG, 2018 CGC, and 2018 CGA.

## 2 | METHODS

### 2.1 | Study design and population

Data for this study were derived from the CHS, which was conducted from October 2012 to December 2015 by our team. The study design of CHS was published elsewhere.<sup>16</sup> The CHS included a sample of Chinese residents aged  $\geq 15$  years from 31 provinces of mainland China. A stratified multistage random sampling method was used to ensure that the sample was a good representative of the population. First, four urban cities and four rural counties within each province were selected. Then, the simple random sampling method was used to obtain two districts or two townships within each city or county; the same method was used to select three communities or villages within each district

or township, respectively. Finally, according to lists compiled from the local government registers of households, we selected a given number of individuals from each of the 14 sex/age strata from each community or villages. A total of 479 842 participants were eligible who had completed records in the survey. The overall response rate of the survey was 66.4%. After excluding participants over 18 years of age, we finally included 28 715 adolescents aged 15–17 years in this study. Written informed consent was obtained from every person before data collection. The study was approved by the Ethics Committee of Fuwai Hospital (Beijing, China, Approve NO.:2014-402).

### 2.2 | Data collection

Information about demographics, social-economic factors, lifestyle factors, history of disease was obtained by a team of trained investigators using a standardized questionnaire developed by Fuwai Hospital. A standard right-angle device and a fixed measurement tape (to the nearest 5 mm) were used to measure height without shoes. Body weight was measured in standing position with light clothing using an OMRON body fat and weight measurement device (V-body HBF-371, OMRON, Kyoto, Japan). An automated oscillometric device (OMRON HBP-1300, Professional Portable Blood Pressure Monitor OMRON, Kyoto, Japan) with a proper sized cuff was used to measure BP on the right arm positioned at heart level in a seated position three times with 30 seconds between each measurement. Before the measurement, the participant was made to sit at rest for 5 minutes. The average of three measurements was recorded for analysis.

### 2.3 | Definitions

Firstly, HTN was defined as measured systolic BP (SBP) and (or) diastolic BP (DBP) values  $\geq 95^{\text{th}}$  percentile of the age-, sex-, and height-specific BP reference according to the latest CGC.<sup>14</sup> SBP and (or) DBP between the 90<sup>th</sup> and 95<sup>th</sup> (including the 90<sup>th</sup> percentile and excluding the 95<sup>th</sup> percentile) were used to identify elevated BP cases. People with SBP  $\geq 140$  and/or DBP  $\geq 90$  mmHg were considered to be having HTN according to CGA.<sup>14</sup> Elevated BP was defined as an SBP from 120 to 139 mmHg and/or DBP from 80 to 89 mmHg. Based on the 2017 CPG, for adolescents aged  $\geq 13$  years, HTN was defined as or SBP  $\geq 130$  and/or DBP  $\geq 80$  mmHg, and elevated BP was defined as 120/ < 80–129/ < 80 mmHg.<sup>13</sup>

The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters ( $\text{kg}/\text{m}^2$ ). The BMI groups were classified according to the “Working Group on Obesity in China” criteria.<sup>17</sup> The participant was defined as overweight if the BMI was between 85<sup>th</sup> and 95<sup>th</sup> percentile specific to sex and age, and obesity was defined if the BMI  $\geq 95^{\text{th}}$  percentile.

The sex- and age-specific height Z scores were taken from the Centers for Disease Control growth charts (<https://www.cdc.gov/growthcharts/>)<sup>18</sup> and used to categorized the height groups. The height groups were categorized as high-height group (Z-score > 1.0),

**TABLE 1** Characteristics of the study participants stratified by sex

Characteristics	Total	Sex		P value
		Boy	Girl	
No. (%)	28715	14 578 (50.8)	14 137 (49.2)	
Age, No. (%)				
15	5993 (20.9)	2988 (20.5)	3005 (21.3)	.238
16	11 772 (41.0)	5982 (41.0)	5790 (41.0)	
17	10 950 (38.1)	5608 (38.5)	5342 (37.8)	
Height (cm)	164.3 ± 8.7	169.5 ± 7.6	159.0 ± 6.3	<.001
Waist circumference (cm)	72.6 ± 9.1	74.2 ± 9.7	70.8 ± 8.2	<.001
BMI (kg/m <sup>2</sup> )	21.0 ± 3.4	21.0 ± 3.7	20.9 ± 3.2	.356
SBP (mmHg)	116.7 ± 11.7	119.8 ± 11.6	113.5 ± 10.9	<.001
DBP (mmHg)	68.4 ± 8.3	68.6 ± 8.4	68.2 ± 8.3	<.001
BMI group, No. (%)				
Thin and Normal	24 005 (83.6)	11 947 (82)	12 058 (85.3)	<.001
Overweight	3237 (11.3)	1735 (11.9)	1502 (10.6)	
Obesity	1473 (5.1)	896 (6.1)	577 (4.1)	
Region, No. (%)				
West	10 278 (35.8)	5236 (35.9)	5042 (35.7)	.882
Central	8459 (29.5)	4294 (29.5)	4165 (29.5)	
East	9978 (34.7)	5048 (34.6)	4930 (34.9)	

Data are represented as mean ± standard deviations, unless otherwise indicated.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

medium-height ( $-1.0 \leq Z\text{-score} \leq 1.0$ ), and low-height group ( $Z\text{-score} < -1.0$ ), according to the classification described elsewhere.<sup>19</sup>

## 2.4 | Statistical methods

The prevalence of HTN stratified by age, gender, and height in Chinese adolescents aged 15–17 years was estimated. The continuous variables were described by the mean and standard deviation (SD) or medians (interquartile ranges). The statistical differences between groups were evaluated by Student's t-test or Wilcoxon rank-test. The categorical variables were described by frequency (%), and  $\chi^2$  test was used to perform comparison in different groups. Besides, the potential heterogeneities in the prevalence of HTN were explored by trend test among different age, BMI and height groups. SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and R 4.0 were used to conducted statistical analyses, and  $P$  values  $< .05$  were considered as statistically significant (two-sided).

## 3 | RESULTS

### 3.1 | Characteristics of participants

The basic characteristics of participants in this study were summarized in Table 1. A total of 28 715 participants (14 578 boys and 14 137 girls)

were included in the analysis. Compared with girls, boys were significantly more overweight or obese, and the boys had significantly higher height, waist circumference, SBP, and DBP than girls ( $P < .001$ ).

### 3.2 | Comparison of HTN and elevated BP prevalence by different criteria

We observed a significant variation in the prevalence of HTN and elevated BP derived from different criteria (Table 2). The highest prevalence of HTN was obtained from CGC (24.4%, 95% CI 23.9%-24.9%), followed by CPG (18.6%, 95% CI 18.1%-19.0%), and CGA (3.5%, 95% CI 3.3%-3.7%). The highest prevalence of elevated BP was obtained from CGA (37.0%, 95% CI 36.5%-37.6%), which was about 2.5 times from CGC (15.0%, 95% CI 14.6%-15.4%) and 1.7 times from CPG (21.1%, 95% CI 20.6%-21.6%). Subgroup analysis showed that the prevalence of HTN obtained from CGC was higher than those obtained from CGA and CPG in each group. We also calculated the prevalence of HTN and elevated BP based on the percentile-based definition from CPG (Supplementary Table S1).

The prevalence of HTN increased with the increase of BMI among boys and girls ( $P$  for trend  $< .05$ ), no matter which criterion was used (Figure 1B). However, the prevalence declined with growing when CGC and CPG were used in girls ( $P$  for trend  $< .05$ , Figure 1A). Across the height spectrum, the prevalence of HTN increased significantly with an increase in height in the case of CPG and CGA ( $P$  for trend  $< .05$ , Figure 1C).

**TABLE 2** Prevalence of elevated BP and hypertension in the study participants according to three criteria

Characteristics	American Standards for Children [% (95% CI)]		Chinese Standards for Children [% (95% CI)]		Chinese Standards for Adults [% (95% CI)]	
	Elevated BP	Hypertension	Elevated BP	Hypertension	Elevated BP	Hypertension
Overall	21.1 (20.6-21.6)	18.6 (18.1-19.0)	15.0 (14.6-15.4)	24.4 (23.9-24.9)	37.0 (36.5-37.6)	3.5 (3.3-3.7)
Gender						
Boy	26.1 (25.3-26.8)	24.1 (23.4-24.8)	15.7 (15.1-16.3)	25.2 (24.5-25.9)	46.1 (45.3-46.9)	5.2 (4.8-5.5)
Girl	15.9 (15.3-16.6)	12.9 (12.4-13.5)	14.3 (13.7-14.9)	23.5 (22.8-24.2)	27.7 (26.9-28.4)	1.7 (1.5-2.0)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Age						
15	22.0 (21.0-23.1)	18.8 (17.8-19.8)	15.1 (14.2-16.1)	26.2 (25.1-27.3)	38.2 (37.0-39.4)	3.4 (3.0-3.9)
16	20.8 (20.1-21.6)	17.9 (17.2-18.6)	15.1 (14.5-15.8)	24.4 (23.7-25.2)	36.3 (35.4-37.2)	3.4 (3.1-3.7)
17	20.8 (20.1-21.6)	19.2 (18.5-19.9)	14.7 (14.1-15.4)	23.3 (22.5-24.1)	37.2 (36.2-38.1)	3.6 (3.3-4.0)
P value	.138	.048	.663	<.001	.047	.602
BMI group						
Thin	16.8 (15.4-18.3)	13.7 (12.4-15.1)	12.6 (11.4-14.0)	17.2 (15.8-18.8)	28.9 (27.1-30.7)	2.2 (1.7-2.9)
Normal	20.7 (20.2-21.3)	15.6 (15.2-16.1)	15.0 (14.5-15.5)	21.4 (20.9-22.0)	34.9 (34.3-35.6)	2.2 (2.0-2.4)
Overweight	25.5 (24.0-27.0)	28.2 (26.7-29.8)	16.5 (15.3-17.8)	35.4 (33.7-37.0)	48.5 (46.8-50.2)	6.5 (5.7-7.4)
Obesity	23.6 (21.5-25.8)	47.7 (45.2-50.3)	15.8 (14.0-17.7)	54.3 (51.8-56.9)	55.7 (53.2-58.2)	17.5 (15.6-19.5)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Height group						
Low	20.0 (19.2-20.8)	15.5 (14.8-16.2)	15.3 (14.6-16.0)	24.7 (23.9-25.6)	33.7 (32.8-34.6)	2.6 (2.3-2.9)
Medium	21.6 (21.0-22.3)	19.7 (19.1-20.3)	14.8 (14.3-15.3)	24.1 (23.4-24.7)	38.6 (37.8-39.3)	3.7 (3.4-4.0)
High	21.3 (19.3-23.5)	26.1 (23.8-28.4)	15.4 (13.6-17.4)	25.5 (23.2-27.8)	40.8 (38.2-43.4)	7.5 (6.3-9.0)
P value	.006	<.001	.470	.272	<.001	<.001
Family history of hypertension						
No	21.1 (20.6-21.6)	18.2 (17.7-18.7)	15.0 (14.6-15.5)	24.0 (23.5-24.6)	36.9 (36.4-37.5)	3.2 (3.0-3.4)
Yes	20.6 (19.0-22.2)	22.5 (20.9-24.2)	14.4 (13.0-15.8)	27.9 (26.1-29.7)	37.9 (36.0-39.8)	6.3 (5.4-7.3)
P value	.511	<.001	.371	<.001	.362	<.001
Region						
West	20.2 (19.4-21.0)	15.7 (15.0-16.4)	15.0 (14.3-15.7)	22.1 (21.3-22.9)	34.5 (33.6-35.4)	2.1 (1.9-2.4)
Central	23.7 (22.8-24.6)	18.0 (17.2-18.9)	15.3 (14.6-16.1)	24.0 (23.1-24.9)	39.4 (38.4-40.5)	3.3 (2.9-3.7)
East	19.8 (19.0-20.5)	22.0 (21.2-22.8)	14.7 (14.0-15.4)	27.0 (26.1-27.9)	37.6 (36.6-38.5)	5.0 (4.6-5.5)
P value	<.001	<.001	.466	<.001	<.001	<.001

Data are represented as percent (95% CI).

Abbreviation: BP, blood pressure.

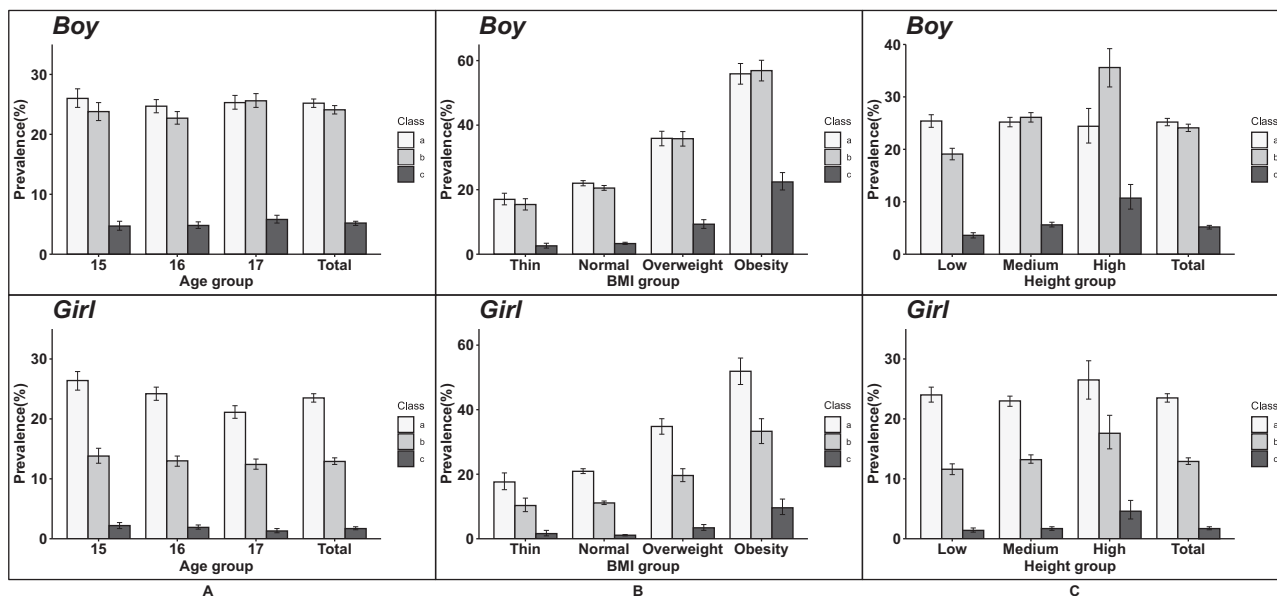
### 3.3 | Comparison of the BP level by gender, age, and height percentile

The 95<sup>th</sup> percentile of SBP/DBP for boys and girls aged 15–17 years at each height group according to CGC was given in Table 3. The 95<sup>th</sup> percentile SBP was higher than the corresponding reference values in CGC for boys and girls in the same age and height group. Especially for boys, the values were very close to 140 mmHg, and even exceeded 140 mmHg at the height percentile  $P_{62.5}$  ( $P_{82.5-1}$ ) and above. For DBP, a higher 95<sup>th</sup> percentile was found across each age-height-specific group for both sexes compared with reference values in CGC.

## 4 | DISCUSSION

In the current study, we estimated the prevalence of HTN in Chinese adolescents using a large national sample of approximately 28 715 participants. We observed a great variation in the prevalence of HTN according to HTN criteria outlined in different guidelines.

The age-, gender-, BMI-, height-specific prevalence of HTN defined by CGC was the highest, followed by CPG and CGA, irrespective of which criterion was used. Similar results were obtained in previous studies. Fan and associates<sup>20</sup> compared the HTN criteria of CGC, CPG, the US Fourth Report, and International Standards in Chinese



**FIGURE 1** Prevalence of hypertension across Age, BMI, and height groups, stratified by gender. a, the Chinese standards for children; b, the American standards for children; c, the Chinese standards for adults

children, and concluded that CGC criterion yielded a higher prevalence. Ma and associates<sup>21</sup> compared CGC, CPG, Internal Standards, and 2018 Health Industry Pediatric Blood Pressure guidelines, and came to the same conclusion. These findings indicated that the prevalence of HTN derived from CGC was the highest in Chinese adolescents when compared with the prevalence of HTN obtained from other criteria.

Although the continual rise of BP in children and adolescents is alarming, it is still difficult to clinically defined HTN in children and adolescents. Only with a few follow-up studies,<sup>21–23</sup> there are not enough data to define an exact BP level in children and adolescents that leads to adverse cardiovascular events in adulthood. In addition, even normal BP changes with age, height, and body size, the adolescents were in continual growth from prepubertal to pubertal status,<sup>12</sup> resulting in substantially varied blood pressure. These changes led to the use of age-, sex-, and height-specific percentiles to define the high blood pressure.<sup>13,14</sup> At present, a few studies have reported country-specific (including China) BP reference for children and adolescents.<sup>24–26</sup> As per a recent study from the China Health and Nutrition Survey, approximately 22.1% of Chinese adolescents aged 13–17 years had HTN as per the CGC criterion.<sup>10</sup> However, we observed a higher prevalence of 24.4% when CGC criterion was used in the present study.

According to previously study,<sup>27</sup> the influence of height on BP may even be greater than age, the BP reference in children without consideration of height may result in inaccurate BP evaluation, and the height played an important role in the definition of HTN in adolescents.<sup>11</sup> In the present study, we also observed an increased trend of prevalence with the increase of height, when CPG and CGA were used. In the past few decades, with the rapid development of the Chinese economy, the nutrition and health conditions in children and adolescents have

greatly improved, and the level of physical development has also been continuously improving.<sup>28</sup> For instance, the average height of adolescents aged 15–17 years have become close to or even higher than that of adults. According to the National Physique Monitoring Bulletin published by China,<sup>15</sup> the average height of adolescents aged 15, 16, and 17 years was 169.8, 171.4, and 172.0 cm for boys and 159.4, 159.8, and 159.4 cm for girls, respectively. However, the average height in adults aged 20–24 is 171.9 cm for men and 159.9 cm for women. Overall, the average height was similar between adolescents aged 15–17 and adults aged 20–24, and a similar result was seen in the present study. Besides, previous studies showed that the major metrics of the body such as height, weight and chest size increase greatly in the age of 9–13 years and become stabilized during adolescence (ages of 15 to 17).<sup>29–31</sup> Therefore, it is considerable that the adult definition of HTN is also applicable to adolescents aged 15–17, such as American did.

The 90th percentile for adolescents  $\geq 13$  years of age in the New Pediatric BP Tables published by the AAP in 2017 was close to a SBP of 120Hg and diastolic BP of  $< 80$  mmHg. Also, the 95th BP percentile reference of SBP in adolescents  $\geq 13$  years was close to 130 Hg.<sup>11,32</sup> The AAP recommended a cutoff of 130/80 mmHg to diagnose HTN among adolescents aged 13 years or older to align with the 2017 American Heart Association and American College of Cardiology Hypertension guidelines for adults; however, a percentile-based definition of HTN was still requested for children less than 13 years of age. In the present study, the 95th percentile of BP in adolescents aged 15–17 was higher than the CGC reference, and even exceeded the cutoff of adult HTN. Hence, the CGA criterion might also be appropriate for defining HTN in adolescents aged 15–17.

Comparing the diverse HTN criteria in a large sample was a novel approach toward formulating suitable criteria. The large sample size made it possible to perform a subgroup analysis to obtain age-, sex-,

**TABLE 3** BP levels for boys and girls by age and height percentile

Age	Height Percentile	Boy				Girl			
		95th, SBP		95th, DBP		95th, SBP		95th, DBP	
		BP Percentile (mmHg)	CGC reference (mmHg)	BP Percentile (mmHg)	CGC reference (mmHg)	BP Percentile (mmHg)	CGC reference (mmHg)	BP Percentile (mmHg)	CGC reference (mmHg)
15	<P <sub>7.5</sub>	133	120	81	79	131	120	82	79
	P <sub>7.5</sub> - (P <sub>17.5</sub> -1)	136	121	82	79	130	121	83	79
	P <sub>17.5</sub> - (P <sub>37.5</sub> -1)	137	122	81	79	132	122	83	79
	P <sub>37.5</sub> - (P <sub>62.5</sub> -1)	139	123	82	79	131	123	81	79
	P <sub>62.5</sub> - (P <sub>82.5</sub> -1)	140	123	81	79	134	123	83	79
	P <sub>82.5</sub> - (P <sub>92.5</sub> -1)	144	124	84	79	132	124	82	79
	≥P <sub>92.5</sub>	144	124	82	79	140	124	88	79
16	<P <sub>7.5</sub>	134	121	81	79	129	121	81	79
	P <sub>7.5</sub> - (P <sub>17.5</sub> -1)	136	121	82	79	132	121	82	79
	P <sub>17.5</sub> - (P <sub>37.5</sub> -1)	138	122	82	79	130	122	82	79
	P <sub>37.5</sub> - (P <sub>62.5</sub> -1)	138	123	83	79	132	123	82	79
	P <sub>62.5</sub> - (P <sub>82.5</sub> -1)	140	123	83	79	132	123	82	79
	P <sub>82.5</sub> - (P <sub>92.5</sub> -1)	145	124	84	79	134	124	82	79
	≥P <sub>92.5</sub>	143	124	82	79	139	124	85	79
17	<P <sub>7.5</sub>	137	121	84	79	130	121	82	79
	P <sub>7.5</sub> - (P <sub>17.5</sub> -1)	138	122	82	79	131	122	82	79
	P <sub>17.5</sub> - (P <sub>37.5</sub> -1)	139	122	84	80	129	122	81	80
	P <sub>37.5</sub> - (P <sub>62.5</sub> -1)	138	123	83	80	131	123	82	80
	P <sub>62.5</sub> - (P <sub>82.5</sub> -1)	141	124	84	80	132	124	81	80
	P <sub>82.5</sub> - (P <sub>92.5</sub> -1)	144	124	83	80	131	124	83	80
	≥P <sub>92.5</sub>	148	124	85	80	134	124	82	80

The Height Percentile group was based on the Chinese Standards for Children.

Abbreviations: CGC, The Chinese Standards for Children; DBP, Diastolic blood pressure.; SBP, Systolic blood pressure.

and height-specific prevalence according to different criteria. And the present study might be so far the first study which compared the adult HTN diagnosed criterion with the other pediatric HTN criteria in the same population.

Our study should be interpreted in the context of several limitations. First, the data for this study came from a national hypertension survey, differing from the standard practice of measuring BP on three different days, three measurements on the same day were recorded, so the BP value may be overestimated. Second, we did not follow up the participants. Finally, the relationship between HTN in adolescents and the risk of cardiovascular events was not available.

## 5 | CONCLUSION

The current study showed that the prevalence of HTN in Chinese children varied considerably according to different criteria. The prevalence of HTN in Chinese adolescents was higher according to CGC criterion as compared with other criteria. Considering the body metrics

(especially height) of the adolescents aged 15–17 years old were very close to that in adults, the CGA criterion may also be appropriate for adolescents aged 15–17 years. However, further validation studies are required.

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## CONFLICTS OF INTERESTS

The authors of this paper indicated no competing interest.

## AUTHOR CONTRIBUTIONS

WZ contributed to conception, design, application, data collection of the study. ZH and LS contributed equally to investigation, data collection, statistical analysis and writing of the manuscript as the Co-first author. WX, CZ, ZL, SL, TY, ZC, CL, CX, MM, CXL contributed to the investigation and data collection of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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