Original Article

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Predictors for progressions of brachial–ankle pulse wave velocity and carotid intima–media thickness over a 12-year follow-up: Hanzhong Adolescent Hypertension Study

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Objective: Atherosclerotic diseases are the leading cause of death worldwide. This study aimed to investigate the predictors of brachial–ankle pulse wave velocity (baPWV) and carotid intima–media thickness (CIMT) progression in a Chinese cohort over a 12-year follow-up period and to determine whether these predictors differ by follow-up time.

Methods: A total of 202 participants were recruited from a previously established cohort in Shaanxi Province, China. Both baPWV and CIMT were measured in 2013 and 2017. Multivariable regression was used to determine the predictors of CIMT and baPWV progression.

Results: Men had higher CIMT and baPWV and a higher rate of CIMT progression during two follow-ups than women. A 4-year change in SBP was associated with baPWV progression, whereas a 12-year change in DBP was associated with baPWV progression. The increased progression of baPWV presented a linear trend when subgrouping all the participants according to SBP and DBP changes over 4 and 12 years, respectively. In addition, heart rate (HR) change over 4 and 12 years was consistently associated with CIMT progression, and a linear trend was also seen when subgrouping the population.

Conclusion: Our study demonstrated that SBP and DBP contributed differently in different stages to the progression of arterial stiffness in this Chinese cohort. Moreover, HR was consistently involved in the increased progression of CIMT in all periods. These findings underline the importance of early detection and control of blood pressure and resting HR for the prevention of arterial stiffness progression.

Keywords: arterial stiffness, intima–media thickness, progression, pulse wave velocity, risk factors

Abbreviations: baPWV, brachial–ankle pulse wave velocity; BP, blood pressure; CIMT, carotid intima–media thickness; CVD, cardiovascular disease; IMT, intima–media thickness

INTRODUCTION

Arterial stiffness, which is caused by the loss of normal elastin and an increase in abnormal collagen, is one of the earliest functional changes in the vascular aging process [1]. Increased arterial stiffness is an important determinant of cardiovascular disease (CVD) risk [2]. Several epidemiological studies have reported that increased arterial stiffness predicts morbidity and mortality independently of other cardiovascular risk factors [3,4]. In addition, arterial stiffness contributes to the hypertrophy and remodeling of microcirculation [5], which leads to microvascular diseases, such as diabetic retinopathy and lacunar infarction [6,7]. The key factor for the primary prevention of arterial stiffness is the identification of asymptomatic individuals who are at a high risk [8] and then the implementation of strategies that are directed at risk factors, which are known to be related to clinical events.

Stiffness of the large arteries, which is measured using pulse wave velocity (PWV) – the gold standard method for assessing this parameter – has been associated with measures of subclinical atherosclerosis and CVD [5,7]. Brachial–ankle pulse wave velocity (baPWV) measurement is a validated method for quantifying arterial stiffness [9].

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baPWV is easy and convenient to perform and can be widely used in large-scale populations and clinical settings [9–11]. Prior studies have suggested that the principal determinants of PWV progression are a number of cardiovascular risk factors, such as dyslipidemia, obesity, diabetes, elevated blood pressure (BP), higher heart rate (HR) and chronic kidney disease [12–16]. However, these observations were based on short-term studies and on cross-sectional observational studies, whereas the different effects of risk-factor changes in the short term and long term on the progression of baPWV have not yet been understood.

In recent years, high-resolution B-mode ultrasonography has been shown in large populations to be a valid noninvasive method of monitoring atherosclerotic changes such as progression of carotid intima–media thickness (CIMT). CIMT, which is a surrogate marker of subclinical arterial stiffness, is thought to predict future cardiovascular events and stroke [17,18]. Accelerated progression in CIMT is increasingly used as a marker of arterial stiffness development [19]. Several studies have investigated the predictors of CIMT and plaque progression [20,21]. Although the risk factors for arterial stiffness progression are well known, their differential effect between the short-term and long-term time frames is still unclear. In addition, data on the differences in risk factors between two predictors of arterial stiffness progression (baPWV and CIMT) have not been published previously.

In the current study, we used our previously established cohort to examine the associations between short-term and long-term changes in traditional risk factors and the progression of arterial stiffness. In the analyses, we also investigated the differences in risk factors between the predictors of the increased progression of baPWV and CIMT.

METHODS

Cohort of study

In March and April 1987, we established the Hanzhong Adolescent Hypertension Study cohort based on a baseline survey of 4623 adolescents aged 6–15 years from over 20 schools in three towns (Qili, Laojun and Shayan) in Hanzhong, Shaanxi, China. Detailed study design and procedures have been published previously [22,23]. Using an isometric sampling method, we randomly selected every tenth participant ($K = 10$) from the large cohort, and 338 participants were successfully followed up in 2005 [10]. Therefore, we created a small cohort of 338 participants as the baseline.

We followed up with this small cohort in 2013 and 2017, and baPWV and intima–media thickness (IMT) were measured during these two visits. The current study included all participants who had undergone baPWV and IMT assessments for both surveys. Among the 338 eligible participants, 99 were lost to follow-up in 2013 and 31 were lost in 2017. In addition, participants who had missing IMT or baPWV data from 2013 or 2017 were also excluded from the present analysis. One participant had an established history of stroke. The remaining 202 participants with complete data from the two examinations were used for the analysis (a flowchart of the participants' inclusion is shown in Fig. 1). No significant difference in results was observed when these participants were excluded from the cohort (Supplementary Table S1, http://links.lww.com/HJH/B45).

The Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University reviewed and approved the study, and written informed consent was obtained from each participant at each examination phase. The study complied with the principles of the Helsinki Declaration. Trial Registration Number: NCT02734472. Date of registration: 12/04/2016.

Physical measurements

Information on education, occupation, smoking habits, alcohol consumption, physical activity, medical conditions and medication use were collected using a self-administered questionnaire. Body height, weight and waist circumference were measured. BMI was calculated as weight (kg) divided by height (m^2). BP was measured using a standard mercury sphygmomanometer as previously described [24,25]. The average of three measurements was used in the analyses. Hypertension was defined as SBP or DBP at least 140/90 mmHg or current use of antihypertensive medications.

Biochemical assays

Venous blood samples were taken after the participant had fasted for 12 h. Blood samples were separated and then were frozen at −80 °C and shipped on dry ice to the certified clinical laboratory at the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China). Standardized measurements for nonfasting serum lipid profile, serum creatinine, homocysteine, blood glucose and serum C-reactive protein were performed as described previously [10,22,24,25]. Diabetes was defined as a fasting blood glucose level of at least 126 mg/dl or current treatment for diabetes.

Intima–media thickness measurement

High-resolution B-mode ultrasound was performed in a blinded manner to evaluate the arterial wall thickness in the carotid arteries with an Acuson 128XP/10 system (Acuson, Mountain View, California, USA) and a probe of 10–12 MHz. Details about scanning and reading procedures have been reported previously [26]. To minimize the influence of sonographer and reader variability, all examinations were performed by the same sonographer, whereas the CIMT readings were performed by another person blinded to the identity of the participants. According to the guidelines of the joint European Society of Hypertension/European Society of Cardiology, in the current study, we defined patients with early stages of atherosclerosis as those with an asymptomatic CIMT of at least 0.9 mm [27].

Pulse wave velocity measurement

The baPWV was measured using a volume-plethysmographic apparatus (BP-203RPEII; Nihon Colin, Tokyo, Japan). Details about the methodology have been described elsewhere [10,11]. The baPWV was calculated by time-phase analysis between the right brachial and volume waveforms at both ankles. Participants with a baPWV less than 1400 cm/s were considered normal; by contrast, participants with a baPWV at least 1400 cm/s were defined as high [10,11].

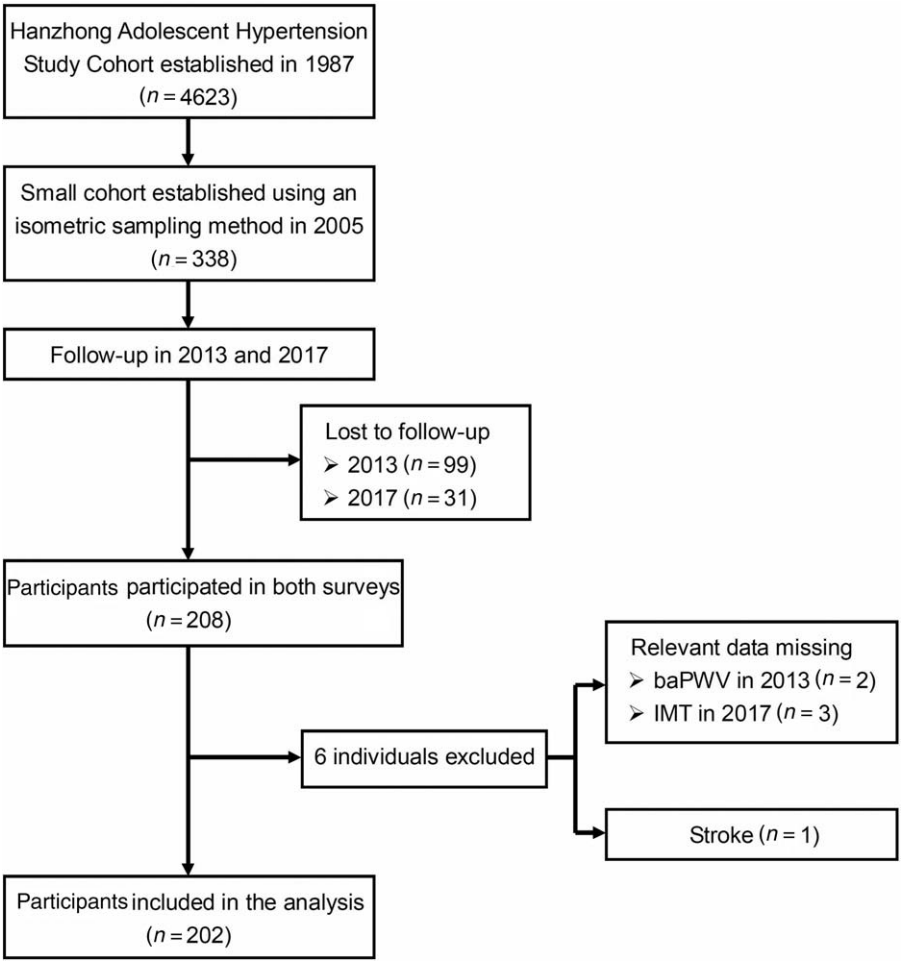

FIGURE 1 Flow diagram showing the selection of the study population.

Statistical analysis

Data are expressed as the means ± SDs for normally distributed values, as median (25 and 75th percentile) for non-normally distributed values, and as percentages. Statistically significant differences among the groups were calculated using the χ^2 test for categorical variables, Student's *t* test for continuous variables in normally distributed data and the Mann–Whitney test for non-normally distributed data. The independent relationships between risk factors and IMT and baPWV at follow-up and their progressions were assessed by multivariate linear regression analysis. Logistic regression analysis was conducted to investigate the predictive effect of risk factors on the incidence of arterial stiffness. In addition, to test the robustness of our findings, we performed a sensitivity analysis. Individuals with active treatment, such as antihypertensive, hypoglycemia or lipid-lowering agents, were excluded. All statistical analyses were performed using SPSS 16.0 (SPSS, Inc., Chicago, Illinois, USA). Statistical significance is set as a two-tailed *P* value of less than 0.05.

RESULTS

Characteristics of study participants

A total of 202 individuals who met the inclusion criteria were finally followed up and included in the current analyses. Table 1 compares the demographic, anthropometric and biochemical characteristics of the experimental population at baseline and follow-up. Individuals had higher CIMT, BMI, higher total cholesterol and lower homocysteine levels and a higher proportion of hypertension, diabetes and alcohol use with extended follow-up (*P* for trend <0.05, Table 1).

Men had higher CIMT and baPWV during the two follow-ups than women, and men also had a higher rate of CIMT progression (31.5 ± 3.4 vs. 20.1 ± 4.0 μm/year, $P = 0.029$). However, baPWV progression rates in men (5.7 ± 4.1 cm/s/year) and women (2.1 ± 6.3 cm/year) were not significantly different ($P = 0.612$, Table 2).

Baseline risk factors for intima–media thickness and brachial–ankle pulse wave velocity

The results of stepwise multivariable regression analyses including baseline risk factors in predicting CIMT and baPWV measured in 2013 and 2017 and their progressions (2013–2017) are shown in Table 3. Age was significantly associated with CIMT values in 2013, and sex was significantly associated with CIMT in 2017, whereas sex and HR were independently associated with IMT progression. Furthermore, SBP and triglycerides were independently associated with cross-sectionally measured baPWV in both study years. LDL-cholesterol (LDL-C) was directly

TABLE 1. Characteristics of the study participants at baseline and during follow-ups ($n = 202$)

Characteristics	Baseline in 2005	Follow-up in 2013	Follow-up in 2017	*P* for trend
Sex (M/F)	114/88	114/88	114/88	–
Age (years)	29.0 (27.0–32.0)	37.0 (35.0–40.0)	41.0 (39.0–44.0)	<0.001
Current smoking (%)	72 (35.6)	77 (38.3)	80 (39.6)	0.412
Alcohol consumption (%)	73 (36.1)	84 (41.8)	51 (25.2)	0.021
Hypertension, *n* (%)	36 (17.8)	50 (24.8)	72 (35.6)	<0.001
Diabetes mellitus, *n* (%)	1 (0.5)	2 (1.0)	9 (4.5)	0.004
BMI (kg/m^2)	22.9 ± 3.2	24.6 ± 3.6	24.6 ± 3.5	<0.001
Heart rate (bpm)	73.0 (68.0–78.0)	72.0 (66.0–80.0)	74.0 ± 10.8	0.821
SBP (mmHg)	121.7 ± 14.8	122.7 ± 19.9	124.7 ± 16.3	0.082
DBP (mmHg)	78.3 ± 10.6	82.1 ± 14.1	78.4 ± 11.1	0.929
Fasting glucose (mmol/l)	4.75 ± 0.67	4.49 (4.23–4.71)	4.56 (4.26–4.88)	0.340
Total cholesterol (mmol/l)	4.36 ± 0.69	4.30 ± 0.76	4.57 ± 0.79	0.013
Triglycerides (mmol/l)	1.20 (0.95–1.63)	1.37 (0.95–2.07)	1.36 (0.94–1.93)	0.056
LDL-cholesterol (mmol/l)	2.59 ± 0.44	2.37 ± 0.59	2.53 ± 0.68	0.313
HDL-cholesterol (mmol/l)	1.10 (0.98–1.20)	1.70 (1.43–1.87)	1.20 ± 0.26	<0.001
C-reactive protein (μmol/l)	0.38 (0.18–0.87)	0.48 (0.21–0.97)	–	0.190
Homocysteine (μmol/l)	12.3 (9.90–16.2)	8.2 (5.9–11.2)	–	<0.001

C-reactive protein and homocysteine were not detected in 2017. Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD or *n* (%).

TABLE 2. Change of the intima–media thickness and brachial–ankle pulse wave velocity over time

	Male participants	Female participants	*P* value
No. of sujects	118	84	–
CIMT data			
CIMT 2013 (mm)	0.50 (0.50–0.60)	0.50 (0.50–0.60)	0.003
CIMT 2017 (mm)	0.67 (0.60–0.75)	0.60 (0.50–0.70)	<0.001
CIMT progression (μm)	121.1 ± 13.4	80.4 ± 15.8	0.029
CIMT progression rate (μm/year)	31.5 ± 3.4	20.1 ± 4.0	0.029
baPWV data			
baPWV 2013 (cm)	1303.0 (1164.3–1466.6)	1154.0 (1050.5–1318.3)	<0.001
baPWV 2017 (cm)	1359.2 ± 194.8	1235.0 ± 178.2	<0.001
baPWV progression (cm)	22.9 ± 16.3	8.4 ± 25.0	0.612
baPWV progression rate (cm/year)	5.7 ± 4.1	2.1 ± 6.3	0.612

Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean ± SD. baPWV, brachial–ankle pulse wave velocity; CIMT, carotid intima–media thickness.

TABLE 3. Predictors of intima–media thickness and brachial–ankle pulse wave velocity at follow-up and progression in stepwise multivariable regression analysis

	IMT 2013		IMT 2017		IMT progression		baPWV 2013		baPWV 2017		baPWV progression	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Age (years)	**0.193**	**0.007**	0.096	0.158	−0.038	0.582	−0.046	0.467	0.040	0.495	0.103	0.143
Sex (M/F)	−0.09	0.201	**−0.263**	**<0.001**	**−0.163**	**0.021**	−0.037	0.593	−0.093	0.148	−0.056	0.440
Current smoking (%)	0.077	0.274	−0.140	0.119	−0.164	0.075	0.094	0.156	0.110	0.071	−0.008	0.909
Alcohol consumption (%)	0.026	0.717	0.018	0.830	0.045	0.596	0.087	0.188	<0.001	1.000	−0.092	0.196
Hypertension, *n* (%)	0.072	0.309	0.023	0.736	−0.027	0.703	0.018	0.828	0.083	0.273	0.043	0.545
Diabetes mellitus, *n* (%)	0.038	0.588	−0.123	0.072	−0.131	0.060	0.085	0.176	0.021	0.720	−0.083	0.235
BMI (kg/m^2)	0.091	0.209	0.107	0.119	0.027	0.703	−0.055	0.419	0.032	0.605	0.114	0.113
Heart rate (bpm)	0.082	0.242	−0.128	0.063	**−0.178**	**0.012**	0.006	0.921	−0.005	0.931	−0.028	0.691
SBP (mmHg)	0.056	0.43	−0.092	0.221	−0.0981	0.233	**0.409**	**<0.001**	**0.506**	**<0.001**	0.017	0.819
DBP (mmHg)	−0.007	0.923	0.001	0.984	0.012	0.868	0.086	0.317	0.077	0.335	−0.015	0.838
Fasting glucose (mmol/l)	−0.033	0.638	0.013	0.850	0.034	0.629	−0.048	0.457	0.020	0.741	0.068	0.335
Total cholesterol (mmol/l)	0.084	0.231	0.024	0.731	−0.028	0.690	0.041	0.529	−0.028	0.644	0.147	0.281
Triglycerides (mmol/l)	0.023	0.747	0.083	0.231	0.123	0.089	**0.159**	**0.014**	**0.188**	**0.002**	−0.005	0.943
LDL-cholesterol (mmol/l)	0.090	0.201	0.016	0.814	−0.044	0.545	0.045	0.495	−0.090	0.142	**−0.142**	**0.045**
HDL-cholesterol (mmol/l)	0.112	0.112	−0.036	0.605	−0.103	0.143	0.076	0.236	0.020	0.741	0.058	0.588
C-reactive protein (μmol/l)	−0.009	0.896	0.023	0.741	−0.009	0.893	0.038	0.754	0.550	0.095	0.029	0.678
Homocysteine (μmol/l)	0.037	0.600	−0.014	0.845	<0.001	0.997	0.061	0.335	0.027	0.655	−0.063	0.377

baPWV, brachial–ankle pulse wave velocity; IMT, intima–media thickness.
Bold indicates statistically significant results.

TABLE 4. Traditional risk factors and their changes for arterial stiffness in stepwise multivariable regression analysis

Variables in the model	High baPWV		High IMT	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Risk factors at baseline				
SBP (mmHg)	**1.102 (1.063–1.143)**	**<0.001**	0.996 (0.904–1.097)	0.934
LDL-cholesterol (mmol/l)	0.760 (0.022–16.148)	0.760	**20.541 (2.332–180.963)**	**0.006**
Triglycerides (mmol/l)	**1.813 (1.078–3.048)**	**0.025**	**0.108 (0.017–0.702)**	**0.020**
12-year change				
DBP (mmHg)	**1.036 (1.001–1.074)**	**0.049**	0.990 (0.913–4.073)	0.805
BMI (kg/m^2)	**1.176 (1.004–1.377)**	**0.045**	1.204 (0.917–1.582)	0.182
Triglycerides (mmol/l)	**0.516 (0.328–0.813)**	**0.004**	1.763 (0.750–4.147)	0.194
HDL-cholesterol (mmol/l)	**0.137 (0.037–0.514)**	**0.003**	1.062 (0.066–17.101)	0.966

Logistic regression analyses were used to test the risk of arterial stiffness, after adjustment for age, sex, BMI, SBP, DBP, heart rate, fasting glucose, total cholesterol, triglycerides, LDL, HDL, C-reactive protein, serum homocysteine, alcohol consumption, smoking status, hypertension and diabetes. baPWV, brachial–ankle pulse wave velocity; CI, confidence interval; IMT, intima–media thickness; OR, odds ratio.
Bold indicates statistically significant results.

associated with baPWV progression in a multivariable model adjusted for multiple confounders.

We also analyzed the association between risk factors at baseline and the incidence of arterial stiffness (Table 4) and found that SBP [1.102 (1.063–1.143)] and triglycerides were independently associated with a risk of high baPWV, and LDL-C and triglycerides were associated with a risk of high CIMT.

Changes in traditional risk factors for carotid intima–media thickness and brachial–ankle pulse wave velocity

Next, we compared the relationships of long-term (2005–2017) and short-term (2013–2017) changes in risk factors and CIMT and baPWV at follow-up and their progressions, which are presented in Table 5. The 4-year change in serum glucose was independently associated with CIMT in 2013, whereas HR change was significantly associated with CIMT measured in 2017 ($\beta = 0.144$, $P = 0.044$) as well as CIMT progression ($\beta = 0.162$, $P = 0.025$). In contrast, we found that the 12-year change in HR was independently associated with CIMT in 2013 ($\beta = -0.155$, $P = 0.03$) and CIMT progression ($\beta = 0.142$, $P = 0.046$) but not with CIMT in 2017 ($\beta = 0.037$, $P = 0.614$, Table 5).

With regard to baPWV, 4-year change in DBP ($\beta = 0.179$, $P = 0.012$) was independently associated with baPWV in 2013, and SBP ($\beta = 0.237$, $P = 0.023$) was significantly associated with baPWV in 2017, whereas 4-year change in age and SBP ($\beta = 0.243$, $P < 0.001$) were associated with baPWV progression. In addition, 12-year changes in DBP ($\beta = 0.357$, $P < 0.001$), triglycerides, HDL-cholesterol and HR were independently associated with baPWV in 2013, and changes in DBP ($\beta = 0.159$, $P = 0.022$) and HDL-cholesterol were significantly associated with baPWV in 2017, whereas only a 12-year change in DBP ($\beta = 0.28$, $P < 0.001$, Table 5) was found to be associated with the progression of baPWV. We further showed that 12-year changes in DBP [1.036 (1.001–1.074)], BMI, triglycerides and HDL-cholesterol were independently associated with the risk of high baPWV but not with high CIMT (Table 4).

Association between blood pressure change and brachial–ankle pulse wave velocity progression

From the above data, we found that 4-year change in SBP was associated with baPWV progression; however, 12-year change in DBP was associated with baPWV progression. To further increase the statistical power of the study, we also subgrouped all the participants into three groups: large decrease (<25%), moderate change (25–75%) and large increase (>75%), based on BP change from baseline to the

TABLE 5. Relationships of risk factors changes and intima–media thickness and brachial–ankle pulse wave velocity at follow-up and progression in stepwise multivariable regression analysis

	IMT 2013		IMT 2017		IMT progression		baPWV 2013		baPWV 2017		baPWV progression	
	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
4-year change												
Age (years)	−0.025	0.739	0.037	0.628	0.027	0.712	−0.089	0.205	−0.057	0.446	**0.184**	**0.008**
Fasting glucose (mmol/l)	**0.161**	**0.032**	0.102	0.178	−0.017	0.810	0.030	0.671	0.038	0.601	−0.003	0.988
SBP (mmHg)	−0.042	0.697	−0.089	0.394	−0.018	0.802	−0.024	0.814	**0.237**	**0.023**	**0.243**	**<0.001**
DBP (mmHg)	−0.053	0.622	0.088	0.409	0.073	0.310	**0.179**	**0.012**	0.197	0.062	0.043	0.667
Heart rate (bpm)	−0.072	0.336	**0.144**	**0.044**	**0.162**	**0.025**	0.075	0.286	0.116	0.110	0.017	0.805
12-year change												
DBP (mmHg)	0.089	0.214	−0.002	0.980	−0.024	0.736	**0.357**	**<0.001**	**0.159**	**0.022**	**0.280**	**<0.001**
Triglycerides (mmol/l)	−0.005	0.946	−0.032	0.738	0.062	0.392	**−0.171**	**0.013**	−0.126	0.078	0.077	0.263
HDL-cholesterol (mmol/l)	−0.008	0.906	−0.174	0.083	−0.088	0.2	**−0.181**	**0.008**	**−0.211**	**0.003**	−0.036	0.599
Heart rate (bpm)	**−0.155**	**0.030**	0.037	0.614	**0.142**	**0.046**	**0.133**	**0.045**	0.016	0.813	−0.114	0.098

baPWV, brachial–ankle pulse wave velocity; IMT, intima–media thickness.
Bold indicates statistically significant results.

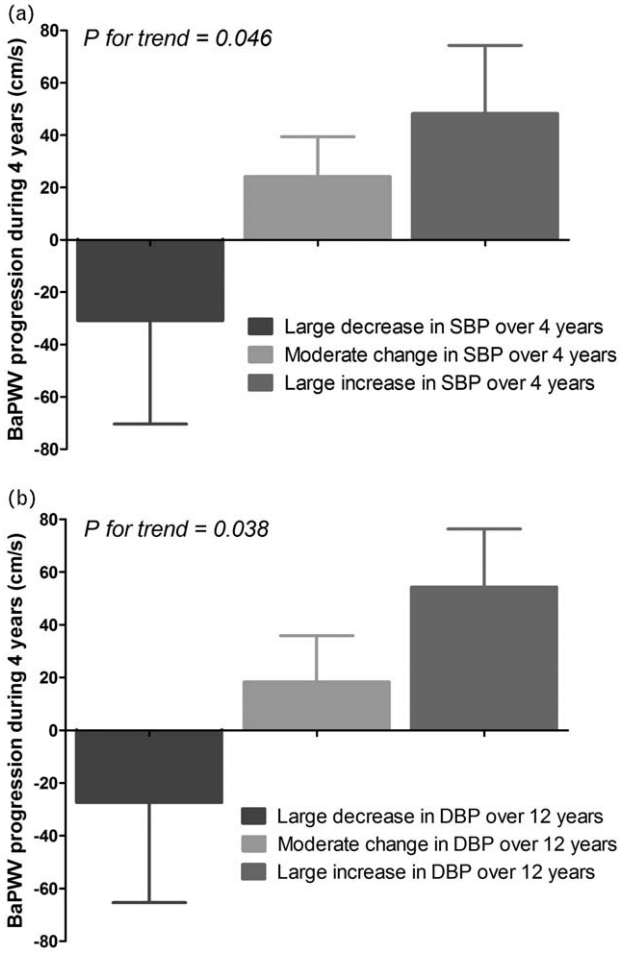

FIGURE 2 Comparisons of brachial–ankle pulse wave velocity progression between participants with large decrease (<25%), moderate change (25–75%) and large increase (>75%) in SBP over 4 years (a) or in DBP over 12 years (b).

follow-up in 2013 and 2017. Figure 2 showed that with regard to SBP during the 4-year change, baPWV progression was −30.8, 24.2 and 48.2 cm/s for large decrease, moderate change and large increase, respectively (P for trend = 0.046). In addition, baPWV progression was −27.4, 18.3 and 54.3 cm/s for large decrease, moderate change and large increase in DBP during 12-year change, respectively (P for trend = 0.038, Fig. 2b).

To further explore the relationship between SBP and baPWV, and its progressions, we divided all the participants into four groups according to the levels of baPWV and SBP in 2013. As shown in Supplementary Table S2, http://links.lww.com/HJH/B45, participants with high baPWV and normal SBP had higher levels of baPWV in 2013 than that in those with normal PWV and high SBP. However, baPWV progression was significantly increased in participants with normal baPWV and high SBP when compared with those with high baPWV and normal SBP (171.7 ± 65.3 vs. −157.0 ± 49.7), indicating that increased SBP was a major contributor to baPWV progression. In addition, no significant differences in CIMT and its progression between these groups were observed, suggesting that BP levels may be not involved in CIMT progression.

Association between heart rate change and carotid intima–media thickness progression

Table 5 shows that short-term and long-term changes in HR were associated with increased progression of CIMT. To further illustrate their relationships, we also subgrouped all the participants into three groups: large decrease (<25%), moderate change (25–75%) and large increase (>75%), in accordance with resting HR change from baseline to the follow-ups. Although CIMT progression was marginally significantly different among the three groups for HR in 12-year change (0.061 mm for large decrease, 0.125 mm for moderate change and 0.116 mm for large increase, P for trend = 0.065, Fig. 3b), CIMT progression presented a linear association with HR change in 4-year change (0.067 mm for large decrease, 0.111 mm for moderate change and 0.143 mm for large increase, P for trend = 0.013, Fig. 3a).

Sensitivity analysis

Sensitivity analysis was conducted to exclude the potential influence of antihypertensive and hypoglycemic medications on the robustness of our results. We removed hypertensive patients and diabetes under treatment ($n = 9$). As shown in Supplementary Tables S3 and S4, http://links.lww.com/HJH/B45, all the results were slightly changed after adjustment for various confounders.

DISCUSSION

The primary finding in our study was that 4-year change in SBP was associated with baPWV progression, whereas 12-year change in DBP was associated with baPWV progression in our study cohort. To the best of our knowledge, this is the first study to investigate the associations between short-term and long-term changes in traditional risk factors and the progression of arterial stiffness.

As of today, a limited number of prior studies suggested that BP was most strongly associated with cross-sectional PWV. However, few longitudinal studies explored the relationship between BP and PWV progression. Birru *et al.* [12] reported a robust association between BP and PWV progression in a subgroup of 303 African-American and white participants over an average of 2.3 years of follow-up. Lin *et al.* [14] showed that elevated BP at baseline and changes in BP were two independent predictors of PWV progression, and increases in BP during follow-up were more strongly associated with PWV progression. Benetos *et al.* [15] further discovered that poorly controlled BP led to a PWV progression rate that was three times faster in hypertensive patients than in those with well controlled BP over a 6-year period. Two longitudinal studies suggested that when mean BP decreased, PWV also decreased (mean decrease of 0.9 mmHg with a PWV decrease of 3.17 m/s) [28], and when BP increased, PWV increased (mean increase of 5.7 mmHg with a PWV increase of 0.83 m/s) [15]. In the current study, we firstly compared the effects of short-term and long-term risk factors on the progression of baPWV. Significantly, we found that the short-term effect of a change in SBP was closely related to the progression of baPWV, whereas a long-term change in DBP was associated with baPWV in this Chinese cohort. Moreover, a linear (positive) trend in baPWV progression

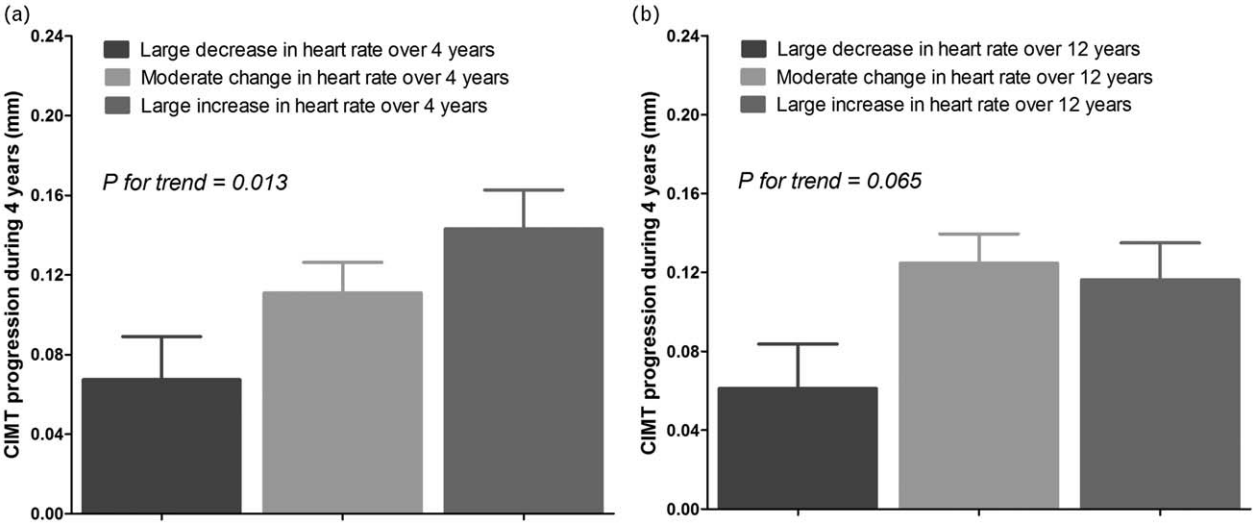

FIGURE 3 Comparisons of carotid intima–media thickness progression between participants with large decrease (<25%), moderate change (25–75%) and large increase (>75%) in heart rate over 4 years (a) or 12 years (b).

was also shown in SBP and DBP changes when conducting the subgroup analyses. Determining the molecular mechanism and signaling molecules underlying this interesting phenomenon can be of great interest. In addition, there was a reciprocal relationship between stiffness parameters and BP. Elevated PWV was found to be a predictor of longitudinal BP progression and incident hypertension [29,30], whereas high BP causes blood vessels to lose their elasticity, which in turn makes the control of BP more difficult. Therefore, early intervention to control BP is an important step to maintain the elasticity of blood vessels.

In recent years, HR has been found to be a powerful and valuable predictor of heart failure, cardiovascular events and mortality [31,32]. The associations between HR and arterial stiffness have been explored in limited studies. In a cross-sectional study consisting of 255 Black and 659 white young adults [33], HR was independently associated with PWV but not with CIMT, which indicated that HR played a different role in the development of arterial stiffness and artery thickness. In the Multi-Ethnic Study of Atherosclerosis, elevated HR was associated with incidence and progression of coronary atherosclerosis measured by coronary artery calcium [34]. Previous studies have generally focused on HR and peripheral or coronary arterial stiffness. The relationship between HR and carotid arterial stiffness, especially carotid thickness, was poorly elucidated. Only one study conducted by Wang *et al.* [35] in a middle-aged and elderly Chinese population showed that HR demonstrated a positive and graded association with both CIMT and carotid plaque. This study further found that compared with participants with resting HRs lower than 67 bpm, those with resting HRs higher than 81 bpm had an approximately three-fold risk of having elevated CIMT and a two-fold risk of having carotid plaque [35]. This observation agrees with the results of our study, in which HR was associated with increased progression of CIMT. The current study builds upon these previous findings by also evaluating the effects of change in HR on the progression of CIMT. HR change over the short term and long term is consistently associated with CIMT progression, and a linear (positive) trend was also seen when subgrouping the population. Moreover, HR variability, which can reflect autonomic nervous activity, was reported to be independently associated with increased carotid IMT in different settings [36]. These findings suggested that maintaining the resting HR at optimal levels is essential because individuals with short-term and long-term optimal HR levels had the lowest progression of carotid arterial stiffness.

Evidence available to date would indicate that traditional risk factors, such as BMI, age, BP, homocysteine levels and serum lipids have strong associations with the progressions of PWV and IMT. For example, Meani *et al.* [13] enrolled 333 hypertensive outpatients and followed 3.7 years, and showed that age, baseline BP were independent predictors of ΔPWV. Similarly, Huang *et al.* [37] analyzed the data from 712 stroke-free and myocardial infarction-free Chinese participants at baseline and after an average interval of 4.3 years. They found that age and smoking were predictors of carotid artery IMT progression [37]. In addition, Bots *et al.* [38] found that participants with elevated plasma total homocysteine levels had a thicker common carotid IMT. Kozakova *et al.* [39] investigated the relationship between body composition and remodeling of common carotid artery (CCA), and finally found that age, CCA diameter, SBP and LDL-C were independently associated with IMT. In line with previous reports, our cohort found that age and sex were significantly associated with CIMT in 2013 and 2017, respectively, whereas SBP and triglycerides were independently associated with baPWV in both study years. LDL-C was significantly associated with baPWV progression after adjusting for multiple confounders.

An interesting observation in this study is that CIMT progression rate seems to be high despite the young age in this cohort. Kozàkovà *et al.* [40] reported that after a 3-year follow-up, the mean IMT changes in CCA, carotid bulb and internal carotid artery (ICA) were 17 ± 48, 56 ± 100 and

52 ± 110 μm, respectively, in 614 healthy men and women from the Carotid Atherosclerosis Progression Study (CAPS). Mackinnon *et al.* [41] found that the mean change in IMT per year of 3-year follow-up was 0.001 mm for CCA-IMT, 0.023 mm for the bifurcation IMT and 0.032 mm for the ICA-IMT in participants from CAPS study. In addition, Rosvall *et al.* [42] reported the IMT in CCA progression rates was 0.011 mm/year for men and 0.010 mm/year for women. However, Koskinen *et al.* [43] demonstrated that IMT progression rate was 54 ± 89 μm for men and 40 ± 79 μm for women in Finnish young adults. In agreement with this study, we found that annual rate of CIMT progression was 31.5 ± 3.4 and 20.1 ± 4.0 μm for male and female participants in this Chinese cohort, respectively. The different study populations, living conditions and lifestyle, sample sizes and racial differences among these various studies may also be the causes of the discrepant results.

The current study has limitations that deserve mention. First, the study population was relatively small and restricted to northern Chinese individuals. Therefore, our results will require replication in other cohorts to determine generalizability to other ethnicities and to populations with different backgrounds. Another potential limitation of our study was the loss of participants during long-term follow-up. However, baseline characteristics in 2005 were similar between participants and nonparticipants, and the study cohort seems to be representative of the original study population. In addition, the study was a single-center, cross-sectional study. A multicenter, prospective trial will be conducted to further understand and confirm the conclusions.

Notwithstanding these limitations, the current study presents a number of important strengths. Our study simultaneously examined two commonly used indicators of arterial stiffness (baPWV and CIMT) and compared the independent predictors for them over a long-term follow-up. Further, we firstly compared the effects of short-term and long-term changes in traditional risk factors and the increased progression of baPWV and CIMT, enhancing our knowledge of the pathophysiological process of arterial stiffness. Finally, our study cohort was racially homogeneous and followed for 12 years, which helps to increase this study's statistical power despite the modest sample size.

In conclusion, the current study showed that SBP and DBP contributed differently at different stages to arterial stiffness progression in this Chinese cohort. Moreover, HR was consistently involved in the increased progression of CIMT in all periods. These findings underline the importance of early detection and control of BP and resting HR for the prevention of arterial stiffness progression. The progression of arterial stiffness is not only associated with BP levels but can also develop silently with increasing HR.

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Author contributions

Y.W. and J.-J.M. conceived and designed the experiments; J.-J.M. and Z.-Y.Y. were responsible for participant recruitment; Y.W., Y.Y., W.-H.G., Y.Y., K.-K.W., J.-W.H., C.C., L.-J.W., K.G., Y.-Y.L., C.C., J.-T.X., Q.M., W.-L.Z. and H.L. performed the experiments; Y.W. and P.-F.Q. analyzed the data; Y.W. and Y.Y. wrote the article. All authors read, critically revised and approved the final article.

Conflicts of interest

There are no conflicts of interest.

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