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ORIGINAL RESEARCH

Long-Term Time in Target Range for Systolic Blood Pressure Since Childhood and Midlife Arterial Stiffness

Yang Wang, MD, PhD,[a,*] Han Qi, PhD,[b,c,*] Hao Jia, MD,[a] Dan Wang, MD,[a] Yue Sun, MD,[a] Bo-Wen Zhang, MPH,[d] Ming-Fei Du, MD,[a] Gui-Lin Hu, MD,[a] Zi-Yue Man, MD,[a] Chao Chu, MD, PhD,[a] Xiao-Jun Yang, MPH,[d] Teng Zhang, MD,[a] Tong-Shuai Guo, MD,[a] Xi Zhang, MD,[a] Yu Yan, MD,[a] Zheng Liu, PhD,[e] Ming-Ke Chang, MD,[a] Hao Li, MD,[f] Fang-Yao Chen, PhD,[g] Yu-Ming Kang, PhD,[h] Jie Ren, MD,[a] Zu-Yi Yuan, MD, PhD,[a] Ling Zhang, PhD,[d] Jian-Jun Mu, MD[a]

ABSTRACT

BACKGROUND Elevated blood pressure (BP) in childhood is associated with adult hypertension and arterial stiffness. However, the effect of long-term time in target range (TTR) for BP since childhood on the risk of arterial stiffness in midlife remains unclear.

OBJECTIVES The purpose of this study was to determine the independent association of TTR for systolic blood pressure (SBP) from childhood to midlife with arterial stiffness in adulthood.

METHODS This study used data from the ongoing cohort of the Hanzhong Adolescent Hypertension Study. SBP-TTR was assessed over 36 years, with the target ranges of SBP defined as the 90th to 95th percentile of SBP for age, sex, and height in childhood, and 110 to 130 mm Hg in adulthood. Arterial stiffness was defined as brachial-ankle pulse wave velocity >1,400 cm/s.

RESULTS Of the total 1,959 participants, 55.5% (1,088 of 1,959) were men, and the mean age was 49 years. The risk of arterial stiffness exhibited a gradual decrease with increasing SBP-TTR over the 36-year follow-up. Compared with the participants in the lowest quartile of SBP-TTR from childhood to midlife, those in the highest quartile showed significantly reduced arterial stiffness risk in midlife. This association persisted even after adjusting for mean SBP and SBP variability. Furthermore, men in the highest quartile of SBP-TTR demonstrated a markedly lower arterial stiffness risk than those in the lowest quartile, whereas this effect was not observed in women.

CONCLUSIONS Higher long-term SBP-TTR from childhood to midlife is associated with a reduced risk of arterial stiffness in midlife, regardless of the mean SBP or SBP variability. (JACC Asia. 2025;5:101-112) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [b]Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders and National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China; [c]Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China; [d]Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing Municipal Key Laboratory of Clinical Epidemiology, Beijing, China; [e]Department of Maternal and Child Health, School of Public Health, Peking University, Beijing, China; [f]Department of Critical Care Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [g]Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University Health Science Center, Xi'an, China; and the [h]Department of Physiology and Pathophysiology, Xi'an Jiaotong University School of Basic Medical Sciences, Shaanxi Engineering and Research Center of Vaccine, Key Laboratory of Environment and Genes Related to Diseases of Education Ministry of China, China. *Drs Yang Wang and Han Qi contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

ARV = average real variability

baPWV = brachial-ankle pulse wave velocity

BP = blood pressure

CVD = cardiovascular disease

SBP = systolic blood pressure

TTR = time in target range

Cardiovascular disease (CVD) is the leading cause of death worldwide, serving as a major contributor to morbidity and mortality among older adults.[1] Arterial stiffness, which is characterized by the deterioration of arterial function and structure, substantially contributes to the development of CVD.[2,3] Brachial-ankle pulse wave velocity (baPWV) is used to estimate vessel stiffness by measuring the velocity of the pressure wave traveling through the arteries, with higher velocities indicating greater stiffness.[4] Although the clinical manifestations and complications of arterial stiffness and atherosclerosis often manifest during middle or older age, the arterial stiffening process is initiated early in life and progresses silently over a long period.[5] Therefore, the early identification and appropriate management of arterial stiffness and its modifiable risk factors are crucial for preventing adverse cardiovascular outcomes.

Elevated blood pressure (BP) is an established major risk factor for accelerated arterial stiffening.[6,7] Despite BP being a continuous and dynamic variable, clinical practice and hypertension studies frequently rely on single or average BP values as a BP monitoring indicator. This approach can make the accurate assessment of the true state of BP challenging.[8] Researchers have recently introduced the concept of "time in target range" (TTR) in hypertension management.[9] This measurement incorporates the degree of BP variability and the mean BP level, thus reflecting the BP fluctuations over time within and outside the target range.[10] A few studies have shown that greater BP control within the target range is significantly associated with a decreased risk of CVD events and mortality.[9,11,12] However, the association of BP-TTR with arterial stiffness has been rarely reported.

Early-life risk factors can elevate CVD risk from childhood, and this risk modification is independent of the risk profile in late adulthood.[13] Further, elevated BP in childhood can persist into adulthood and is linked to adult hypertension and arterial stiffness.[14-16] Although our previous research and other studies have shown that childhood BP and long-term BP variability are significantly associated with adult arterial stiffness,[14,15,17] no evidence currently exists on the association between TTR for systolic blood pressure (SBP) in early life and arterial stiffness. Moreover, prior studies have typically investigated TTR utilizing short-term BP data. For example, the assessment of BP-TTR in SPRINT (Systolic Blood Pressure Intervention Trial) was limited to the first 3 months of follow-up.[11] However, no data are available on the relationship between long-term SBP-TTR from childhood to midlife and arterial stiffness risk in midlife.

Here, we utilized data from the ongoing cohort of the Hanzhong Adolescent Hypertension Study, which initially recruited children and adolescents aged 6 to 18 years and subsequently followed them for 36 years. This study aimed to investigate the long-term SBP-TTR from childhood to midlife and assess the association of long-term SBP-TTR with arterial stiffness risk in midlife.

METHODS

STUDY COHORT. This study was conducted as part of the Hanzhong Adolescent Hypertension Study, which is an ongoing, prospective population-based cohort study in northern China examining the cardiovascular risk factors from childhood to midlife. We used the data collected during the baseline period and 7 follow-up visits spanning from March 10, 1987, to June 17, 2023, with additional details described in previous studies.[18-21] Briefly, in 1987, the cohort initially enrolled 4,623 schoolchildren from 26 rural areas in 3 towns in Hanzhong, Shaanxi, China. Subsequently, a series of follow-up visits were performed in 1989, 1992, 1995, 2005, 2013, 2017, and 2023, resulting in a maximum follow-up period of 36 years. In the present study, participants with fewer than 3 BP measurements from 1987 to 2023 (n = 253), and those with incomplete baPWV data in 2023 (n = 409) were excluded. Ultimately, 1,959 participants were selected for our primary analysis. A flowchart outlining the selection of the participant population in this study is presented in **Figure 1**. This study received approval from the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was obtained during each visit from the participants or their parents/guardians in case of those age <18 years. All study procedures were conducted in compliance with the institutional

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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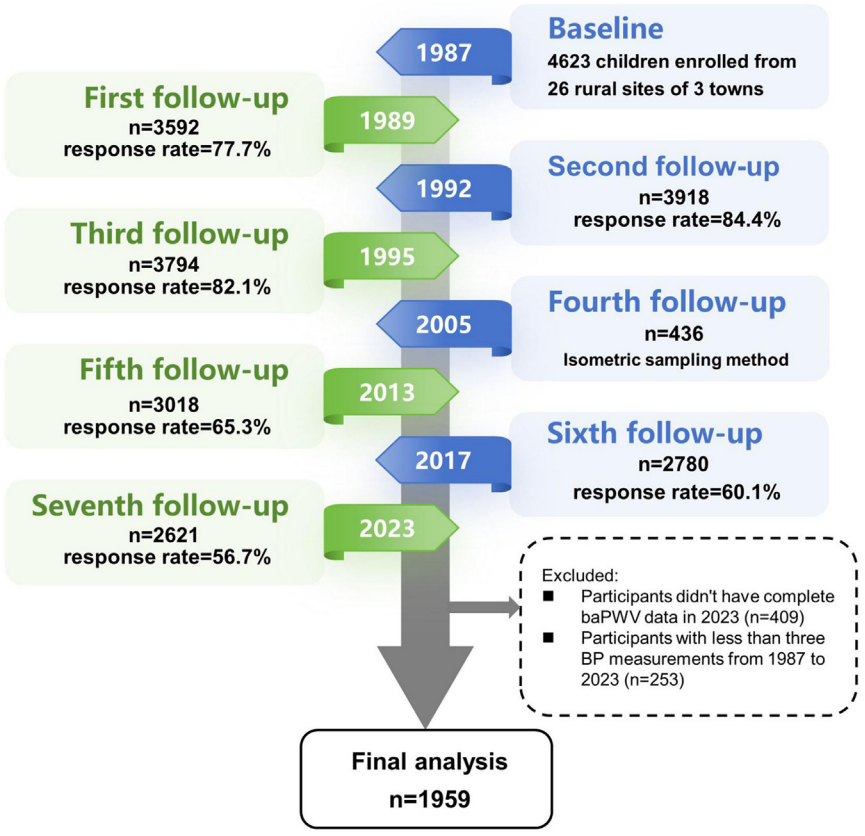
FIGURE 1 Flow Diagram Showing the Selection of the Study Population



The cohort initially enrolled 4,623 schoolchildren in 1987. A series of follow-up visits were performed in 1989, 1992, 1995, 2005, 2013, 2017, and 2023, respectively. In this study, participants with fewer than 3 blood pressure (BP) measurements (n = 253) and those with incomplete brachial-ankle pulse wave velocity (baPWV) data in 2023 (n = 409) were excluded.

guidelines and the principles of the Declaration of Helsinki.

BP MEASUREMENTS AND THE DEFINITION OF TTR.

Participants were instructed to abstain from consuming coffee, alcohol, or tea, and refrain from smoking or engaging in strenuous activity for at least 30 minutes before BP measurement. After a 5-minute rest, 3 BP values were obtained from the right upper arm with 2-minute intervals between each measurement, as previously reported.[18-21] The average of the 3 BP values was then used in our analysis. Trained and certified observers conducted the BP measurements utilizing a standard mercury sphygmomanometer during all follow-up visits, except for the use of an electronic sphygmomanometer (Omron HBP-1100) during the 2017 and 2023 visits, consistent with prior studies.[18-21]

In the current study, the SBP-TTR of each participant was calculated by the percentage (%) of all SBP measurements recorded within the target limits throughout the follow-up period and calculated according to the following formula[22]:

$$x = \frac{Number\ of\ BP\ measurements\ within\ the\ target\ ranges}{Total\ number\ of\ BP\ measurements} \times 100$$

The SBP target range in childhood was defined based on the BP tables issued by the National High Blood Pressure Screening Program,[23] aligning with the Clinical Practice Guideline from the American Academy of Pediatrics.[24] In adulthood, the SBP target range was defined according to the current American guidelines for patients with hypertension,[25] and the adult therapeutic range of 110 to 130 mm Hg adopted in published studies on TTR.[11,26] Therefore, our study defined the target ranges of SBP as the 90th to 95th percentile of SBP for age, sex, and height in childhood and 110 to 130 mm Hg in adulthood. A greater TTR (%)

indicated that the participants had achieved and maintained their target SBP range for a longer duration within the 36-year follow-up period. Additionally, long-term BP variability from childhood to midlife was assessed by calculating the average real variability (ARV). ARV represents the average absolute difference between successive BP measurements and thus takes into account the order of the BP measurements, unlike SD and coefficient of variation.[18]

Additional participant data, including education level, smoking history, alcohol consumption history, physical activity, medication use, and clinical history of CVD, were acquired via self-report questionnaires.[18-21] Details of the blood biochemistry analyses, including fasting glucose, triglyceride, serum creatinine, serum uric acid, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, are available in Supplemental Appendix I.

EVALUATION OF ARTERIAL STIFFNESS. As an indicator of arterial stiffness, baPWV has been widely used in clinical settings.[4,27] It was automatically measured and computed using a validated device (BP-203RPEII, Nihon Colin, Japan) according to previously published methodologies.[20,28,29] Briefly, each participant underwent a 5-minute resting period while cuffs were positioned on both upper arms and ankles. ECG electrodes were affixed to both wrists, and a heart sound sensor was positioned on the left sternal border at the fourth intercostal space, ensuring a quiet and comfortable environment. The device automatically determined the path distance from the suprasternal notch to either the brachium (Lb) or the ankle on the same side (La), as well as the time interval between the brachial and ankle waveforms (ΔT). Subsequently, baPWV was calculated using the following formula: baPWV (cm/s) = (La − Lb)/ΔT. The average value of baPWV from both sides was used for the analysis. In this study, arterial stiffness was characterized as baPWV >1,400 cm/s, according to the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension.[30]

DEFINITIONS. Participants who reported continuous or cumulative cigarette smoking for ≥6 months during their lifetime were classified as smokers. Those who reported consuming alcohol (liquor, beer, or wine) daily for at least 6 months were categorized as alcohol consumers. Marital status included subjects who were married, divorced, or widowed. Hypertension was defined as SBP ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or the use of antihypertensive drugs based on clinical records or self-reported data.[30] Participants with diabetes were identified as those having fasting blood glucose of ≥7.0 mmol/L, currently using antidiabetic medications, or having a previous history of diabetes mellitus.[31] Hyperlipidemia was defined by the presence of any 1 of the following conditions: hypertriglyceridemia (triglycerides ≥2.26 mmol/L), hypercholesterolemia (total cholesterol ≥6.22 mmol/L), high low-density lipoprotein cholesterol level (≥4.14 mmol/L), or low high-density lipoprotein cholesterol level (≤1.04 mmol/L).[32]

STATISTICAL ANALYSES. All statistical analyses were conducted using SAS software (version 9.4, SAS Institute). Normally distributed data were presented as mean ± SD, whereas non-normally distributed data were expressed as geometric means (IQR) and percentages. Group differences were assessed using the chi-square test, Fisher exact test, or Kruskal-Wallis H test as appropriate. The associations of SBP-TTR with mean SBP and SBP variability were analyzed using Spearman correlations.

Moreover, the associations between the quartiles of SBP-TTR (Q1: 0%-16.7%, Q2: 16.7%-33.3%, Q3: 33.3%-50%, and Q4: 50%-100%) and arterial stiffness risk in midlife were assessed using unadjusted and multivariable-adjusted logistic regression models. Initially, unadjusted analyses were performed. In the subsequent step, the covariates of age, gender, body mass index (BMI), education level, smoking history, hypertension, diabetes, and hyperlipidemia in 2023 were adjusted in model 1. Next, further adjustments for clinical and demographic variables in 2023 (including age, gender, BMI, education level, hypertension, diabetes, hyperlipidemia, and smoking history in model 1) and mean BP from childhood to midlife were performed in model 2. Last, SBP variability from childhood to midlife was also adjusted in model 3, along with adjustments for the other variables in models 1 and 2. Additionally, E-values were calculated to reflect the minimum strength for the unmeasured confounders to explain away the associations between SBP-TTR and arterial stiffness.[33] Inverse probability weighting was used to adjust biases arising from missing data. Initially, a logistic regression incorporating age, gender, BMI, education level, smoking history, hypertension, diabetes, and hyperlipidemia was conducted to predict the likelihood of nonmissing samples. Subsequently, the weights were computed as the inverse of the probabilities. Finally, the samples without missing SBP-TTR values were used in the logistic regression analysis to investigate the relationship between SBP-TTR groups and arterial stiffness risk in midlife. Due to the physiological, hormonal, lifestyle, and risk profile

TABLE 1 Demographic Characteristics and Cardiovascular Risk Factors According to Time in Target Range Quartiles

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* Value
Baseline in 1987						
Age, y	13.0 (10.0-15.0)	12.0 (9.0-14.0)	12.0 (9.0-14.0)	13.0 (10.0-15.0)	14.0 (13.0-16.0)	<0.001
Sex						0.408
Boys	1,088 (55.5)	281 (56.7)	195 (55.6)	368 (57.1)	244 (52.2)	
Girls	871 (44.5)	215 (43.3)	156 (44.4)	277 (42.9)	223 (47.8)	
SBP, mm Hg	104.0 (97.3-111.3)	100.7 (95.3-110.0)	100.3 (96.7-110.0)	103.3 (97.0-111.3)	108.0 (100.6-115.3)	<0.001
DBP, mm Hg	64.0 (60.0-70.7)	62.7 (58.7-70.0)	63.3 (58.7-70.7)	64.6 (60.0-70.7)	66.0 (60.0-72.0)	0.012
MAP, mm Hg	78.4 (72.6-84.2)	76.7 (71.4-83.1)	77.5 (72.0-83.7)	78.6 (73.1-84.0)	80.6 (74.0-85.7)	<0.001
Heart rate, beats/min	78.0 (72.0-84.0)	78.0 (72.0-84.0)	78.0 (72.0-84.0)	78.0 (72.0-84.0)	76.0 (72.0-84.0)	0.002
Bust, cm	64.5 (58.0-71.0)	62.0 (56.0-69.0)	61.0 (57.0-69.0)	65.0 (58.0-71.3)	67.1 (61.8-73.0)	<0.001
BMI, kg/m^2	16.3 (14.9-18.3)	15.7 (14.6-17.6)	15.9 (14.7-17.7)	16.3 (15.0-18.5)	17.3 (15.8-18.8)	<0.001
Follow-up in 2023						
Age, y	49.00 (46.00-51.00)	48.00 (45.00-51.00)	48.00 (45.00-50.00)	49.00 (46.00-51.00)	50.00 (48.00-52.00)	<0.001
BMI, kg/m^2	24.51 (22.58-26.58)	24.53 (22.35-26.98)	24.68 (22.95-26.63)	24.61 (22.61-26.59)	24.09 (22.50-26.01)	0.107
Smoking	802 (41.5)	208 (42.7)	152 (43.8)	271 (42.6)	171 (37.0)	0.157
Drinking	526 (27.2)	147 (30.2)	90 (26.0)	174 (27.4)	115 (24.9)	0.298
Hypertension	705 (36.8)	256 (52.2)	152 (43.9)	208 (33.2)	89 (19.6)	<0.001
Diabetes	181 (9.4)	59 (12.1)	24 (6.9)	66 (10.4)	32 (7.0)	0.014
Hyperlipidemia	950 (49.1)	248 (50.8)	168 (48.1)	316 (49.5)	218 (47.3)	0.715
Education						0.037
Primary school and below	143 (7.4)	35 (7.2)	24 (6.9)	39 (6.2)	45 (9.7)	
Middle school	1,159 (60.1)	287 (59.1)	205 (59.1)	376 (59.4)	291 (63.0)	
High school	408 (21.2)	94 (19.3)	76 (21.9)	151 (23.9)	87 (18.8)	
College and above	218 (11.3)	70 (14.4)	42 (12.1)	67 (10.6)	39 (8.4)	
Married	1,834 (95.5)	465 (95.9)	332 (95.7)	598 (95.1)	439 (95.4)	0.766
Antihypertensive medications						0.303
Diuretic	6 (3.8)	1 (1.5)	1 (2.6)	3 (7.9)	1 (6.3)	
ACEI/ARB	55 (34.6)	22 (33.3)	20 (51.3)	8 (21.1)	5 (31.3)	
CCBs	81 (50.9)	35 (53.0)	16 (41.0)	21 (55.3)	9 (56.3)	
Beta-receptor blockers	4 (2.5)	3 (4.5)	0 (0)	1 (2.6)	0 (0)	
Others	13 (8.2)	5 (7.6)	2 (5.1)	5 (13.2)	1 (6.3)	
SBP, mm Hg	125.3 (115.0-137.7)	133.7 (107.7-145.5)	130.3 (115.0-142.3)	125.0 (115.9-135.3)	122.0 (116.7-128.1)	<0.001
DBP, mm Hg	83.3 (75.7-91.3)	87.0 (73.3-96.3)	85.7 (77.0-96.7)	83.0 (77.0-90.3)	81.00 (75.0-86.7)	<0.001
Fasting glucose, mmol/L	5.3 (4.9-5.8)	5.3 (4.9-5.9)	5.3 (5.0-5.8)	5.3 (4.9-5.8)	5.3 (5.0-5.7)	0.890
Triglycerides, mmol/L	1.6 (1.1-2.3)	1.6 (1.1-2.4)	1.5 (1.1-2.3)	1.6 (1.1-2.3)	1.5 (1.1-2.1)	0.751
Total cholesterol, mmol/L	4.7 (4.2-5.3)	4.7 (4.2-5.3)	4.7 (4.2-5.2)	4.8 (4.3-5.3)	4.7 (4.3-5.4)	0.496
LDL-C, mmol/L	2.6 (2.3-3.1)	2.6 (2.2-3.0)	2.6 (2.3-3.0)	2.7 (2.3-3.1)	2.6 (2.3-3.1)	0.590
HDL-C, mmol/L	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	1.1 (1.0-1.3)	0.234
SUA, μmol/L	285.2 (234.3-339.2)	285.5 (236.2-344.1)	288.5 (227.0-339.5)	285.8 (234.2-341.3)	281.9 (236.7-333.1)	0.829
Serum creatinine, μmol/L	73.6 (65.2-82.6)	72.8 (64.8-82.8)	73.8 (63.4-83.0)	73.7 (65.4-83.3)	73.7 (65.6-80.7)	0.730
baPWV, cm/s	1,287.0 (1,185.1-1,418.9)	1,304.8 (1,178.8-1,464.3)	1,300.5 (1,207.0-1,441.5)	1,287.5 (1,188.0-1,405.0)	1,265.5 (1,177.0-1,366.5)	0.001

Values are median (Q1-Q3) or n (%).

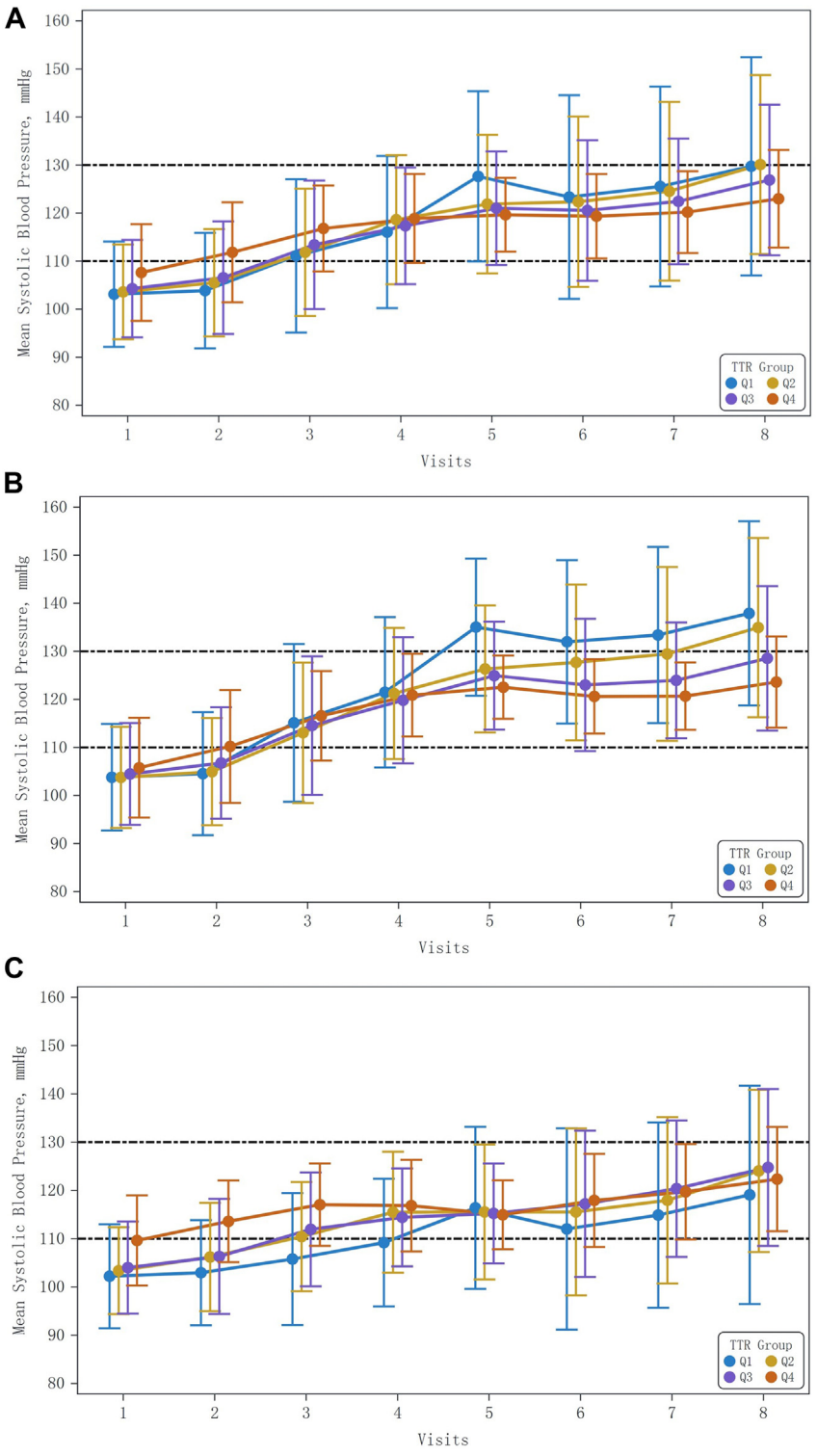
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; baPWV = brachial-ankle pulse wave velocity; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MAP = mean arterial pressure; SBP = systolic blood pressure; SUA = serum uric acid.

differences between men and women, which may affect the impact of SBP-TTR on arterial stiffness, we conducted sex-stratified analyses. A 2-sided *P* value <0.05 was considered statistically significant in all analyses.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION. A total of 1,959 participants were ultimately included in this prospective cohort study, with a follow-up period of 36 years. The characteristics of the study participants from childhood to midlife grouped according to the SBP-TTR quartiles are presented in Table 1. The median age of the participants was 49 years, and 55.5% (1,088 of 1,959) were men. Overall, participants in the highest SBP-TTR quartile were more likely to be older; have lower SBP, DBP, and education levels; and exhibit a lower prevalence of hypertension and diabetes. Further, the values of

FIGURE 2 Systolic Blood Pressure Changes Over 8 Visits During 36 Years



Time in target range for systolic blood pressure was assessed over 36 years of follow-up from childhood to midlife among the 4 TTR groups in total population (A), men (B) and women (C). The target ranges of systolic blood pressure were defined as the 90th to 95th percentile of systolic blood pressure for age, sex, and height in childhood, and 110 to 130 mm Hg in adulthood. Men exhibited a notably steeper increase in systolic blood pressure than women from childhood to middle age. Furthermore, women with higher TTR achieved and sustained their systolic blood pressure in the target range for a longer duration than men.

TABLE 2 Associations of Systolic Blood Pressure TTR From Childhood to Midlife With the Risk of Arterial Stiffness in Midlife

		Unadjusted		Model 1		Model 2		Model 3	
TTR Groups	No. of cases (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Quartile 1	168 (33.8)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Quartile 2	108 (30.8)	0.868 (0.647-1.163)	0.343	1.025 (0.735-1.430)	0.884	1.052 (0.744-1.488)	0.774	1.009 (0.721-1.412)	0.959
Quartile 3	164 (25.4)	0.666 (0.515-0.861)	0.002	0.778 (0.577-1.048)	0.099	0.789 (0.578-1.077)	0.135	0.790 (0.585-1.066)	0.124
Quartile 4	91 (19.5)	0.473 (0.352-0.635)	<0.001	0.642 (0.452-0.911)	0.013	0.651 (0.454-0.978)	0.020	0.662 (0.463-0.947)	0.024

Model 1: adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, and smoking. Model 2 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and mean systolic blood pressure from childhood to midlife. Model 3 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and average real variability of systolic blood pressure from childhood to midlife.

TTR = time in target range.

baPWV progressively decreased from the lowest to highest quartiles of SBP-TTR (Q1: 1,304.8 cm/s, Q2: 1,300.5 cm/s, Q3: 1,287.5 cm/s, and Q4: 1,265.5 cm/s; *P* for trend = 0.001) (**Table 1**). Supplemental Table 1 lists the detailed information on SBP across the age groups during the 36-year follow-up. The distribution of the children across the various SBP percentiles based on sex, age, and height percentiles in 1987 is presented in Supplemental Table 2. Overall, 7.9% (139 of 1,754) of the children exhibited SBP within the 90th to 95th percentile range, with the SBP of most children falling below the 90th percentile threshold. As shown in Supplemental Table 3, there were no significant differences in characteristics between missing and nonmissing samples of SBP-TTR. Supplemental Figure 1 shows the number of effective and missing BP measurements at each follow-up over the 36-year follow-up period. Moreover, **Figure 2A** illustrates the changes in mean SBP from childhood to midlife in the SBP-TTR quartiles. As expected, participants with higher TTR achieved and maintained their SBP in the target range for a longer period.

ASSOCIATIONS OF SBP-TTR FROM CHILDHOOD TO MIDLIFE WITH ARTERIAL STIFFNESS IN MIDLIFE. During the 36 years of follow-up, 531 participants developed arterial stiffness, resulting in an incidence rate of 27.1% (531 of 1,959; 95% CI: 25.1%-29.1%), which was 5.66 of 1,000 person years. Arterial stiffness incidences from the lowest to highest quartiles of SBP-TTR were 33.8% (168 of 496; 95% CI: 30.0%-38.1%), 30.8% (108 of 351; 95% CI: 25.9%-35.6%), 25.4% (164 of 645; 95% CI: 22.1%-28.8%), and 19.5% (91 of 467; 95% CI: 15.9%-23.1%) , respectively (*P* for trend <0.001). Compared with the participants in the lowest quartile of SBP-TTR, those in the highest quartile showed a significant association with a decreased risk of arterial stiffness in midlife in the full adjusted model (OR: 0.642; 95% CI: 0.452-0.911; *P* = 0.013; model 1) (**Table 2**). SBP-TTR was inversely correlated with SBP variability from childhood to midlife (r = −0.205 [95% CI: −0.251 to −0.162]; *P* < 0.001) and also positively correlated with mean SBP (r = 0.051 [95% CI: 0.004-0.101]; *P* = 0.024) in the whole population (Supplemental Figure 2). Therefore, in the multivariate model further adjusted for mean SBP from childhood to midlife, the OR was 0.651 (95% CI: 0.454-0.978) (model 2, **Table 2**). When we used ARV of SBP from childhood to midlife instead of mean SBP from childhood to midlife as an adjustment factor, the results were similar (model 3, **Table 2**). Additionally, the E-values and their CIs are presented in Supplemental Table 4. In model 1, the E-value for the association between the highest quartile of SBP-TTR and arterial stiffness was calculated as 1.80, suggesting that the relatively weaker unmeasured confounders could explain away the relationships between SBP-TTR and arterial stiffness.

ASSOCIATIONS OF SEX-SPECIFIC SBP-TTR FROM CHILDHOOD TO MIDLIFE WITH ARTERIAL STIFFNESS IN MIDLIFE. Men exhibited a notably steeper increase in SBP than women from childhood to middle age. Furthermore, women with higher TTR achieved and sustained their SBP in the target range for a longer duration than men (**Figures 2B and 2C**). After adjusting for multiple confounders, including mean SBP from childhood to midlife, for men, the highest quartile of SBP-TTR was significantly associated with a decreased risk of arterial stiffness (OR: 0.432 [95% CI: 0.262-0.710]; *P* = 0.001) compared with those in the lowest quartile, whereas no such significant difference was observed in women (**Table 3**). Consistent results were obtained when using ARV of SBP from childhood to midlife as an adjustment factor.

SENSITIVITY ANALYSES. Several sensitivity analyses were performed to confirm the robustness of our primary findings. Initially, the inverse probability weighting showed that the inverse associations between the higher TTR group and arterial stiffness remained robust in the population without missing TTR data (**Table 4**). Then, excluding individuals using

TABLE 3 Associations of Systolic Blood Pressure TTR From Childhood to Midlife With Risk of Arterial Stiffness Stratified by Sex

TTR Groups	No. of Cases (%)	Unadjusted		Model 1		Model 2		Model 3	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male (n = 1,088)									
Quartile 1	124 (44.1)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Quartile 2	73 (37.4)	0.758 (0.521-1.101)	0.145	0.861 (0.565-1.311)	0.485	0.929 (0.603-1.432)	0.739	0.839 (0.549-1.282)	0.416
Quartile 3	100 (27.2)	0.472 (0.340-0.656)	<0.001	0.563 (0.383-0.829)	0.004	0.627 (0.422-0.933)	0.021	0.575 (0.390-0.848)	0.005
Quartile 4	45 (18.4)	0.286 (0.192-0.427)	<0.001	0.361 (0.223-0.586)	<0.001	0.432 (0.262-0.710)	0.001	0.363 (0.221-0.597)	<0.001
Female (n = 871)									
Quartile 1	44 (20.4)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Quartile 2	35 (22.4)	1.124 (0.681-1.856)	0.647	1.292 (0.728-2.291)	0.381	1.138 (0.618-2.098)	0.678	1.293 (0.723-2.314)	0.386
Quartile 3	64 (23.1)	1.158 (0.757-1.801)	0.483	1.193 (0.721-1.972)	0.492	0.983 (0.571-1.693)	0.950	1.194 (0.718-1.987)	0.494
Quartile 4	46 (20.6)	1.010 (0.635-1.606)	0.966	1.265 (0.733-2.182)	0.399	0.918 (0.512-1.645)	0.774	1.343 (0.767-2.353)	0.302

Model 1: adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, and smoking. Model 2 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and mean systolic blood pressure from childhood to midlife. Model 3 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and average real variability of systolic blood pressure from childhood to midlife.

TTR = time in target range.

antihypertensive medications did not affect the significant associations of SBP-TTR with arterial stiffness in midlife, as demonstrated in Supplemental Table 5. In addition, after adjusting for the types and number of antihypertensive medications, the significant associations of SBP-TTR and arterial stiffness remained consistent (Supplemental Tables 6 and 7). Subsequently, we performed additional adjustments for SBP at baseline (1987), and the associations of SBP-TTR with arterial stiffness were similar (Supplemental Table 8). Further, we used the definition of arterial stiffness according to the cutoff value of baPWV >1800 cm/s specified in the 2023 European Society of Hypertension guidelines, and similar results were obtained (Supplemental Table 9). Finally, excluding the samples with missing SBP-TTR data yielded similar results (Supplemental Table 10).

DISCUSSION

In this prospective study, we explored the SBP-TTR of participants across their life course, including childhood, adolescence, youth, adulthood, and middle age, over a 36-year period, which coincides with the initiation of the Reform and Opening-Up Policy and notable lifestyle changes in China. Our prospective data revealed that more time with SBP levels within the proposed optimal target range from childhood to midlife was associated with a reduced risk of arterial stiffness in midlife (**Central Illustration**). Further, this association remained significant even after adjusting for mean SBP or SBP variability. All of these findings suggest that long-term SBP-TTR offers favorable benefits from early life, thereby emphasizing the significance of managing SBP by not only achieving the target range but also by maintaining it for a prolonged period.

TTR is a new metric for BP management that estimates the proportion of time maintained by the patients within a target BP range, which reflects the average BP value and the degree of BP variability during long-term follow-up.[34] A growing body of evidence indicates that assessing the consistency of BP control over time may more accurately predict CVD events and mortality.[10,35] A recent post hoc

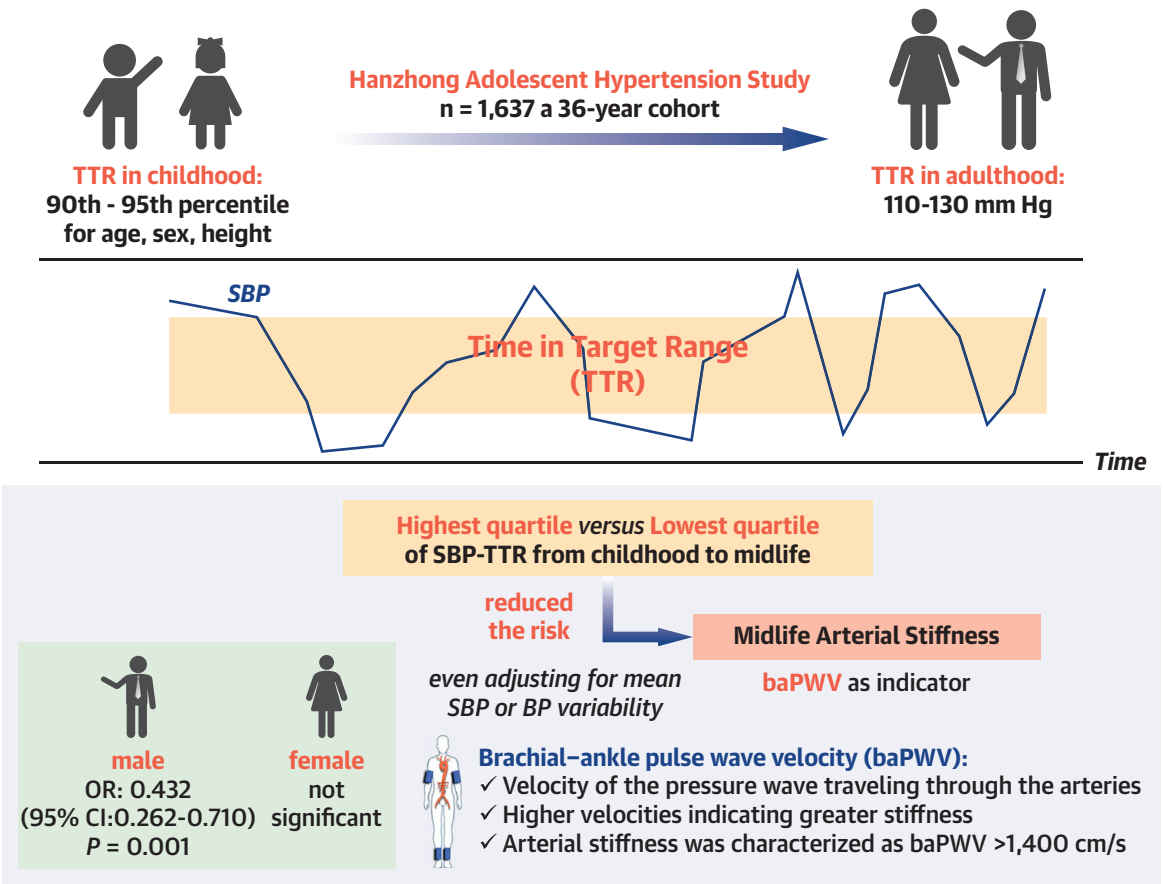
TABLE 4 Associations of Systolic Blood Pressure TTR With Arterial Stiffness Risk in Nonmissing Populations Adjusted by Inverse Probability Weighting

TTR Groups	No. of Cases (%)	Unadjusted		Model 1		Model 2		Model 3	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Quartile 1	138 (28.5)	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Quartile 2	150 (30.9)	0.361 (0.260-0.500)	<0.001	0.252 (0.170-0.374)	<0.001	0.196 (0.128-0.300)	<0.001	0.209 (0.139-0.315)	<0.001
Quartile 3	182 (37.5)	0.205 (0.151-0.279)	<0.001	0.132 (0.089-0.195)	<0.001	0.145 (0.095-0.220)	<0.001	0.128 (0.085-0.192)	<0.001
Quartile 4	15 (3.1)	0.037 (0.021-0.065)	<0.001	0.025 (0.013-0.049)	<0.001	0.021 (0.011-0.041)	<0.001	0.038 (0.019-0.074)	<0.001

Model 1: adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, and smoking. Model 2 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and mean systolic blood pressure from childhood to midlife. Model 3 was adjusted for age, gender, body mass index, education, hypertension, diabetes, hyperlipidemia, smoking, and average real variability of systolic blood pressure from childhood to midlife.

TTR = time in target range.

CENTRAL ILLUSTRATION **An Inverse Association Between Long-Term Time in Target Range for Systolic Blood Pressure and Arterial Stiffness**



Wang Y, et al. JACC Asia. 2025;5(1):101–112.

Time in target range (TTR) for systolic blood pressure (SBP) was assessed over 36 years from childhood to midlife, with the target ranges of SBP defined as the 90th to 95th percentile of SBP for age, sex, and height in childhood, and 110 to 130 mm Hg in adulthood. Arterial stiffness was defined as brachial-ankle pulse wave velocity >1,400 cm/s.

analysis of the SPRINT trial revealed that a longer TTR was independently associated with a reduced risk of cardiovascular events.[11] Similarly, Buckley et al[12] showed that higher SBP-TTR was associated with lower risks of adverse kidney and cardiovascular events in adults with hypertension. In addition, Lin et al[36] reported that higher long-term SBP-TTR was associated with a significantly decreased risk of cardiovascular events in older individuals with hypertension, regardless of their mean SBP. Arterial stiffness, an important determinant of cardiovascular health,[37] contributes significantly to the development of CVD,[2,3] and arterial stiffness can independently predict the risk of cardiovascular events.[38] Numerous studies have demonstrated that long-term BP control is associated with hypertension-mediated vascular damage. Studies from The Multiethnic Study of Atherosclerosis have indicated that higher long-term SBP variability may be a risk factor for arterial stiffness progression independent of mean BP.[39] In addition, Liu et al[40] found that the long-term SBP trajectory was associated with baPWV progression. However, existing research on SBP-TTR has largely focused on cardiovascular events in middle-aged and older adults. Although the clinical manifestations and complications of arterial stiffness, such as CVD and cerebrovascular disease, usually appear in middle or older age, the process of arterial stiffness actually begins early in life and develops silently over a long time.[5] Our study is the first attempt to investigate SBP-TTR from childhood to midlife and found an

inverse association with adult baPWV and the risk of arterial stiffness over 36 years of follow-up.

SBP-TTR serves as a valuable parameter because it assesses SBP over time as well as the degree of SBP variation. Furthermore, obtaining mean SBP within the normal range or low SBP variability is plausible even when the SBP values are mostly outside of the adequate range. Therefore, TTR provides a more accurate assessment of the consistency of SBP control and additional prognostic value beyond mean SBP or SBP variability, particularly in situations where mean SBP lies within the target range or SBP variability is low. As shown by our results, the relationship between high TTR and low risk of arterial stiffness was independent of mean SBP or SBP variability. In addition, previous studies showed that age, diabetes, dyslipidemia, and smoking were also associated with arterial stiffness.[41] In the present study, the association between SBP-TTR and arterial stiffness remained robust even after adjusting for these cardiovascular risk factors. Thus, our study underscores that SBP management should involve not only achieving the target range of SBP but also maintaining SBP-TTR from childhood to mitigate arterial stiffness risk and subsequent cardiovascular events later in life.

A higher TTR reflects stable BP with lower variability over a specific period. Several potential mechanisms may be attributed to the underlying relationship between high TTR and reduced arterial stiffness risk. One explanation could be the link between greater consistency in shear stress and reduced tears and fragmentation in the internal elastic lamina of the arteries,[42] which could decrease the development of arterial stiffness.[43] Another explanation could be that the reduced activation of intracellular signal transduction pathways induced by mechanical factors can stabilize intracellular function.[44,45] The aging process can lead to the decreased elasticity of the blood vessels via the degradation of elastin and subsequent collagen accumulation.[46,47] Impaired arterial function during aging is associated with arterial remodeling, with higher TTR potentially preventing adaptive remodeling from progressing to maladaptive remodeling by playing a crucial role in maintaining arterial function.

An interesting finding of the present study was that the association between SBP-TTR and the risk of arterial stiffness is more pronounced in men; however, the underlying mechanisms of this gender difference remain unclear. One possibility is that female hormones, particularly estrogen, may be critically involved in these mechanisms. Previous studies have demonstrated that premenopausal women have a lower risk of coronary artery disease and atherosclerosis than age-matched men, with these differences diminishing after menopause.[48,49] Furthermore, Mitchell et al[50] reported that before 60 years of age, women have lower PWV and pulse pressure compared to men, but these metrics increase rapidly in women thereafter, resulting in comparable PWV and higher pulse pressure in older women. Moreover, estrogen therapy has been shown to improve endothelium-dependent vasodilation and reduce arterial stiffness in postmenopausal women.[51,52] Along with estrogen, the renin-angiotensin-aldosterone system (RAAS) may also be involved in these sex-based differences. Recent studies have implicated aldosterone receptors in age-related arterial stiffness and vascular fibrosis in male mice.[53] However, in vitro studies have shown that estrogen receptor-α may mediate some effects attributed to aldosterone receptors,[54] suggesting that premenopausal women may be protected from the adverse effects of aldosterone receptors. A study by DeMarco et al[55] also highlighted the pivotal role of aldosterone receptors in arterial stiffness progression in female mice fed on a high sugar and fat diet. In terms of the arterial structural changes, Qiu et al[56] revealed that alterations in collagen isomer composition and elastin reduction in older male monkeys might be the primary drivers of increased arterial stiffness, a phenomenon not observed in female monkeys. However, animal studies directly comparing the impact of BP on arterial stiffness between genders are limited, with 1 investigation reporting sex-specific genetic loci influencing arterial stiffness in Dahl salt-sensitive hypertensive rats.[57] Therefore, further research on the potential associations of the sex-specific differences between SBP-TTR and arterial stiffness is warranted.

STUDY STRENGTHS AND LIMITATIONS. This study has several noteworthy strengths. For example, this research was conducted on a large prospective cohort over a follow-up duration of 36 years, which captured BP changes during the beginning of the Reform and Opening-Up policy of China. Additionally, this cohort comprised individuals transitioning from childhood to middle age, thus providing a unique opportunity to explore the impact of long-term SBP-TTR on arterial stiffness. However, our study has a few limitations that should be acknowledged. The use of antihypertensive medications, the specific types and dosages of these medications, and nonadherence to the prescribed treatment among our participants may have influenced the obtained TTR values in this study. Nonetheless, this concern was partially alleviated by the sensitivity analysis, which showed that the

observed associations of SBP-TTR with arterial stiffness remained significant even after excluding individuals using antihypertensive drugs. Furthermore, given that all participants in this study were of Han Chinese ethnicity, the generalizability of our findings to other ethnic and racial groups may be limited. The relatively small number of midlife CVD events in our participant population also made it impractical to assess the relationship between SBP-TTR and cardiovascular events or mortality. Finally, the potential influence of other unmeasured confounders, such as environmental factors, gut microbiome, and genomics, on the associations between SBP-TTR and arterial stiffness should also be considered.

CONCLUSIONS

This prospective study revealed that a high SBP-TTR throughout early life is independently associated with a reduced risk of arterial stiffness in midlife, irrespective of mean SBP and SBP variability. These findings endorse TTR as a valuable measure for assessing BP control. In the future, BP management strategies should incorporate a multifaceted approach, including encouraging the utilization of BP monitoring devices and establishing data platforms to advance precision medicine. These programs should be aimed at enhancing the treatment strategies, effectiveness of BP control, patient adherence, prognosis, and overall quality of life in this specific population. Last, formulating relevant policies and standards to alleviate the health care system burden, improve medical insurance efficiency, and achieve optimal utilization of health care resources is imperative.

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ADDRESS FOR CORRESPONDENCE: Prof Ling Zhang, Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, 10 Xitoutiao, Youanmenwai, Beijing 100069, China. E-mail: zlilyepi@ccmu.edu.cn. OR Prof Jian-Jun Mu, Department of Cardiovascular Medicine, First Affiliated Hospital of Xian Jiaotong University, 277 Yanta West Road, Xi'an 710061, China. E-mail: mujjun@163.com.

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KEY WORDS arterial stiffness, blood pressure, early life course, longitudinal cohort study, time in target range

APPENDIX For supplemental tables and figures, please see the online version of this paper.