Original Article

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Isolated diastolic hypertension in childhood and risk of adult subclinical target organ damage: a 30-year prospective cohort study

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Background: Data on the association of isolated diastolic hypertension (IDH) in childhood with adult cardiovascular risk are scarce. This study aimed to estimate the prevalence of IDH in adolescents and to explore the impact of IDH in childhood on adult subclinical target organ damage (STOD).

Methods: This longitudinal study consisted of 1738 school children (55.4% boys) aged 6–15 years from rural areas of Hanzhong, Shaanxi, who were followed for 30 years. Their blood pressure was recorded to define the hypertension subtypes: normotension, IDH, isolated systolic hypertension (ISH) and mixed hypertension. Tracked STOD included arterial stiffness ($n = 1738$), albuminuria ($n = 1652$) and left ventricular hypertrophy (LVH) ($n = 1429$).

Results: Overall, the prevalence of IDH, ISH and mixed hypertension was 5.4, 2.2 and 3%, respectively, and there was no gender difference. Over 30 years, 366 (21.1%) of participants developed arterial stiffness, 170 (10.3%) developed albuminuria and 68 (4.8%) developed LVH. Compared with normotensive participants, IDH in childhood had higher risk ratio (RR) of experiencing arterial stiffness (RR, 1.66; 95% CI, 1.01–2.76) and albuminuria (RR, 2.27; 95% CI, 1.35–4.16) in adults after being fully adjusted but not LVH. However, if the elevated blood pressure in children was used as the reference standard, IDH in childhood was associated with adult LVH (RR, 2.48; 95% CI, 1.28–4.84).

Conclusion: IDH accounts for a higher proportion of adolescent hypertension subtypes and can increase the risk of adult STOD. These results highlight the necessity of improving the prevention, detection and treatment of IDH in adolescents.

Keywords: epidemiology, hypertension subtypes, isolated diastolic hypertension, prospective cohort study, subclinical target organ damage

Abbreviations: AUC, area under the curve; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy; MH, mixed hypertension; SBP, systolic blood pressure; STOD, subclinical target organ damage; uACR, urinary albumin-to-creatinine ratio

INTRODUCTION

Hypertension remains the predominant driver of cardiovascular disease [1,2]. According to hypertension guidelines, hypertension can be subdivided into IDH, ISH and mixed hypertension using the proposed thresholds of various blood pressure components [3]. DBP used to be regarded as an important risk predictor as it reflects the peripheral resistance that the heart has to overcome to eject blood [4]. The 2018 ESC/ESH Guidelines indicated that the association between the DBP treatment target and cardiovascular end-point events remains a knowledge gap in the field of hypertension [5].

Recently, based on NHANES 2013–2016 and ARIC Study, McEvoy *et al.* [6] found that IDH was not significantly associated with an increased risk of adverse cardiovascular outcomes. Similarly, prior studies have suggested that IDH is generally not associated with atherosclerotic cardiovascular disease outcomes independent of baseline SBP [7,8]. On the contrary, Li *et al.* [9] reported that DBP levels were a major driver of cardiovascular death, total death, and all cardiovascular end events in the population under 50 years. From the early 1970s, Framingham Heart Study investigators and other researchers found that with advancing age,

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there was a gradual shift from DBP to SBP as the main predictor of cardiovascular risk. DBP was the strongest predictor of cardiovascular outcomes below 50 years of age [10].

In brief, it has been shown that the relationship between IDH and cardiovascular outcomes is strongly associated with age. However, previous studies have focused on adults, or the elderly. Data on the association of IDH in childhood with adult cardiovascular outcomes are scarce. Consequently, the aims of this study are to estimate the prevalence of IDH in adolescents and to explore the impact of IDH in childhood on adult subclinical target organ damage.

METHODS

Study population

This study is based on the Hanzhong Adolescent Hypertension Cohort, an ongoing prospective cohort study. The study began in 1987, when 4623 schoolchildren aged 6–15 years were enrolled from Hanzhong, Shaanxi, China. Later, information was collected in 1989 ($n = 3592$), 1992 ($n = 3918$), 1995 ($n = 3794$) and 2013 ($n = 3018$). The follow-up rates were 77.7, 84.8, 82.1 and 65.3%, respectively. The most recent follow-up of our cohort was in 2017, with a maximum follow-up of 30 years and a follow-up rate of 60.1% ($n = 2780$). The reasons for loss of follow-up mainly included death and mental illness (about 5%), military service (about 10%), and migration (about 85%). The detailed study design and procedures have been published previously [11,12]. Individuals who had no blood samples and/or missing measurements and were unable to provide informed consent at follow-up were excluded, and finally, 1738 individuals were included in the analysis. The participant selection process is described in Fig. 1.

This study followed the principles of the Helsinki Declaration. This study 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 participants younger than 18 years of age at baseline, informed consent from a parent/guardian was obtained.

Blood pressure measurement

Seated BP was measured in a quiet environment by trained and certified staff according to the procedures recommended by the WHO. Participants were required to avoid coffee/tea, alcohol, cigarette smoking and strenuous exercise for at least 30 min before the BP measurement. 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.

The hypertension subtypes included normotension, IDH, ISH and mixed hypertension. Normotension (SBP <95th percentile and DBP <95th percentile), IDH (SBP <95th percentile and DBP ≥95th percentile), ISH (SBP ≥95th percentile and DBP <95th percentile) and mixed hypertension (SBP ≥95th percentile and DBP ≥95th percentile) were defined according to the Chinese Guidelines for Pediatric Hypertension (Blood Pressure Reference Standard Tables on the basis of age, sex, and height tables of Chinese children aged 3–17 years old) [13].

Other measurements

We used questionnaires to obtain basic personal information, family medical history, smoking status and alcohol consumption habits. Height, body weight, the waist and hip circumferences were measured. BMI was calculated as kilograms per square meters. Fasting venous blood samples were obtained after the participants had fasted for 8–10 h and stored at −80 °C until analysis. Urine samples were collected for the first time in the morning and were kept frozen at −40 °C until analysis. Standardized measurements of the serum lipid profile, blood glucose, serum uric acid, urine creatinine and albumin levels were evaluated with an automatic biochemical analyzer (model 7600; Hitachi Ltd., Tokyo, Japan). Details of these assays were described previously [14,15]

Assessment of subclinical target organ damage

The brachial–ankle pulse wave velocity (baPWV) was assessed using an automatic arteriosclerosis diagnostic device (BP-203RPEII; Nihon Colin, Tokyo, Japan). The baPWV was calculated by time-phase analysis between the right brachial and volume waveforms at both ankles. A baPWV of 1400 cm/s or greater was defined as a high-risk baPWV level for arterial stiffness [16].

Albuminuria has been identified as the most sensitive marker for abnormal kidney function. Measuring albumin levels from a 24-h urine sample has been considered the gold standard. The urinary albumin-to-creatinine ratio (uACR) is convenient and equivalent to the gold standard technique, with ratio greater than 30 mg/g being classified albuminuria [17].

The internationally used Cornell product index was adopted to access the occurrence of LVH [18]. Routine 12-lead ECG examinations were conducted under quiet conditions. The Cornell product index (mm ms) was calculated as $(RavL + Sv3) \times QRS$ for men or $(RavL + Sv3 + 8) \times QRS$ for women. A Cornell product index at least 2440 mm ms was used as the diagnostic criterion for LVH [19].

Statistical analysis

Continuous data are reported as the mean ± SDs if normally distributed; otherwise, they are reported as medians (25th, 75th percentile ranges). Categorical data are presented as frequencies and percentages. Differences between continuous variables were analyzed by one-way ANOVA for the four groups when the distribution and variance met the conditions; otherwise, the Kruskal–Wallis test was used. Categorical variables between different groups were compared with chi-squared tests. Multivariable-adjusted logistic regression analysis were used to determine the association between IDH in childhood and adult STOD. To make the results more accurate, we made the corresponding model adjustment as follows: model 1 is adjusted for sex, age; model 2 is adjusted for model 1 plus BMI, bust and heart rate at baseline; model 3 is adjusted for model 2 plus smoking, drinking, family history of hypertension, fasting

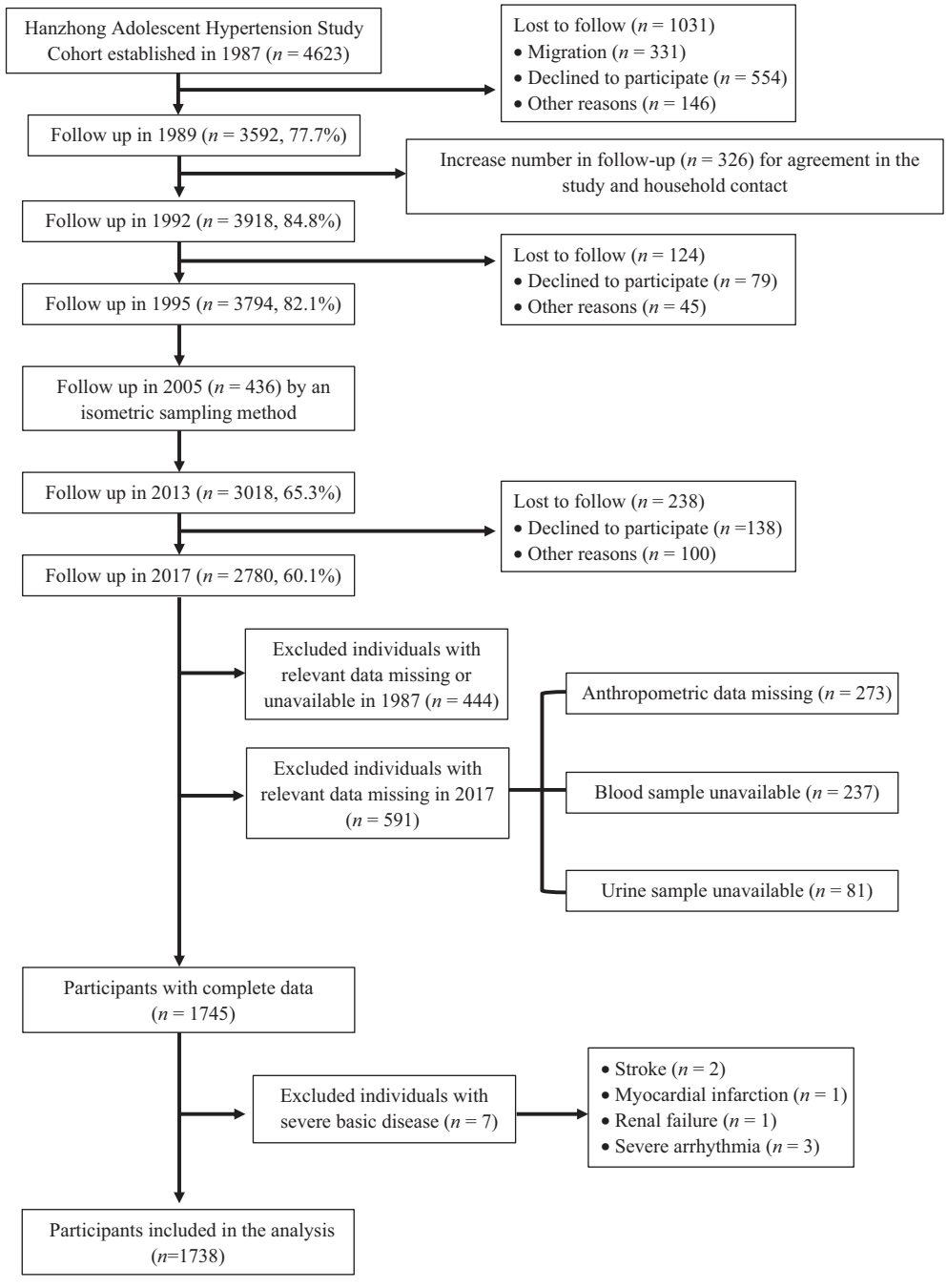

FIGURE 1 Flow of participants.

plasma glucose and serum uric acid at follow-up. Several sensitivity analyses were also conducted to test the robustness of our findings. All statistical analyses were performed using Python version 3.7 and SPSS version 25.0 (IBM, Armonk, New York, USA). Statistical significance was set as a two-tailed *P* value of less than 0.05.

RESULTS

Demographic and clinical characteristics

The median age of the 1738 participants was 12 (9, 14) years old at baseline. Among them, 963 participants (55.4%) were boys, and 775 (44.6%) were girls. The characteristics of the participants according to different hypertension subtypes are shown in Table 1. Individuals with IDH, ISH and mixed hypertension were younger than normotensive individuals, and thus, had lower BMI and a smaller bust at baseline. Over 30 years, these individuals had higher blood glucose and serum uric acid than normotensive individuals. BMI, waist, hips, serum lipid profile, smoking, drinking and family history of hypertension among different hypertension subtypes were not different. Compared with the normotension group, Individuals with IDH, ISH and mixed hypertension in childhood have higher baPWV ($P = 0.027$),

TABLE 1. Demographic characteristics and cardiovascular risk factors of the different hypertension subtypes

	Normotension	Isolated diastolic hypertension	Isolated systolic hypertension	Mixed hypertension	*P* value
Number of patients	1553 (89.4%)	94 (5.4%)	39 (2.2%)	52 (3.0%)	–
Gender (M/F)	862/691	54/40	21/18	26/26	0.845
Baseline (children)					
Age (years)	12 (9, 14)	10 (8, 12)	10 (8, 13)	10 (8, 11)	<0.001
SBP (mmHg)	102.2 ± 9.6	107.8 ± 6.9	118.6 ± 6.0	119.5 ± 6.4	<0.001
DBP (mmHg)	62.7 (58.7, 69.3)	77.3 (73.0, 80.0)	65.9 (62.0, 70.9)	80.0 (76.2, 84.7)	<0.001
Height (cm)	137.6 (124.8, 149.0)	130.2 (119.0, 142.7)	126.6 (116.9, 141.3)	127.3 (119.9, 134.5)	<0.001
Weight (kg)	30.1 (23.3, 39.4)	24.1 (20.9, 34.2)	24.5 (20.3, 39.4)	25.3 (22.1, 29.0)	<0.001
BMI (kg/m^2)	16.0 (14.8, 17.7)	15.4 (14.5, 17.1)	15.6 (14.7, 18.2)	15.5 (14.7, 16.4)	0.014
HR (bpm)	78 (72, 84)	80 (72, 84)	80 (72, 88)	80 (76, 86)	0.016
Bust (cm)	62.0 (57.1, 68.0)	60.0 (56.3, 64.5)	60.0 (55.9, 65.5)	58.8 (54.8, 62.3)	0.001
Follow-up (adults)					
Age (years)	42 (39, 44)	40 (38, 42)	40 (38, 43)	40 (38, 41)	<0.001
SBP (mmHg)	120.7 (112.0, 130.3)	125.7 (116.3, 133.8)	122.8 (115.0, 132.8)	132.0 (121.3, 139.0)	<0.001
DBP (mmHg)	76.7 ± 11.5	80.7 ± 11.2	77.7 ± 8.3	82.6 ± 11.9	<0.001
Height (cm)	162.9 ± 7.9	164.0 ± 7.9	162.3 ± 8.0	162.0 ± 6.6	0.314
Weight (kg)	64.2 ± 10.7	65.2 ± 11.9	62.9 ± 12.1	64.3 ± 9.5	0.612
BMI (kg/m^2)	24.1 ± 3.2	24.1 ± 3.1	23.7 ± 3.1	24.2 ± 2.8	0.799
HR (bpm)	73 (66, 80)	72 (68, 82)	77 (68, 84)	77 (71, 83)	0.027
Waist (cm)	85.0 ± 9.3	84.6 ± 10.0	85.6 ± 8.9	85.6 ± 9.3	0.423
Hips (cm)	92.5 ± 5.4	92.6 ± 5.3	91.8 ± 5.1	92.6 ± 5.0	0.700
Smoking (%)	679 (43.7%)	39 (41.5%)	15 (38.5%)	22 (42.3%)	0.893
Drinking (%)	465 (29.9%)	25 (26.6%)	7 (17.9%)	11 (21.2%)	0.192
FH.hypertension (%)	810 (52.2%)	51 (54.3%)	16 (41.0%)	31 (59.6%)	0.354
TC (mmol/l)	4.51 (4.04, 5.03)	4.24 (3.90, 5.00)	4.55 (3.91, 4.96)	4.55 (4.21, 4.94)	0.179
HDL-C (mmol/l)	1.14 (0.99, 1.33)	1.14 (0.99, 1.32)	1.22 (1.05, 1.47)	1.14 (0.99, 1.35)	0.403
LDL-C (mmol/l)	2.53 ± 0.65	2.45 ± 0.64	2.46 ± 0.76	2.53 ± 0.57	0.526
Triglycerides (mmol/l)	1.37 (0.97, 1.97)	1.24 (0.93, 1.78)	1.04 (0.83, 1.75)	1.39 (0.87, 2.03)	0.134
Fasting glucose (mmol/l)	4.57 (4.28, 4.91)	4.50 (4.20, 4.85)	4.61 (4.38, 5.08)	4.76 (4.42, 5.12)	0.010
Serum uric acid (mmol/l)	280.3 (226.1, 335.6)	301.8 (220.0, 369.0)	254.9 (199.9, 306.4)	260.8 (215.1, 316.4)	0.015
uACR (mg/g)	8.37 (5.53, 14.74)	8.64 (5.97, 16.71)	8.54 (6.12, 13.77)	12.52 (8.74, 21.48)	0.014
baPWV (cm/s)	1209.5 (1089.0, 1355.0)	1267.0 (1108.5, 1413.0)	1266.8 (1155.3, 1375.4)	1273.8 (1128.3, 1581.8)	0.027
Cornell index (mm ms)	1378.0 (1044.0, 1728.0)	1589.5 (1209.8, 1842.0)	1536.0 (1299.4, 1688.0)	1462.5 (1102.7, 1793.6)	0.017

Continuous variables were shown as mean ± SDs if normally distributed or median (quartile 1, quartile 3) if nonnormally distributed. Categorical variables were expressed as numbers and percentages of participants. Statistical ANOVA was performed by one-way ANOVA when normally distributed; otherwise, the Kruskal–Wallis test was used. Differences between groups of categorical variables were compared with chi-squared tests. baPWV, brachial-ankle pulse wave velocity; FH.hypertension, history of hypertension; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; uACR, urinary albumin-to-creatinine ratio.

uACR ($P = 0.014$) and Cornell index ($P = 0.017$) than normotensive individuals at follow-up.

Prevalence and target organ measurements of different hypertension subtypes

The prevalence of different hypertension subtypes in adolescents is shown in Fig. 2. The prevalence of IDH, ISH, and mixed hypertension was 5.4, 2.2 and 3% (5.6, 2.2 and 2.7% for boys vs. 5.2, 2.2 and 3.4% for girls), respectively and there were no gender differences. The levels and differences of the target organ measurements in the different hypertension subtype groups are shown in Fig. 3. Compared with normotension group, the IDH group had higher baPWV (1267 vs. 1209.5 cm/s, $P = 0.047$), uACR (8.64 vs. 8.37 mg/g, $P = 0.042$) and Cornell index (1589.5 vs. 1378.0 mm ms, $P = 0.010$). The mixed hypertension group had higher baPWV ($P = 0.035$) and uACR ($P = 0.002$) than the normotension group but not Cornell index ($P = 0.324$). There was no difference in the target organ measurements between the normotension group and the ISH group (all $P > 0.05$).

Association between hypertension subtypes in childhood and adult subclinical target organ damage

We used multivariable adjusted logistic regression to examine the associations of different hypertension subtypes in childhood with adult STOD. The results are shown in Table 2. After adjusting for sex, age, BMI, bust, heart rate at baseline and smoking, drinking, family history of hypertension, fasting plasma glucose and serum uric acid at follow-up, participants in the IDH group had higher risk of arterial stiffness (RR, 1.66; 95% CI, 1.01–2.76) and albuminuria (RR, 2.27; 95% CI, 1.35–4.16) than normotensive participants, but not LVH (RR, 1.79; 95% CI, 0.73–4.39). Furthermore, we redefined the hypertension subtypes in childhood according to the 90th percentile of SBP/DBP (elevated blood pressure reference criterion in children according to Chinese Guidelines for Pediatric Hypertension) and reassessed the associations. As shown in Table 3, IDH in childhood was still associated with adult LVH (RR, 2.48; 95% CI, 1.28–4.84).

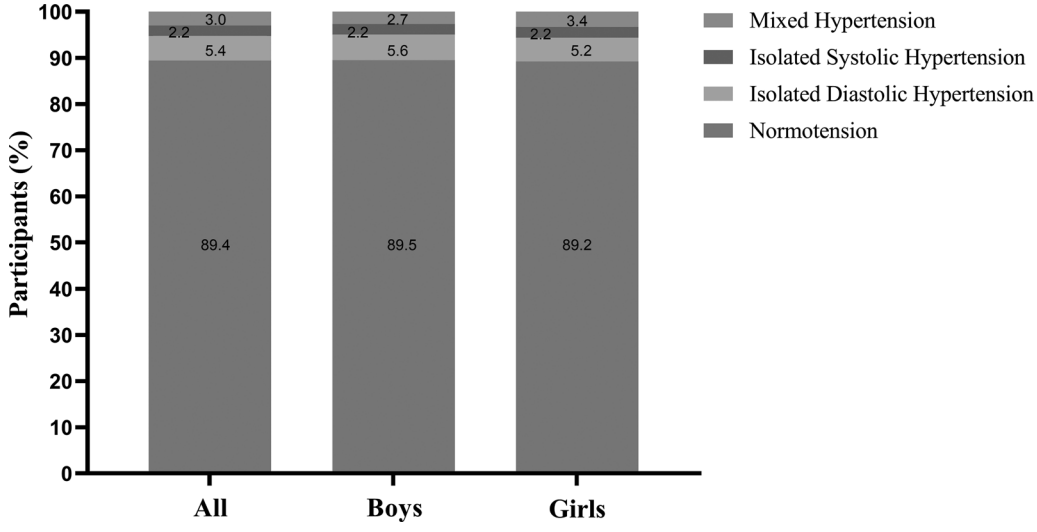

FIGURE 2 Prevalence of different hypertension subtypes in adolescents.

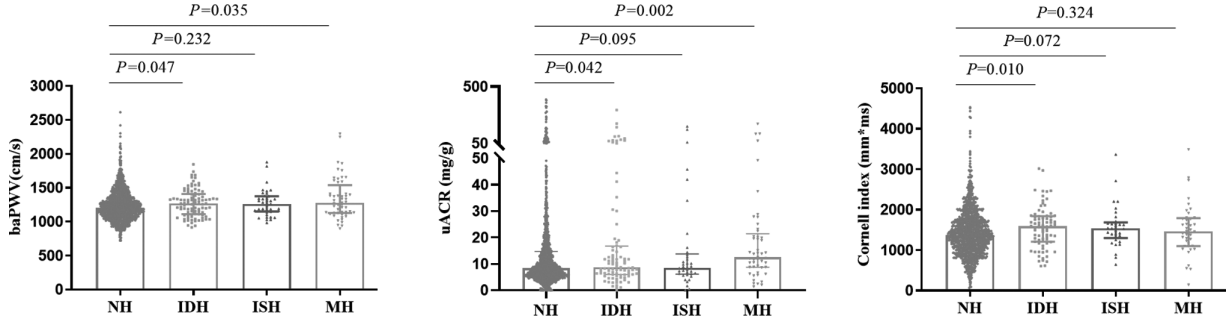

FIGURE 3 The levels and differences of the target organ measurements (a: baPWV; b: uACR; c: Cornell index) in the different hypertension subgroups. baPWV, brachial–ankle pulse wave velocity; IDH, isolated diastolic hypertension; ISH, isolated systolic hypertension; MH, mixed hypertension; uACR, urinary albumin-to-creatinine ratio.

We performed additional analyses after excluding individuals who had received antihypertensive drugs to eliminate the effect of this factor on the results. And the results remained the same (Supplemental Table 1, http://links.lww.com/HJH/B957). Compared with the normotension group, the IDH in childhood had higher risk of arterial stiffness (RR, 1.72; 95% CI, 1.02–2.91) and albuminuria (RR, 2.28; 95% CI, 1.27–4.10) than normotensive participants, but not LVH (RR, 1.14; 95% CI, 0.55–2.37). Taken together, the results of our study indicated that IDH in

TABLE 2. Multivariable-adjusted risk ratio of the association between different hypertension subtypes in children and adult subclinical target organ damage

Subclinical target organ damage	Percentage (%)	Model 1	Model 2	Model 3
Arterial stiffness ($n = 1738$)				
Normotension	20.5%	Ref	Ref	Ref
Isolated diastolic hypertension	26.6%	1.68 (1.02–2.74)	1.67 (1.02–2.76)	1.66 (1.01–2.76)
Isolated systolic hypertension	20.5%	1.18 (0.53–2.65)	1.19 (0.53–2.67)	1.29 (0.56–2.99)
Mixed hypertension	28.8%	2.05 (1.08–3.90)	2.05 (1.07–3.90)	1.95 (1.01–3.79)
Albuminuria ($n = 1652$)				
Normotension	9.2%	Ref	Ref	Ref
Isolated diastolic hypertension	19.4%	2.33 (1.34–4.05)	2.29 (1.32–3.98)	2.27 (1.35–4.16)
Isolated systolic hypertension	15.8%	1.82 (0.75–4.45)	1.73 (0.70–4.23)	1.61 (0.62–4.14)
Mixed hypertension	22.4%	2.76 (1.37–5.58)	2.70 (1.33–5.45)	2.51 (1.21–5.21)
Left ventricle hypertrophy ($n = 1429$)				
Normotension	4.5%	Ref	Ref	Ref
Isolated diastolic hypertension	7.7%	1.75 (0.72–4.25)	1.77 (0.73–4.30)	1.79 (0.73–4.39)
Isolated systolic hypertension	6.1%	1.36 (0.32–5.84)	1.41 (0.33–6.08)	1.60 (0.37–6.99)
Mixed hypertension	7.5%	1.71 (0.51–5.78)	1.75 (0.52–5.93)	1.63 (0.47–5.61)

Model 1 is adjusted for sex, age; model 2 is adjusted for model 1 plus body mass index, bust and heart rate at baseline; model 3 is adjusted for model 2 plus smoking, drinking, family history of hypertension, fasting plasma glucose and serum uric acid at follow-up.

TABLE 3. Multivariable-adjusted risk ratio of the association between different hypertension subtypes by the reference standard of elevated blood pressure in children, and adult subclinical target organ damage (sensitivity analysis)

Subclinical target organ damage	Percentage (%)	Model 1	Model 2	Model 3
Arterial stiffening ($n = 1738$)				
Normotension	19.1%	Ref	Ref	Ref
Isolated diastolic hypertension	27.1%	1.76 (1.21–2.57)	1.78 (1.22–2.60)	1.81 (1.24–2.66)
Isolated systolic hypertension	24.8%	1.53 (0.95–2.47)	1.57 (0.97–2.55)	1.57 (0.95–2.57)
Mixed hypertension	28.8%	2.01 (1.34–3.00)	2.06 (1.37–3.09)	2.04 (1.35–3.09)
Albuminuria ($n = 1652$)				
Normotension	9.0%	Ref	Ref	Ref
Isolated diastolic hypertension	13.7%	1.58 (0.97–2.56)	1.52 (0.93–2.47)	1.59 (0.97–2.62)
Isolated systolic hypertension	13.1%	1.52 (0.82–2.81)	1.44 (0.72–2.67)	1.42 (0.75–2.67)
Mixed hypertension	15.8%	1.85 (1.12–3.04)	1.78 (1.08–2.94)	1.76 (1.06–2.95)
Left ventricle hypertrophy ($n = 1429$)				
Normotension	3.9%	Ref	Ref	Ref
Isolated diastolic hypertension	8.8%	2.39 (1.24–4.60)	2.48 (1.28–4.79)	2.48 (1.28–4.84)
Isolated systolic hypertension	3.7%	0.89 (0.27–2.95)	0.91 (0.27–3.02)	0.94 (0.28–3.15)
Mixed hypertension	8.1%	2.13 (1.00–4.51)	2.11 (1.00–4.49)	2.14 (1.00–4.58)

Model 1 is adjusted for sex, age; model 2 is adjusted for model 1 plus body mass index, bust and heart rate at baseline; model 3 is adjusted for model 2 plus smoking, drinking, family history of hypertension, fasting plasma glucose and serum uric acid at follow-up.

childhood was important for the development of STOD in later life.

Association of the long-term burden and trends of DBP from childhood to adulthood with target organ measurements

The BP growth curves of 1553 individuals aged 6–15 years who had been examined four or more times for BMI and BP since childhood were constructed using a random-effects model. The long-term burden and trends of BP were measured as the area under the curve (AUC) [20]. A cubic curve was fit for SBP and DBP. As seen in Fig. 4, the total AUC (a + b) can be considered a measure of the long-term cumulative burden; the incremental AUC (a), determined by the within-participants variability, represents a combination of linear and nonlinear longitudinal trends [21].

Table 4 shows the association of the long-term burden and longitudinal trends of DBP from childhood to adulthood with target organ measurements in adults. After adjusting for sex, age, BMI, bust, heart rate and SBP at baseline, the long-term burden of DBP from childhood to adulthood was all associated with adult baPWV ($\beta = 7.74$; $P < 0.001$), uACR ($\beta = 0.57$; $P < 0.001$) and Cornell index ($\beta = 7.97$; $P = 0.001$). The longitudinal trend of DBP was associated with adult baPWV ($\beta = 2.34$; $P < 0.001$) and uACR ($\beta = 0.33$; $P < 0.001$), but not LVH ($\beta = 1.72$; $P = 0.364$).

DISCUSSION

Our analysis included 1738 school children aged 6–15 years who were enrolled from rural China in 1987 and followed for 30 years. In this study, we assessed the prevalence of different hypertension subtypes in adolescents and explored the impact of IDH in childhood on adult STOD. We found that IDH accounts for a higher proportion of adolescent hypertension subtypes. The key finding was that IDH in childhood significantly increased the risk of some measures of subclinical target organ damage in adults. The cumulative long-term burden and longitudinal trends of DBP from childhood to adulthood was also associated with target organ measurements in adults.

With the change to a sedentary lifestyle and an increasing prevalence of obesity, diabetes, and other metabolic disorders, hypertension patients have shown a tendency to be younger. In the early phase of hypertension or in young adults, diastolic hypertension with or without elevation of SBP was a major subtype of hypertension [22]. Mahajan

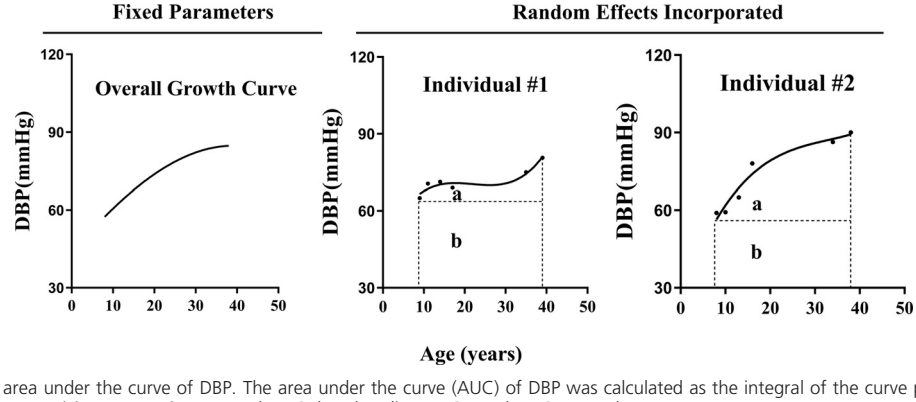

FIGURE 4 Illustration of the area under the curve of DBP. The area under the curve (AUC) of DBP was calculated as the integral of the curve parameters during the follow-up period in each of these two participants. a = incremental AUC; b = baseline AUC; total AUC = a + b.

TABLE 4. Multiple-adjusted liner regression of measures of target organ at follow-up on the long-term burden and longitudinal trends of DBP

Measure of target organ	*N*	Long-term burden of DBP (TAUC)		Longitudinal trend of DBP (IAUC)	
		B (95% CI)	*P* value	*B* (95% CI)	*P* value
Pulse wave velocity (cm/s)	1553				
A		8.39 (7.15–9.63)	<0.001	3.97 (2.98–5.00)	<0.001
FA		7.74 (6.49–8.99)	<0.001	2.34 (1.36–3.32)	<0.001
uACR (mg/g)	1477				
A		0.61 (0.37–0.86)	<0.001	0.47 (0.27–0.66)	<0.001
FA		0.57 (0.32–0.82)	<0.001	0.33 (0.15–0.52)	<0.001
Cornell index (mm ms)	1278				
A		8.26 (3.63–12.88)	<0.001	0.85 (-2.69–4.38)	0.639
FA		7.97 (3.25–12.69)	0.001	1.72 (-1.99–5.43)	0.364

Adjusted models (A) is adjusted for sex, age, BMI, bust and heart rate at baseline; fully adjusted models (FA) is adjusted for adjusted models (A) plus baseline SBP. IAUC, incremental area under the curve; TAUC, total area under the curve; uACR, urinary albumin-to-creatinine ratio.

et al. used data from the China PEACE Million Persons aged 35–75 years between 2014 and 2018 and assessed the prevalence, awareness and treatment of IDH. The results show that IDH affected a large number of adults in China, especially in the young-aged and middle-aged population. With increasing age, there was a gradual shift from IDH to ISH and mixed hypertension [23]. From these, the younger the age, the more likely the prevalence of IDH. However, few studies have focused on the prevalence of IDH in adolescents and the impact of adolescent IDH on long-term cardiovascular risk. Our study found that the prevalence of IDH was higher in adolescents than in adults. And among the different hypertension subtypes in adolescents, the proportion of IDH was higher than that of ISH and mixed hypertension. The most likely explanation for the higher prevalence of IDH in adolescents than in adults is the fall in DBP because of increased large artery stiffness with increasing age [24]. Therefore, the effect of IDH on long-term target organ damage cannot only focus on middle-aged or elderly people nor simply be used to understand IDH as 'not a disease'. It is more important and meaningful to assess the impact of IDH in adolescents on long-term target organ damage.

Brachial–ankle pulse wave velocity measured noninvasively is often used as an indicator of arterial stiffness and is closely related to long-term cardiovascular events and all-cause mortality [25]. Our results found that IDH and mixed hypertension in adolescents significantly increased the risk of adult arterial stiffness. In fact, this finding is similar with an early Framingham report. In patients less than 50 years of age, DBP was predictive of CHD risk and SBP was not, with hazard ratios of 1.42 ($P = 0.001$) and 0.95 ($P = 0.49$), respectively [10]. The finding was also consistent with increased peripheral resistance being dominant in determining the CHD risk in young hypertensives. DBP and isolated diastolic hypertension drive arterial stiffness in younger participants. IDH in adolescents and young adults is an important risk factor for long-term arterial stiffness that must be treated.

Albuminuria has already been widely used as the most sensitive marker of kidney damage. Fangfei *et al.* analyzed the association of kidney damage with 24-h DBP levels and found that 24-h DBP and IDH related to the uACR below middle age (<55 years old) [22]. However, the participants in this study were still adults. Differently, but more importantly, our results complement the data on IDH in children and adolescents and provide direct evidence of the association between IDH in childhood and long-term renal injury. We emphasize the importance of prevention, detection, and treatment of IDH, especially among adolescents.

Left ventricular hypertrophy independently predicts increased cardiovascular morbidity and mortality. Levy *et al.* [26] concluded that approximately 30% of hypertensive patients may have LVH, and the detection rate of LVH is positively correlated with the severity of hypertension. Our study assessed the impact of the different hypertension subtypes in adolescents on adult LVH and found that hypertension (including all the hypertension subtypes) in childhood was not associated with adult LVH. However, when the cutoff levels for adolescent hypertension were the levels of the 90th percentile of SBP and DBP, IDH in adolescents increased the risk of adult LVH. Although the association between mixed hypertension in adolescents and adult LVH was not statistically significant, there was a similar trend. The failure to reach significance was mainly because of the small number of patients with LVH as detected by electrocardiography [27]. Our results have also shown an association between a long-term cumulative burden of DBP from childhood to adulthood and the Cornell index in adults. Therefore, IDH in adolescents is indeed a risk factor for LVH in adults. This result was in line with the finding from the Bogalusa Heart Study that indicated adverse influence of elevated BP levels on LVH begins in childhood [21]. Our findings underscore the importance of BP control during childhood especially the control of IDH for long-term cardiac health.

The strength of this study is that a large number of Chinese school-going children were randomly selected and followed for 30 years into adulthood. This longitudinal cohort allowed us to fully explore the impact of childhood risk factors on adult outcome events. In this study, we focused on exploring the impact of different hypertension subtypes in adolescents, especially IDH, on subclinical target organ damage in adults. To our knowledge, this impact has rarely been explored in previous studies. Our current study has some potential limitations. First, the participants were recruited from multiple rural areas in northern China, and most of them were of Han ethnicity. Therefore, the findings of this study have important

implications for most Chinese populations and even Asian populations. However, our results will require replication in other cohorts to determine their generalizability to other ethnicities and to populations with different backgrounds. Second, the absence of fitness or physical activity data and dietary habits is also an important limitation of this study. Third, participants with a mean age of 42 years at the last follow-up had a relatively low prevalence of LVH, possibly as we used the Cornell index rather than the Gold standard echocardiography as an indicator of LVH or as the young people themselves may have a lower prevalence of LVH. Finally, as our cohort consisted mainly of young adults, we could not investigate the association between different hypertension subtypes in childhood and adult cardiovascular endpoint events. Instead, we used subclinical target organ damage as outcome variables. The prospective design of our study provides us an opportunity to perform further follow-ups to determine the future risk of cardiovascular events.

In conclusion, the present study demonstrated that IDH accounts for a higher proportion of adolescent hypertension subtypes and can increase the risk of adult STOD. These results highlight the necessity to improve the prevention, detection and treatment of IDH in adolescents.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lewington S, Lacey B, Clarke R, Guo Y, Kong XL, Yang L, *et al.* The burden of hypertension and associated risk for cardiovascular mortality in China. *JAMA Intern Med* 2016; 176:524–532.
2. Hall JE, Granger JP, Reckelhoff JF, Sandberg K. Hypertension and cardiovascular disease in women. *Hypertension* 2008; 51:951.
3. Li Y, Wei FF, Wang S, Cheng YB, Wang JG. Cardiovascular risks associated with diastolic blood pressure and isolated diastolic hypertension. *Curr Hypertens Rep* 2014; 16:489.
4. Staessen JA, Wang J, Bianchi G, Birkenhäger WH. Essential hypertension. *Lancet* 2003; 361:1629–1641.
5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, *et al.* 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39:3021–3104.
6. McEvoy JW, Daya N, Rahman F, Hoogeveen RC, Blumenthal RS, Shah AM, *et al.* Association of isolated diastolic hypertension as defined by the 2017 ACC/AHA Blood Pressure Guideline With Incident Cardiovascular Outcomes. *JAMA* 2020; 323:329–338.
7. Strandberg TE, Salomaa VV, Vanhanen HT, Pitkälä K, Miettinen TA. Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. *J Hypertens* 2002; 20:399–404.
8. Pickering TG. Isolated diastolic hypertension. *J Clin Hypertens (Greenwich)* 2003; 5:411–413.
9. Li Y, Wei FF, Thijs L, Boggia J, Asayama K, Hansen TW, *et al.* Ambulatory hypertension subtypes and 24-h systolic and diastolic blood pressure as distinct outcome predictors in 8341 untreated people recruited from 12 populations. *Circulation* 2014; 130:466–474.
10. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, *et al.* Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; 103:1245–1249.
11. Zheng W, Mu J, Chu C, Hu J, Yan Y, Ma Q, *et al.* Association of blood pressure trajectories in early life with subclinical renal damage in middle age. *J Am Soc Nephrol* 2018; 29:2835–2846.
12. Chu C, Dai Y, Mu J, Yang R, Wang M, Yang J, *et al.* Associations of risk factors in childhood with arterial stiffness 26 years later: the Hanzhong Adolescent Hypertension Cohort. *J Hypertens* 2017; 35 (Suppl 1): S10–S15.
13. Chinese guidelines for hypertension prevention and treatment (2018 revision). *Chin J Cardiovasc Med* 2019; 24:24–56.
14. Wang Y, Yuan Y, Gao WH, Yan Y, Wang KK, Qu PF, *et al.* Predictors for progressions of brachial-ankle pulse wave velocity and carotid intima-media thickness over a 12-year follow-up: Hanzhong Adolescent Hypertension Study. *J Hypertens* 2019; 37:1167–1175.
15. Liao YY, Ma Q, Chu C, Wang Y, Zheng WL, Hu JW, *et al.* The predictive value of repeated blood pressure measurements in childhood for cardiovascular risk in adults: the Hanzhong Adolescent Hypertension Study. *Hypertens Res* 2020; 43:969–978.
16. Tanaka A, Tomiyama H, Maruhashi T, Matsuzawa Y, Miyoshi T, Kabutoya T, *et al.* Physiological diagnostic criteria for vascular failure. *Hypertension* 2018; 72:1060–1071.
17. Raja P, Maxwell AP, Brazil DP. The potential of albuminuria as a biomarker of diabetic complications. *Cardiovasc Drugs Ther* 2021; 35:455–466.
18. Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE, *et al.* Cornell product left ventricular hypertrophy in electrocardiogram and the risk of stroke in a general population. *Hypertension* 2009; 53:28–34.
19. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, *et al.* Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: the Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. *Circulation* 2003; 108: 684–690.
20. Chen W, Li S, Srinivasan SR, Boerwinkle E, Berenson GS. Autosomal genome scan for loci linked to blood pressure levels and trends since childhood: the Bogalusa Heart Study. *Hypertension* 2005; 45:954–959.
21. Lai CC, Sun D, Cen R, Wang J, Li S, Fernandez-Alonso C, *et al.* Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: the Bogalusa Heart Study. *J Am Coll Cardiol* 2014; 64:1580–1587.
22. Wei FF, Li Y, Zhang L, Xu TY, Ding FH, Staessen JA, *et al.* Association of target organ damage with 24-h systolic and diastolic blood pressure levels and hypertension subtypes in untreated Chinese. *Hypertension* 2014; 63:222–228.
23. Mahajan S, Zhang D, He S, Lu Y, Gupta A, Spatz ES, *et al.* Prevalence, awareness, and treatment of isolated diastolic hypertension: insights from the China PEACE Million Persons Project. *J Am Heart Assoc* 2019; 8:e012954.
24. Franklin SS, Gustin Wt, Wong ND, Larson MG, Weber MA, Kannel WB, *et al.* Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; 96:308–315.
25. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605.
26. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; 322:1561–1566.
27. Lehtonen AO, Puukka P, Varis J, Porthan K, Tikkanen JT, Nieminen MS, *et al.* Prevalence and prognosis of ECG abnormalities in normotensive and hypertensive individuals. *J Hypertens* 2016; 34:959–966.