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ARTICLE

The predictive value of repeated blood pressure measurements in childhood for cardiovascular risk in adults: the Hanzhong Adolescent Hypertension Study

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Abstract

There is currently a lack of strong evidence linking childhood elevated blood pressure to long-term cardiovascular risk in adulthood. Repeated observations of abnormal blood pressure in childhood may enhance the prediction of cardiovascular risk in adulthood compared with a single observation. The study included 1738 individuals in rural areas of Hanzhong City, Shaanxi, who had been followed for 30 years since baseline (1987, at which time participants were aged 6–15 years). According to four independent measurements of blood pressure in 1987, 1989, 1992, and 1995, childhood elevated blood pressure was defined as 2 in-person examinations with blood pressure values above the 90th percentile. Arterial stiffness and left ventricular hypertrophy in adulthood were assessed by brachial-ankle pulse wave velocity and the Cornell product index, respectively. Childhood elevated blood pressure was associated with an increased risk of adult hypertension (OR, 2.01; 95% CI, 1.53–2.65), arterial stiffness (OR, 1.69; 95% CI, 1.32–2.16) and left ventricular hypertrophy (OR, 1.86; 95% CI, 1.13–3.05) (all $P < 0.05$). Cardiovascular risk in adults increased with increasing childhood blood pressure levels. In addition, two abnormal childhood blood pressure observations predicted an increased likelihood of hypertension in adulthood (0.77 for 2 versus 0.70 for 1 observation, $P < 0.001$). Our study provides strong evidence that elevated blood pressure in childhood predicts cardiovascular risk in adults. The prediction was enhanced by two observations of abnormal blood pressure in childhood compared with a single measurement. We emphasize the importance of childhood blood pressure monitoring and control in the prevention of cardiovascular diseases.

Keywords Adulthood · Blood pressure · Childhood · Cardiovascular risk · Cohort study.

Introduction

Hypertension-related adult cardiovascular diseases are among the leading causes of death worldwide, and there are direct correlations between different blood pressure (BP) levels and rates of myocardial infarction and stroke and the risk of end-stage renal damage [1, 2]. In contrast, hypertension-related cardiovascular events are rare in children and young adults, but cardiovascular risk, such as subclinical target organ damage, is present in these populations. Elevated BP is alarmingly common in the adolescent population, and hypertension observed in adults has a high chance of childhood onset [3]. At present, there is a lack of strong evidence linking childhood elevated BP to long-term cardiovascular risk in adults [4].

The effect of childhood BP on long-term cardiovascular risk has always been the focus of concern and research, and related studies are also constant. Some cross-sectional studies have shown an association between childhood BP and concurrent target organ damage, including left ventricular hypertrophy (LVH), increased carotid intimal thickness, and arterial stiffness (AS) [5]. Some longitudinal studies, such

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as the Muscatine Study [6], the Bogalusa Study [7], and the Young Finns Study [8], all reported correlations between childhood BP and adulthood hypertension. Furthermore, a recent article pooling the observational data from the Bogalusa, Young Finns, Childhood Determinants of Adult Health (Australia), and Muscatine ($n = 4380$) studies found a significant effect of BP measured at ~12 years old and adult carotid thickness [9]. Some intervention studies in hypertensive youths have demonstrated that antihypertensive therapy leads to a regression of LVH [10, 11], a reduction in carotid thickness, an improvement in metabolic syndrome components [12], and a reversal of microalbuminuria [13]. However, the USPSTF indicated that the current evidence is insufficient to support screening for primary hypertension in asymptomatic children to prevent subsequent cardiovascular disease in adulthood [4]. Although studies on the effect of childhood BP on long-term cardiovascular risk have been ongoing, there is still no comprehensive and direct evidence linking childhood elevated BP to long-term cardiovascular risk in adults due to research limitations.

The National Heart, Lung, and Blood Institute, the American Academy of Pediatrics and the American Heart Association have recommended measurement of BP in healthy children as part of routine health maintenance [14–16]. Flynn indicated that high BP in childhood has detrimental short-term and long-term effects and encouraged more investigators to add further evidence [17]. Can repeated observations of abnormal BP in childhood improve prediction? If so, repeated observations of abnormal BP in childhood may provide stronger evidence for the association between BP in childhood and long-term cardiovascular risk.

We aimed to explore the associations of elevated BP, different BP levels, and the number of times abnormal BP was observed in childhood with cardiovascular risk in adulthood based on longitudinal data from the Hanzhong adolescent hypertension cohort recruited in 1987 and to provide further evidence linking childhood elevated BP to long-term cardiovascular risk in adults, especially in the Chinese population.

Methods

Study participants

This study is based on the Hanzhong adolescent hypertension cohort, an ongoing prospective study. A total of 4623 students aged 6–15 years from 26 rural areas in three towns (Qili, Laojun, and Shayan) in Hanzhong City, Shaanxi, China, who had no chronic diseases in their medical history and who could communicate normally in Mandarin were recruited into the cohort from March to April 1987 [18]. The cohort was followed up in 1989, 1992, 1995, and 2017, and the longest follow-up time was 30 years. The response rate was 77.7% ($n = 3592$) in 1989, 84.8% ($n = 3918$) in 1992, 82.1% ($n = 3794$) in 1995, and 60.1% ($n = 2780$) in 2017. Reasons for loss to follow-up mainly included mental illness, military service, migration, and death. Individuals who had severe cardiovascular disease, cerebrovascular disease, stroke, no blood samples, and/or missing measurements or those who were unable to provide informed consent at follow-up were excluded; a total of 1738 subjects were included in the study. The study protocol was approved by the Academic Committee of the First Affiliated Hospital of Xi'an Jiaotong University (XJTU1AF2015LSL-047) and was clinically registered (NCT02734472). All participants in this study signed informed consent forms at baseline and during follow-up. For minors under 18 years of age at baseline, the consent form was signed by a guardian.

Anthropometric measurements

Personal basic information, personal or family medical history, smoking status, and alcohol consumption history were collected using a unified questionnaire by trained staff. Height, body weight, hip and waist circumferences, and bust size were measured with the participants in underwear and without shoes using appropriate instruments and a uniform standard. Two measurements of these indicators were performed, and the mean values were used for analysis. Body mass index (BMI) was calculated as kilograms per square meter (kg/m^2).

Blood pressure measurements

Seated BP was measured in a quiet environment by trained and certified staff according to the procedures recommended by the WHO. A Hawksley random zero sphygmomanometer was used [19] for the first four visits, and an Omron M6 (Omron, Kyoto, Japan) device was used [20] for BP measurements in 2017. Participants were required to avoid coffee/tea, alcohol, cigarette smoking, and strenuous exercise for at least 30 min before BP measurement. The right upper arm BP measurement was taken with an appropriately sized cuff while the participants were in a sitting position after a 5 min rest. Using the Korotkoff sound method, the first and fifth sounds were used to determine SBP and DBP, respectively. The BP was measured three times, with an interval of 2 min between each measurement, and the BP levels were defined as the mean values of the three BP measurements.

Biochemical parameter measurements

Fasting venous blood samples were obtained by experienced nurses in the morning after the participants had fasted for 8–10 h. The serum isolated from the blood samples was centrifuged at a centrifugal radius of 16 cm at 3000 r/min for 10 min at room temperature and stored at −80 °C in aliquots. A Hitachi 7060 automatic biochemical analyzer was used to detect the serum biochemical parameters, including fasting glucose, uric acid (UA), total cholesterol (TC), triglycerides (TGs), LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C). Urinary UA, creatinine, and albumin levels were evaluated with an automatic biochemical analyzer. Serum creatinine was used to evaluate the estimated glomerular filtration rate (eGFR), and urine microalbumin and creatinine were used to evaluate the urinary albumin creatinine ratio (uACR). The specific formula is as follows: $\mathrm{eGFR} = 175 \times \mathrm{serum\ creatinine}^{-1.234} \times \mathrm{age}^{-0.179}$ (×0.79 for girls/women), where the serum creatinine concentration is in milligrams per deciliter and age is in years [21]. The uACR was calculated as urine albumin in milligrams divided by the urine creatinine in millimoles (milligrams per millimole).

Evaluation of arterial stiffness

The brachial-ankle pulse wave velocity (baPWV) was assessed using an automatic arteriosclerosis diagnostic device BP-203RPE III (Colin Co. Ltd; Komaki, Japan) in a quiet and comfortable environment. Measurements were performed with the patient in a supine position after a rest period of 5 min. PWV, BP, electrocardiograph, and heart sounds were simultaneously recorded by the instrument. The time interval between the upper arm and ankle (DT) was defined as the time interval between the wave front of the brachial waveform and that of the ankle waveform. The path length from the suprasternal notch to the brachium (Lb) or to the ankle on the same side (La) was automatically calculated according to the patient's height using the following formulae: $\mathrm{Lb\ (cm)} = 0.2195 \times \mathrm{height} - 2.0734$ and $\mathrm{La\ (cm)} = 0.8129 \times \mathrm{height} + 12.328$. Finally, the bilateral baPWV was automatically calculated as follows: $\mathrm{baPWV\ (cm/s)} = (\mathrm{La} - \mathrm{Lb})/\Delta T$. The average of the baPWV from both sides was used for the analysis.

Evaluation of left ventricle hypertrophy

The internationally used Cornell product index was adopted to reflect the LVH degree [22, 23]. A routine 12-lead electrocardiogram examination was conducted under quiet conditions. The paper speed was 25 mm/s, and the standard voltage was 1 mV. The amplitude of RavL and Sv3 and the width of QRS were measured manually by professionals on the surface electrocardiogram, and then the Cornell product index was calculated. Cornell product index (mm ms) = (RavL + Sv3) × QRS (male) or (RavL + Sv3 + 8) × QRS (female).

Definitions

For all subjects, smoking was defined as continuous or cumulative smoking for 6 months or more in a lifetime [18]. Alcohol consumption was defined as drinking alcohol daily (spirits, beer or wine) for 6 months [24]. Normal BP was defined in childhood as SBP and DBP ≤90th percentile with the use of the BPRS tables (Blood Pressure Reference Standard Tables of Chinese children aged 3–17 years old) for age, sex, and height or SBP/DBP <120/80 mm Hg. Elevated BP was diagnosed in childhood if SBP or DBP were ≥90th percentile with the use of the BPRS tables for age, sex, and height or SBP/DBP >120/80 mm Hg. Elevated BP in childhood included prehypertension (prehypertension was diagnosed in childhood if SBP or DBP were ≥90th percentile and <95th percentile with the use of the BPRS tables for age, sex, and height or SBP/DBP >120/80 mm Hg) and hypertension (hypertension was diagnosed in childhood if systolic blood pressure (SBP) or DBP were ≥95th percentile with the use of the BPRS tables for age, sex, and height) [25]. Elevated BP in childhood was defined as having met these criteria at least twice between the ages of 6 and 18 (between 1987 and 1995). Prehypertensive and hypertensive patients were identified based on the highest BP level among multiple measurements in childhood (between 1987 and 1995). Adult hypertension was classified as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg or self-reported use of antihypertensive medications. Diabetes was defined as GLU ≥7.0 mmol/L or a physician diagnosis by the secondary hospital. Hyperlipidemia was defined as the occurrence of any one of the following four situations: hypertriglyceridemia (TG ≥2.26 mmol/L), hypercholesterolemia (TC ≥6.22 mmol/L), high levels of LDL-C (≥4.14 mmol/L), or low levels of HDL-C (<1.04 mmol/L) [26]. Subjects with a baPWV <1400 cm/s were considered normal; by contrast, subjects with a baPWV of at least 1400 cm/s were defined as high [27]. A Cornell product index ≥2440 mm ms was used as the diagnostic criterion for left ventricle hypertrophy.

Statistical analyses

Continuous data were reported as the mean ± SD if normally distributed; otherwise, they were reported as medians (25th, 75th percentile ranges). Categorical data are presented as frequencies and percentages. Differences between continuous variables were analyzed by the *t* test for two-group comparisons and one-way ANOVA for three or more

groups when the distribution and variance met the conditions; otherwise, the Mann–Whitney *U* test and Kruskal–Wallis test were used. Categorical variables between two groups were compared with chi-squared tests. Relative risks and 95% confidence intervals were calculated with the use of logistic regression to determine the associations between childhood elevated BP and cardiovascular risk. To make the results more accurate, we performed corresponding model correction. Several sensitivity analyses were performed to examine the associations after excluding individuals who received antihypertensive drugs, hypoglycemic drugs and lipid-lowering drugs, and the associations were determined while taking obesity status into account. All statistical analyses were performed using SPSS 25.0 (SPSS, Inc., Chicago, Illinois, USA). Statistical significance was set as a two-tailed *P* value of <0.05.

Results

General characteristics of the study population

The characteristics of the study population at baseline and during the 30 years of follow-up are summarized in Table 1. A total of 1738 individuals, including 650 EBP children and 1088 NBP children, were enrolled in this cohort study at baseline. The results showed that the EBP group had lower age and higher SBP, DBP, and heart rate at baseline than the NBP group (all $P < 0.005$). The results also showed that SBP, DBP, weight, urine albumin, uACR, baPWV, the Cornell product index, and the prevalence of hypertension in the EBP group were higher than the corresponding values in the NBP group after 30 years of follow-up (all $P < 0.05$). The incidence rate of cardiovascular risk between different BP groups is shown in Fig. 1. To determine whether the representativeness of the baseline sample was maintained in the present cohort, baseline characteristics were compared between the included study participants and excluded subjects at baseline (Supplementary Table 1).

Association of childhood elevated BP with cardiovascular risk in adulthood

We used logistic regression to examine the association between childhood elevated BP and cardiovascular risk in adulthood (Table 2). Compared with the NBP group, the EBP group had higher cardiovascular risk as adults. In multivariable-adjusted model analyses, the ORs (95% CIs) were 2.01 (95% CI, 1.53–2.65) for adult hypertension, 1.69 (95% CI, 1.32–2.16) for adult AS, and 1.86 (95% CI, 1.13–3.05) for adult LVH in comparison with the NBP group (all $P < 0.05$).

Association of different BP levels in childhood with cardiovascular risk in adulthood

The characteristics of the study population based on different BP levels at baseline are summarized in Supplementary Table 2. After adjustment for confounding factors based on Supplementary Table 2, logistic regression was used to examine the association of different BP levels in childhood with cardiovascular risk in adulthood (Table 3). Compared with the normotension group, the prehypertension group and hypertension group had higher levels of cardiovascular risk, and the hypertension group had higher levels of cardiovascular risk than the prehypertensive group (2.78 vs. 1.61 for adult hypertension; 1.81 vs. 1.73 for adult AS; 1.97 vs. 1.81 for adult LVH) (all $P < 0.05$).

Enhancement in prediction of adult cardiovascular risk by the number of times abnormal BP was observed during childhood

To study the clinical value of repeated BP measurements in childhood, we examined the prevalence of cardiovascular risk in adulthood according to the number of times abnormal BP was observed in childhood (Supplementary Table 3). Characteristics of the study participants at baseline and during the follow-up period according to abnormal BP occurring once and three times in childhood are shown in Supplementary Tables 4 and 5, respectively. After adjustment for confounding factors based on Supplementary Tables 4 and 5, logistic regression was used to examine the association of elevated BP in childhood with cardiovascular risk in adults by the number of times abnormal BP was observed during childhood when subjects were aged 6–18 years (Supplementary Table 6). The prediction of adulthood cardiovascular risk was compared between one observation of abnormal BP in childhood and multiple observations by the area under the receiver operating curve (Fig. 2). As shown in Table 4, we found that two abnormal childhood BP observations increased the prediction of hypertension in adulthood (0.766 for 2 versus 0.697 for 1 observation, $P < 0.0001$). Compared with two measurements, the third observation did not provide any significant improvement for prediction (0.692 for 3 versus 0.697 for 1 observation, $P < 0.48$). The number of observations of abnormal BP did not enhance the prediction of AS or LVH.

Additional analyses

We performed additional analyses to evaluate the association of elevated BP in childhood with metabolic syndrome (MetS) and subclinical renal damage (SRD) in adulthood. MetS was defined according to the consensus criteria in 2009 as the presence of ≥3 of the following criteria: elevated

Table 1 Characteristics of the study participants at baseline and during the follow-up period

Variable	NBP group[a]	EBP group[b]	*P* value
No. of patients (M/F)	1088 (591/497)	650 (372/278)	0.237
Baseline			
Age (years)	12 (9, 14)	11 (9, 13)	0.003
SBP (mm Hg)	100.0 (93.3, 106.0)	109.3 (101.3, 116.7)	<0.001
DBP (mm Hg)	61.3 (58.0, 67.3)	70.0 (63.3, 76.0)	<0.001
Height (cm)	138.0 (124.3, 149.0)	134.5 (123.0, 148.0)	0.130
Weight (kg)	30.0 (23.2, 39.0)	29.0 (22.8, 38.5)	0.503
BMI (kg/m^2)	15.9 (14.7, 17.6)	15.9 (14.9, 17.7)	0.187
HR (bpm)	78.0 (72.0, 84.0)	80.0 (72.0, 84.0)	<0.001
Bust (cm)	61.5 (57.0, 68.0)	61.5 (57.0, 68.0)	0.912
Follow-up			
Age (years)	42 (39, 44)	41 (39, 43)	0.003
SBP (mm Hg)	118.7 (110.0, 128.2)	125.7 (117.0, 135.0)	<0.001
DBP (mm Hg)	74.3 (67.3, 81.7)	79.2 (72.7, 86.3)	<0.001
Height (cm)	162.8 (156.4, 168.5)	163.9 (157.5, 168.5)	0.078
Weight (kg)	62.8 (55.4, 71.3)	64.5 (56.6, 72.0)	0.012
BMI (kg/m^2)	23.7 (21.8, 26.0)	24.1 (22.3, 26.2)	0.066
HR (bpm)	73.0 (66.0, 80.0)	74.0 (67.0, 80.0)	0.192
Waist (cm)	84.3 (77.9, 91.4)	84.9 (78.6, 92.0)	0.264
Hips (cm)	92.1 (88.8, 95.5)	92.6 (89.3, 96.2)	0.049
Smoking (%)	471 (43.3%)	284 (43.7%)	0.870
Drinking (%)	306 (28.1%)	202 (31.1%)	0.190
FH. hypertension (%)	545 (50.1%)	367 (56.5%)	0.010
FH. diabetes (%)	169 (15.5%)	110 (16.9%)	0.445
Hypertension (%)	142 (13.1%)	152 (23.4%)	<0.001
Diabetes (%)	25 (2.3%)	14 (2.2%)	0.845
Dyslipidemia (%)	430 (39.5%)	259 (39.8%)	0.894
TC (mmol/l)	4.5 (4.1, 5.0)	4.5 (4.0, 5.0)	0.247
HDL-C (mmol/l)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	0.806
LDL-C (mmol/l)	2.5 (2.1, 2.9)	2.5 (2.1, 2.9)	0.254
Triglycerides (mmol/l)	1.4 (1.0, 2.0)	1.4 (1.0, 2.0)	0.708
Fasting glucose (mmol/l)	4.6 (4.3, 4.9)	4.6 (4.3, 5.0)	0.501
Serum uric acid (mmol/l)	277.0 (255.7, 333.2)	281.3 (224.8, 338.4)	0.527
Urine albumin (mg/l)	7.2 (3.9, 13.3)	8.4 (4.4, 14.9)	0.032
uACR (mg/mmol)	0.9 (0.6, 1.67)	1.0 (0.7, 1.9)	0.020
eGFR (ml/min per 1.73 m^2)	97.8 (87.5, 111.5)	97.2 (87.0, 110.6)	0.869
baPWV (cm/s)	1181.5 (1070.1, 1322.4)	1268.5 (1139.8, 1409.4)	<0.001
Cornell index (mm × ms)	1356.8 (1032.5, 1710.0)	1440.3 (1112.1, 1797.2)	0.004

Continuous variables were shown as mean ± SD if normally distributed or median (quartile 1, quartile 3) if non-normally distributed. Categorical variables were expressed as numbers and percentages of subjects. Continuous variables between two groups were compared using the *t* test or Mann–Whitney *U* test according to the normality of distribution Categorical variables between two groups were compared with chi-squared tests

BMI body mass index, *baPWV* brachial-ankle pulse wave velocity, *DBP* diastolic blood pressure, *EBP* elevated blood pressure, *eGFR* estimated glomerular filtration rate, *HR* heart rate, *FH. hypertension* history of hypertension, *FH. diabetes* history of diabetes, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *NBP* normal blood pressure, *TC* total cholesterol, *SBP* systolic blood pressure, *uACR* urinary albumin-to-creatinine ratio

[a]NBP normal blood pressure; Normal BP was defined in childhood as SBP and DBP ≤90th percentile with the use of the BPRS tables (Blood Pressure Reference Standard Tables of Chinese children aged 3–17 years old) for age, sex, and height or SBP/DBP <120/80 mm Hg

[b]EBP elevated blood pressure; BP was classified as elevated in childhood if SBP or DBP were ≥90th percentile with the use of the BPRS tables for age, sex, and height or SBP/DBP >120/80 mm Hg

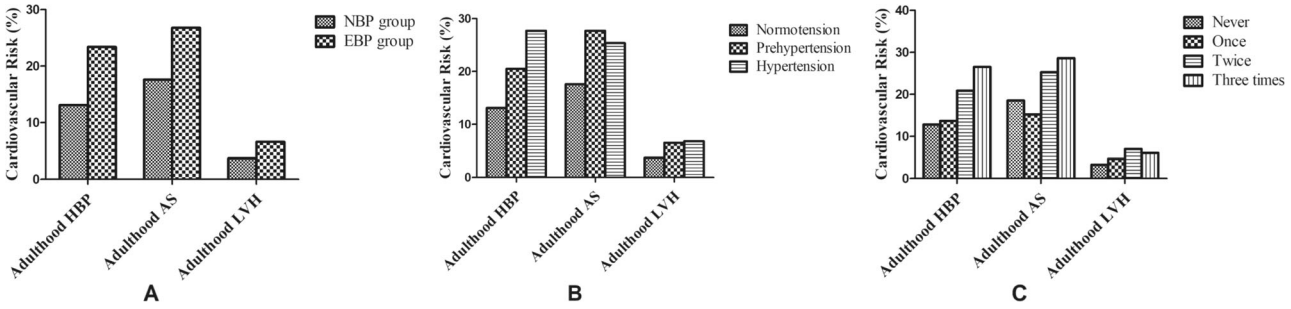

Fig. 1 Proportion of participants with cardiovascular risk according to the different blood pressure groups. **a** Proportion of participants with cardiovascular risk based on increased blood pressure in childhood (defined as two abnormal blood pressure measurements). **b** Proportion of participants with cardiovascular risk based on the different blood pressure levels in childhood (according to the highest one of two abnormal blood pressure measurements). **c** Proportion of participants with cardiovascular risk in adulthood based on the number of times abnormal blood pressure was observed in childhood. AS arterial stiffness, EBP elevated blood pressure, HBP high blood pressure, LVH left ventricular hypertrophy, NBP normal blood pressure

Table 2 Adjusted odds ratios and 95% confidence intervals of the association of elevated blood pressure in childhood with cardiovascular risk in adults

Cardiovascular risk	Odds ratio	95% CI	*P* value
Adult hypertension			
Model 1[a]	2.033	1.58–2.62	<0.001
Model 2[b]	2.025	1.56–2.63	<0.001
Model 3[c]	2.010	1.53–2.65	<0.001
Adult AS			
Model 1[a]	1.706	1.35–2.15	<0.001
Model 2[b]	1.730	1.36–2.21	<0.001
Model 3[c]	1.690	1.32–2.16	<0.001
Adult LVH			
Model 1[a]	1.867	1.15–3.04	0.012
Model 2[b]	1.849	1.13–3.02	0.014
Model 3[c]	1.857	1.13–3.05	0.014

AS arterial stiffness, *LVH* left ventricular hypertrophy

[a]Model 1 was unadjusted

[b]Model 2 was adjusted for age and sex and family history of hypertension

[c]Model 3 adjusted for heart rate at baseline and weight at follow-up based on model 2

waist circumference (≥90 cm in males, ≥80 cm in females); TGs ≥150 mg/dL; HDL-C <40 mg/dL in men and <50 mg/dL in women; BP ≥130/85 mm Hg or on antihypertensive drug treatment in a patient with a history of hypertension; or fasting plasma glucose ≥100 mg/dL [28]. The presence of SRD was defined as an eGFR between 30 and 60 ml/min per 1.73 m^2 [29] or an elevated uACR of at least 2.5 mg/mmol in men and 3.5 mg/mmol in women, as previously described [30]. After adjusting for confounders, elevated BP in childhood was not associated with MetS or SRD in adulthood (Supplementary Table 7). When elevated BP in childhood was further divided into prehypertension and hypertension, we found that hypertension in childhood can predict the risk of MetS and SRD in adulthood, but no significant differences were found in children with prehypertension (Supplementary Table 8). In other words, hypertension in children increases the risk of MetS and SRD in adulthood. Supplementary Table 9 shows the baseline characteristics of the included study participants by sex. Females had higher SBP, BMI, and bust than males in all participants' baseline data. The association of elevated BP in childhood by sex with cardiovascular risk in adults is shown in Supplementary Table 10. The associations between elevated BP in childhood and cardiovascular risk in adults, except for LVH, did not exhibit sex differences.

Discussion

The impact of childhood elevated BP on cardiovascular risk in adults has long been a concern and controversy. More research is needed to explore the association between childhood elevated BP and long-term cardiovascular risk in adults [17, 31]. In the present study, we assessed the association between childhood elevated BP and cardiovascular risk in adults in a Chinese adolescent hypertension cohort with a 30-year follow-up. We found that childhood elevated BP (including prehypertension and hypertension) can increase the risks of adult hypertension, AS and LVH. The higher the BP in childhood is, the higher the cardiovascular risk in adulthood. The accuracy of predicting hypertension in adulthood can be enhanced by multiple BP measurements in childhood compared with prediction models consisting of only a single measurement.

Related research on the effect of childhood elevated BP on long-term cardiovascular risk has been constant. There are many different opinions and comments. Therefore, Flynn and the American Academy of Pediatrics committee encourage more investigators to add further evidence linking childhood elevated BP to long-term cardiovascular risk

Table 3 Adjusted odds ratios and 95% confidence intervals of the association of different BP levels groups in childhood with cardiovascular risk in adults

Cardiovascular risk	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
Adult hypertension						
Normotension[a]	1.00	Ref	1.00	Ref	1.00	Ref
Prehypertension[b]	1.72 (1.27–2.33)	<0.001	1.62 (1.19–2.21)	0.002	1.61 (1.18–2.20)	0.003
Hypertension[c]	2.55 (1.85–3.53)	<0.001	2.82 (1.99–3.98)	<0.001	2.78 (1.96–3.93)	<0.001
Adult AS						
Normotension[a]	1.00	Ref	1.00	Ref	1.00	Ref
Prehypertension[b]	1.79 (1.36–2.34)	<0.001	1.71 (1.29–2.26)	<0.001	1.73 (1.30–2.30)	<0.001
Hypertension[c]	1.59 (1.15–2.19)	0.005	1.77 (1.26–2.49)	0.001	1.81 (1.28–2.55)	0.001
Adult LVH						
Normotension[a]	1.00	Ref	1.00	Ref	1.00	Ref
Prehypertension[b]	1.82 (1.03–3.22)	0.040	1.80 (1.02–3.19)	0.044	1.81 (1.02–3.23)	0.043
Hypertension[c]	1.93 (1.03–3.63)	0.040	1.92 (1.01–3.64)	0.047	1.97 (1.03–3.75)	0.040

Model 1 was unadjusted. Model 2 was adjusted for age, sex, family history of hypertension. Model 3 was adjusted for body mass index, heart rate and bust at baseline on model 2

AS arterial stiffness, *LVH* left ventricular hypertrophy

[a]Normotension group was defined in childhood as SBP and DBP ≤90th percentile with the use of the BPRS tables (Blood Pressure Reference Standard Tables of Chinese children aged 3–17 years old) for age, sex, and height or SBP/DBP <120/80 mm Hg

[b]Prehypertension group was classified in childhood if SBP or DBP were ≥90th percentile and <95th percentile with the use of the BPRS tables for age, sex, and height or SBP/DBP >120/80 mm Hg

[c]Hypertension group was classified in childhood if SBP or DBP were ≥95th percentile with the use of the BPRS tables for age, sex, and height

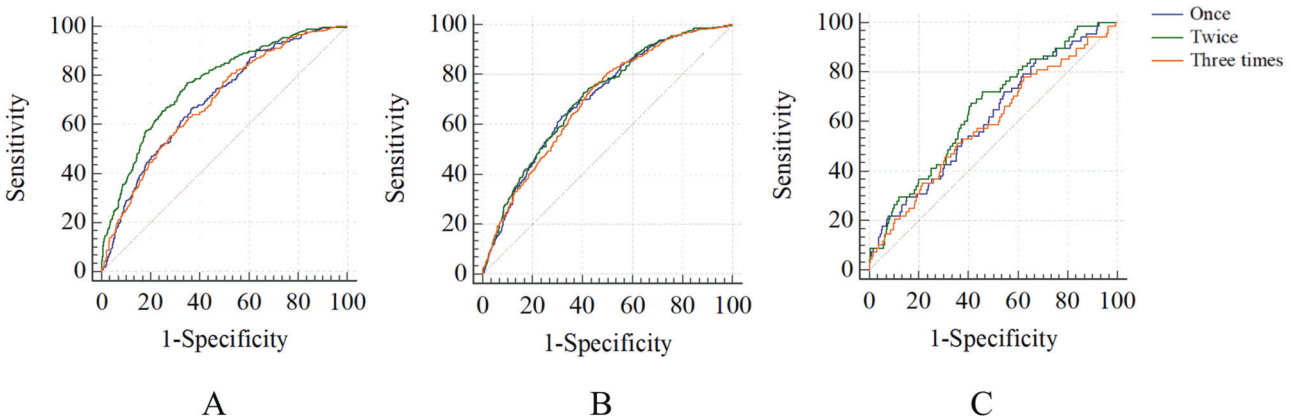

Fig. 2 The receiver operator curve of adult cardiovascular risk for individuals with elevated blood pressure in childhood by the number of times abnormal BP was observed during childhood when subjects were aged 6–18 years. **a** The receiver operator curve of adult hypertension for individuals with elevated blood pressure in childhood. **b** The receiver operator curve of adult arterial stiffness for individuals with elevated blood pressure in childhood. **c** The receiver operator curve of adult left ventricular hypertrophy for individuals with elevated blood pressure in childhood. Blue line: the receiver operator curve of adult cardiovascular risk for individuals with one abnormal blood pressure measurement observed during childhood (adjusted for age, sex, family history of hypertension, heart rate, and height at baseline); Green line: the receiver operator curve of adult cardiovascular risk for individuals with two abnormal blood pressure readings observed during childhood (adjusted for age, sex, family history of hypertension, heart rate at baseline, and weight at follow-up); Orange line: the receiver operator curve of adult cardiovascular risk for individuals with three abnormal blood pressure measurements observed during childhood (adjusted for age, sex, family history of hypertension, heart rate, and body mass index at baseline)

in adults. Our study provides a more comprehensive analysis of the relationship between elevated BP in childhood and cardiovascular risk in adults, including adult hypertension, MetS, AS, LVH, and SRD. Based on our research, individuals with childhood elevated BP are 2.0 times more likely to have hypertension, 1.9 times more likely to have LVH, and 1.7 times more likely to have AS than normal individuals. Our results are in line with the Bogalusa Heart Study, where adult LVH was significantly associated with higher values of SBP and DBP in both childhood and

Table 4 Enhancement in prediction of adult cardiovascular risk by times abnormal BP was observed during childhood when aged 6–18 years

Cardiovascular risk	Abnormal BP observed in childhood	AUC (unadjusted model)	*P* for AUC difference	AUC (multivariable-adjusted model)[a]	*P* for AUC difference
Adult hypertension					
	Once	0.568 (0.545–0.592)	Ref	0.697 (0.675–0.719)	Ref
	Twice	0.586 (0.562–0.609)	0.1012	0.766 (0.745–0.786)	<0.0001
	Three times	0.556 (0.532–0.580)	0.4357	0.692 (0.669–0.713)	0.4777
Adult AS					
	Once	0.537 (0.513–0.560)	Ref	0.702 (0.680–0.724)	Ref
	Twice	0.564 (0.541–0.588)	0.0045	0.708 (0.686–0.729)	0.3997
	Three times	0.537 (0.514–0.561)	0.9706	0.697 (0.674–0.718)	0.2780
Adult LVH					
	Once	0.575 (0.549–0.601)	Ref	0.611 (0.585–0.636)	Ref
	Twice	0.576 (0.550–0.602)	0.9491	0.649 (0.624–0.674)	0.1722
	Three times	0.524 (0.498–0.550)	0.1020	0.587 (0.561–0.613)	0.4487

AS arterial stiffness, *LVH* left ventricular hypertrophy

[a]Multivariable-adjusted model was adjusted for age, sex, family history of hypertension, heart rate, and height at baseline for once; adjusted for age, sex, family history of hypertension, heart rate at baseline, and weight at follow-up for twice; adjusted for age, sex, family history of hypertension, heart rate, and body mass index at baseline for three times

adulthood in a longitudinal analysis of 1,061 individuals [32]. These results are similar to The Cardiovascular Risk in Young Finns Study, in which arteriosclerosis in adulthood was associated with both childhood and adult SBP, with a stronger predictive relationship demonstrated when examining cardiovascular risk factors present in adolescence (12–18 years) compared with those present earlier in childhood (3–9 years) [33].

We further examined the effects of prehypertension and hypertension in childhood on cardiovascular risk in adults. We found that children with prehypertension have 1.6 times the risk of hypertension, 1.8 times the risk for LVH, and 1.7 times the risk for AS in adulthood, while children with hypertension have 2.8 times the risk of hypertension, 2.0 times for LVH, and 1.8 times for AS in adulthood. The higher the BP in childhood is, the higher the cardiovascular risk in adulthood. We also found that hypertension in childhood can predict the risk of MetS and SRD in adulthood, but no significant differences were found in children with prehypertension. Hypertension in children increases the risk of MetS and SRD in adulthood. These results are in accordance with our previous study on the effects of BP from childhood through adulthood on subclinical SRD, where higher BP trajectories were correlated with a higher risk of subclinical renal disease in middle age [34]. Our results are in line with a longitudinal cohort of 1973 individuals, where childhood hypertension increased the risk of MetS [35]. Our study provides strong evidence that childhood elevated BP significantly increases cardiovascular risk in adulthood. We highlight the importance of BP control from childhood in the primary prevention of cardiovascular diseases. As Kawabe et al. concluded by observing the characteristics of adolescent hypertension, BP monitoring beginning in childhood is very important for the prevention of hypertension [36].

To improve the prediction model and the reliability of the results, we compared repeated observations to one observation of BP in childhood in the prediction of future hypertension, AS, and LVH. We found that two abnormal childhood BP observations increased the prediction of hypertension in adulthood compared with a single measurement, but no significant differences were found in three abnormal childhood BP observations. These results are in accordance with the Cardiovascular Risk in Young Finns Study, where two abnormal childhood/youth BP observations increased the prediction of hypertension in adulthood, but a third observation did not provide any significant improvement for correlation or prediction [37]. We observed that those with elevated BP at two consecutive measurements in childhood had, on average, 6.0 mm Hg higher SBP and 4.0 mm Hg higher DBP compared with those who had never had elevated BP in childhood. These results are in line with a 27-year follow-up study on familial aggregation of BP, where children with both parents in the highest BP tertiles had, on average, 2.7 mm Hg higher SBP and 8.5 mm Hg higher DBP in adulthood [38]. We also observed that elevated childhood BP was predictive of high-risk AS and LVH in adulthood. However, the number of BP measurements in childhood was not associated with adult AS and LVH. These results are in accord with the Cardiovascular Risk in Young Finns Study, where the authors observed that the number of BP measurements in childhood/youth did not improve the prediction of adult IMT [37].

The strength of this study is the large randomly selected cohort of young adults followed for 30 years since childhood. We have replicated measures at different time points in childhood, and after comparing the predictive effects of the number of times abnormal BP was observed during childhood on adult cardiovascular risk, we define childhood elevated BP as 2 in-person examinations with SBP/DBP values that were ≥90th percentile according to the BPRS tables or SBP/DBP >120/80 mm Hg. These results make our results more accurate and convincing. However, our study has some limitations that need to be considered in the interpretation of our findings. First, our research mainly included participants from rural areas in northern China, and most of the participants were of Han nationality. Thus, prudence should be exercised when generalizing these conclusions to other races or ethnic groups. However, we can only provide more evidence linking childhood elevated BP to long-term cardiovascular risk in adults, especially in the Chinese population. Second, the incidence of LVH is lower, especially when subgroup analysis was performed based on obesity status. This may be because we used the Cornell index as an indicator of LVH, or it may be that the rate of LVH in young adults is small. Third, since our cohort consists mainly of young adults, we were unable to study the relationship between childhood BP and cardiovascular events. Instead, we used cardiovascular risk. The prospective design of our research provides us with the opportunity for longer follow-up to determine the risk of clinical cardiovascular events.

Our study adds stronger evidence that elevated BP in childhood predicts cardiovascular risk in adulthood, especially in the Chinese population. The higher the BP in childhood is, the higher the cardiovascular risk in adulthood. In addition, two abnormal childhood BP observations increased the prediction of hypertension in adulthood compared with a single measurement. The prediction was enhanced by two observations of abnormal BP in childhood, which makes the research results more reliable. We emphasize the importance of childhood BP monitoring and control in the prevention of cardiovascular diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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