Early life cardiovascular risk factor trajectories and vascular aging in midlife: a 30-year prospective cohort study

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Abstract

Background: Vascular aging, as assessed by structural and functional arterial properties, is an independent predictor of cardiovascular outcomes. We aimed to explore the associations of individual cardiovascular risk factors from childhood to midlife and their accumulation over a 30-year span with vascular aging in midlife.

Methods: Using data from the ongoing cohort of Hanzhong Adolescent Hypertension study, 2180 participants aged 6 to 18 years at baseline were followed for over 30 years. Distinct trajectories of systolic blood pressure (SBP), body mass index (BMI), and heart rate (HR) from childhood to midlife were identified by group-based trajectory modeling. Vascular aging was assessed by carotid intima–media thickness (cIMT) or brachial-ankle pulse wave velocity (baPWV).

Results: We identified 4 distinct SBP trajectories, 3 distinct BMI trajectories and 2 distinct HR trajectories from childhood to midlife. Persistently-increasing SBP, high-increasing BMI, and high-stable HR were all shown to have a positive association with baPWV in midlife. For cIMT, similar associations were observed for persistently-increasing SBP and high-increasing BMI. After further adjustment for SBP, BMI and HR at the time of vascular assessment in 2017, associations were also observed for cardiovascular risk factor trajectories accumulation with baPWV (β=0.656 (95%CI, 0.265-1.047)] and with cIMT [β=0.045 (95%CI, 0.011-0.079)] in adulthood.

Conclusions: Longitudinal exposure to individual cardiovascular risk factors from childhood to midlife and cardiovascular risk factor accumulation were associated with an increased risk of vascular aging in midlife. Our study lends support for early targeting of risk factors in order to prevent cardiovascular disease later in life.

Key Words: Cardiovascular risk factors, cohort studies, pulse wave velocity, carotid intima–media thickness, vascular aging.

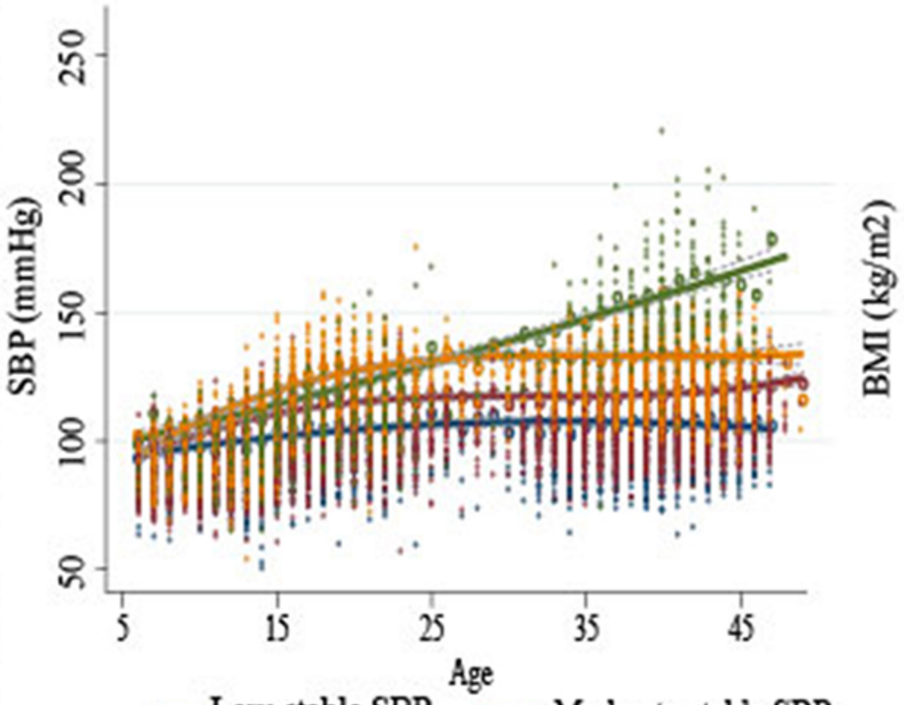
Trajectory

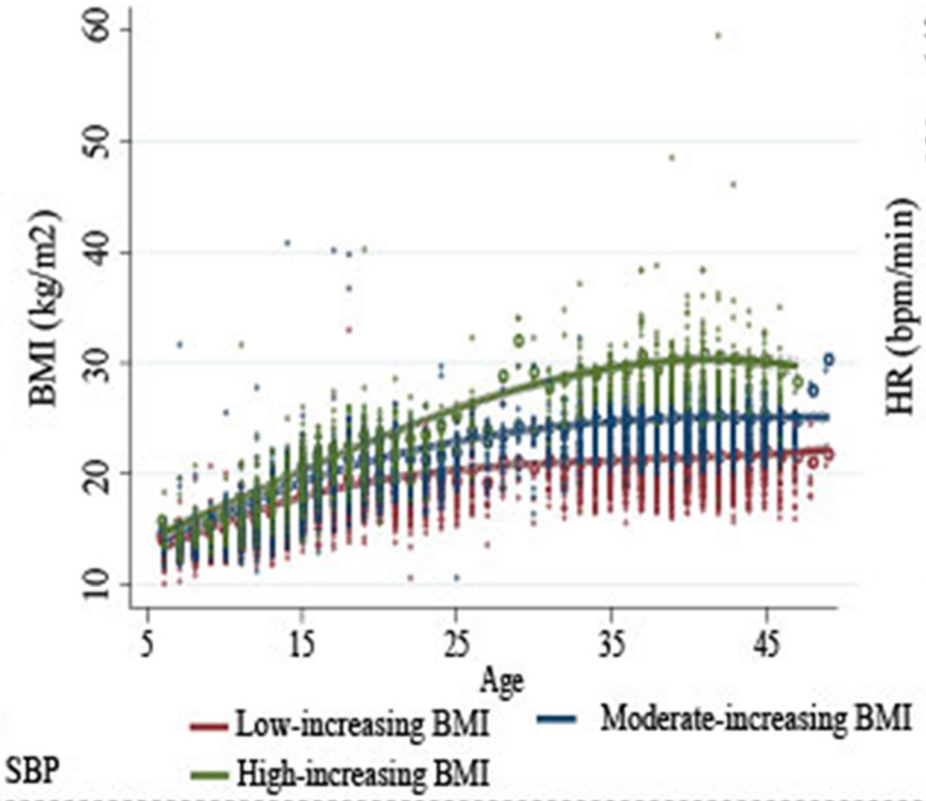
1987

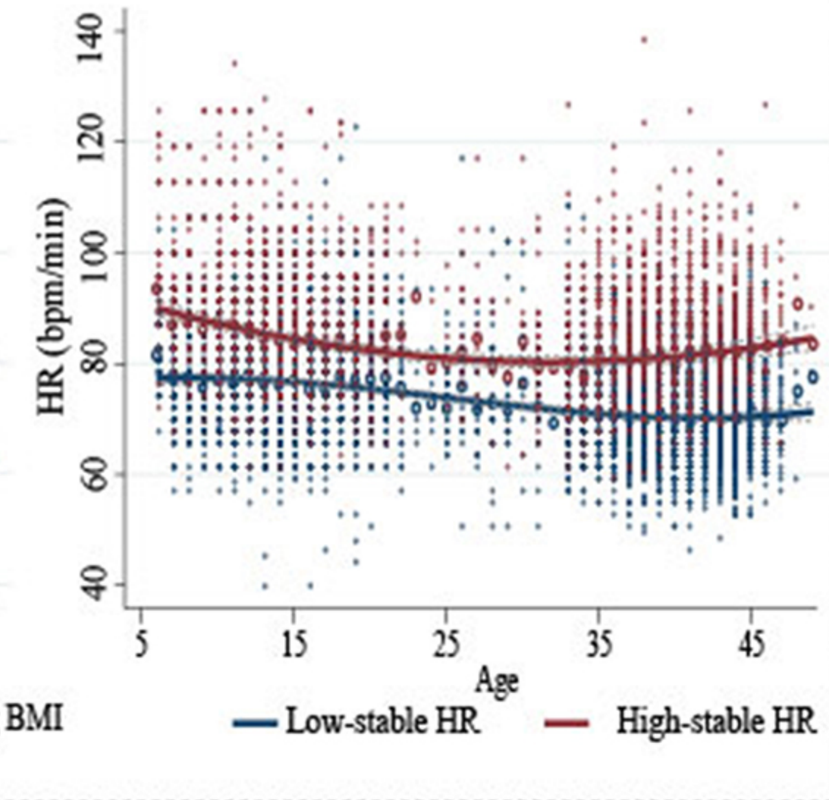
2017

Childhood

Adulthood

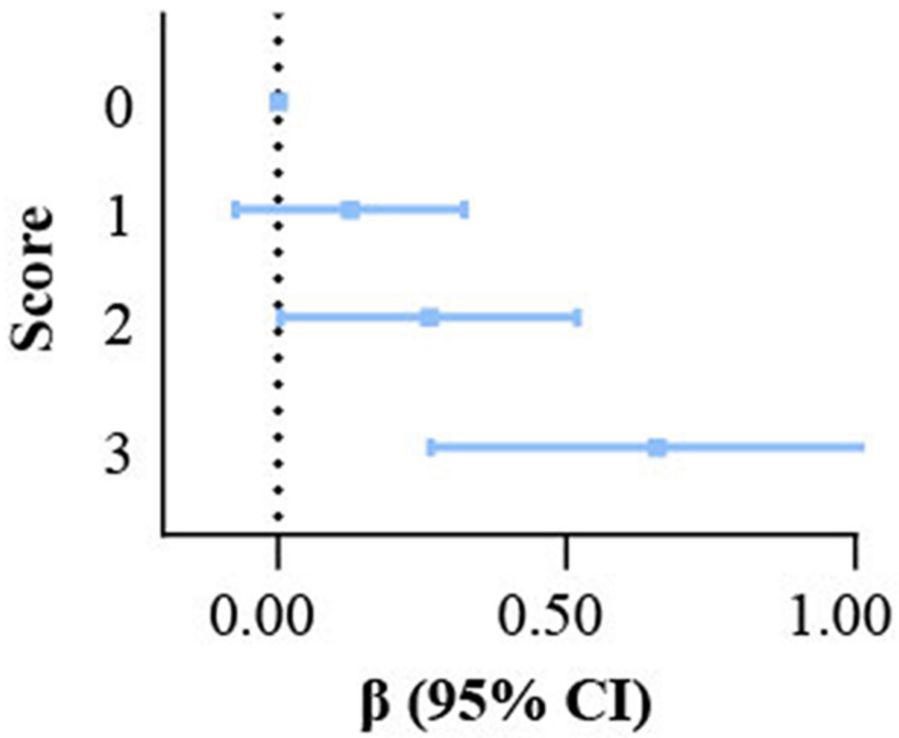




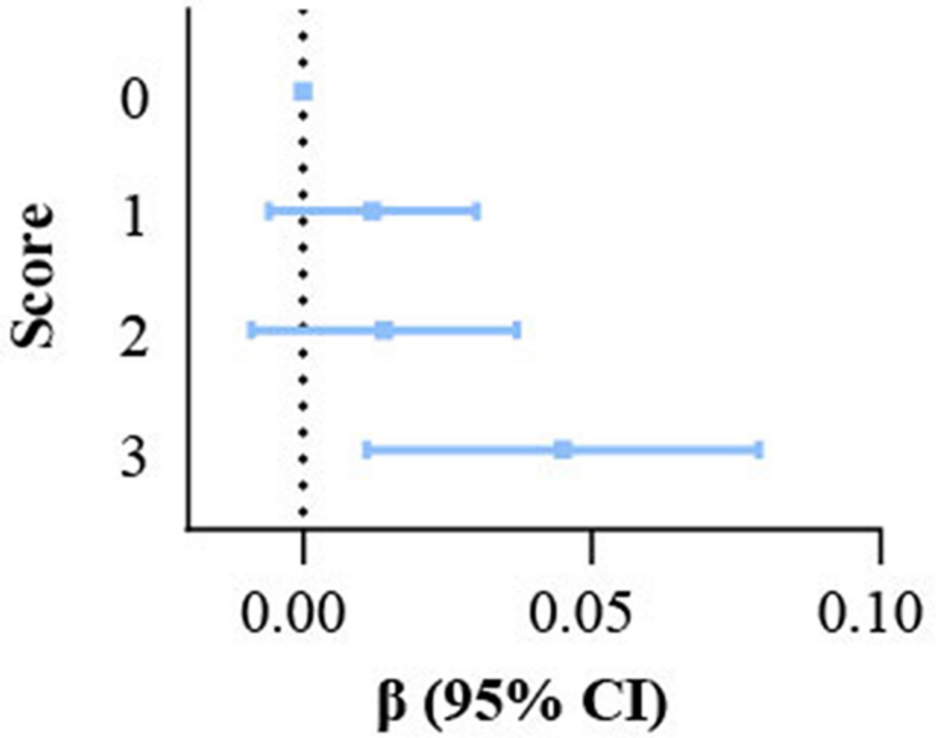


Combined CVRF score

Association between CVRF score and **baPWV** in midlife



Association between CVRF score and **cIMT** in midlife



Nonstandard Abbreviations and Acronyms

CVD, cardiovascular disease

baPWV, brachial–ankle pulse wave velocity

cfPWV, carotid-femoral pulse wave velocity

cIMT, carotid intima–media thickness

CVRF, cardiovascular risk factor

RAP, resting radial artery pulse

AUC, area under the curve

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and the leading cause of death globally, especially in the elderly[1]. Addressing age-related CVD is critical to reducing global disease burden. Vascular aging representing the decline in function and structure of arteries is a major contributor to CVD[2, 3]. Arterial stiffness is the main manifestation of vascular aging, including atherosclerosis, collagen accumulation, fragmentation of the elastic layers, and matrix degeneration[4-6]. Brachial–ankle pulse wave velocity (baPWV) represents the speed of the pressure wave propagating along the arteries, with a higher velocity indicating stiffer vessels[7]. Atherosclerosis itself is also a major component of vascular aging and a major contributing factor to CVD. As a well-established surrogate marker of subclinical atherosclerosis, carotid intima–media thickness (cIMT) measured by ultrasound imaging assesses structural changes in the arterial wall[8]. Our previous study demonstrated a steeper increase in vascular aging during midlife in the Chinese population[9]. Although the clinical manifestations and complications of arterial stiffness and atherosclerosis commonly occur in middle or older age, the aging process of the vascular system has a long silent stage and commences at early age. Structural and functional alterations of the arteries can suggest a functional impairment long before the appearance of clinical lesions[10]. Therefore, it appears essential to identify effect of traditional risk factors on vascular aging as early in life as possible.

Traditional cardiovascular risk factors (CVRFs) including high blood pressure (BP), high body mass index (BMI), and elevated heart rate (HR), are important risk factors for vascular aging[2, 11-14]. Importantly, CVRFs persisting or tracking from childhood into adulthood are better predictors of CVD risk in adults compared to CVRFs assessed at single time points[15]. Childhood CVRFs were associated with increased PWV and cIMT in midlife[16-18]. However,

available evidence on the associations of childhood CVRFs with cIMT or PWV either had small sample sizes, were cross-sectional studies, or relied on single CVRF measurements[19-23], and the trajectories and correlates of CVRFs earlier in life have not been elucidated. In addition, previous studies have mainly focused on the effects of individual CVRFs exposures, whereas no previous study has explored the association between CVRFs accumulation since childhood and vascular aging in midlife.

Here, we used data from the cohort of ongoing Hanzhong Adolescent Hypertension Study, which recruited children and adolescents in 1987 and followed them up for 30 years, to identify population subgroups according to unique systolic BP (SBP), BMI, and HR trajectories from childhood to middle age. In addition, this study aimed to examine the accumulation of CVRFs from childhood to midlife and their association with vascular aging in midlife.

Materials and Methods

Study Cohort

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was conducted with data from the cohort of Hanzhong Adolescent Hypertension Study, an ongoing longitudinal study designed to evaluate the development of CVRFs since childhood. Details on the objectives and design of the study have been described elsewhere[24, 25]. Briefly, the study began in 1987 when 4623 school children were enrolled from 26 rural sites from three towns (Qili, Laojun, and Shayan) in Hanzhong, Shanxi, China. During the baseline survey, the inclusion criteria were as follows: elementary and middle school students in 1987; no chronic disease by medical records; the ability to communicate fluently in Mandarin; and volunteered to participate in this study.

Participants were excluded if the participants or their parents/guardians refused to participate, or if they had a chronic disease based on the clinical data or self-report. Subsequently, follow-up examinations were performed in 1989, 1992, 1995, 2005, 2013 and 2017. In 2005, we obtained information from 436 participants from the large cohort using an isometric sampling method on every tenth participant (K=10). Except for the visit in 2005, other follow-ups were large in scale and aimed to visit each individual enrolled in 1987. The response rates were 77.7% (n=3592) in 1989, 84.8% (n=3918) in 1992, 82.1% (n=3794) in 1995, 65.3% (n=3018) in 2013, and 60.1% (n=2780) in 2017 (**Figure 1**). Reasons for loss of follow-up mainly included migrant workers, emigration, military service, and death due to accidents. In the present study, to explore association between cardiovascular risk trajectories and vascular aging, we excluded participants who did not complete baPWV or cIMT measurements in 2017. In addition, in order to model fitted cardiovascular risk (SBP, BMI and HR) trajectories, we only included participants with at least three measurements during 1987 and 2017. A flow diagram showing the selection of study population is shown in **Figure 1**.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Code: XJTU1AF2015LSL-047). All participants in this study given informed consent at each visit, and for those under the age of 18 at the time of enrollment, the consent of a parent/guardian was acquired. The principles of the Helsinki Declaration were followed in this study, and all study procedures were carried out in compliance with institutional protocols (URL: https://www.clinicaltrials.gov; unique identifier: NCT02734472).

Cardiovascular risk factors

Participants were required to abstain from tea, coffee, alcoholic beverages, smoking, and

strenuous exercise for at least 30 minutes. BP was measured by trained and certified observers using a standard mercury sphygmomanometer for the first 6 visits and electronic sphygmomanometer (Omron M6, Kyoto, Japan) in the 2017 follow-up as previously described[19, 24-27]. For children, BP was measured using standardized pediatric techniques with appropriate cuff size. Reading at Korotkoff phase I as SBP and the reading at Korotkoff phase V as diastolic BP (DBP). In the case of children (< 12 years of age), the Korotkoff sound of phase IV (when the sound changes abruptly) were determined as DBP. The resting radial artery pulse (RAP) has been widely used to reflect the HR in the population at low risk of atrial fibrillation. The RAP was measured using traditional methods by palpation of the left radial artery with three fingers at the wrist over the radius for 1 minute after resting for half an hour[28]. The HR data were obtained using the resting RAP for the first six visits and were read directly using Omron's electronic sphygmomanometer in 2017. BP and HR were measured three times, and the mean values were used for analysis. Height and weight were measured with the person wearing light clothing and without shoes and were rounded to the nearest cm (height) and half kilogram (weight). Body mass index (BMI) was calculated as weight (in kg) divided by squared value of height (in m).

Vascular aging assessments

Vascular aging was assessed in 2017. As an indicator of arterial stiffness, baPWV has been widely used in clinical fields[7, 29]. BaPWV was measured using a volume-plethysmographic device (BP-203RPEII, Nihon Colin, Japan) as previously reported[19, 26, 30, 31]. The average value of baPWV measurements on both sides was used for analysis. cIMT measurements were used to assess early stages of carotid atherosclerosis. cIMT, defined as the distance from the intima-luminal interface to the media-adventitial interface, was measured as described elsewhere[19, 26, 30, 31]. The same investigator who was blinded to the subjects' clinical status

carried out all the measurements. Three images were obtained for each common carotid artery, and the average of the six measurements was used for analysis.

Data collection and definitions

Personal information, including demographic characteristics, personal/family medical history, cigarette smoking, and drinking history, was obtained through a questionnaire as previously described[19, 25, 27, 30, 32]. All survey and physical examinations were performed by trained nurses or physicians. Blood samples collected by peripheral venous puncture and immediately centrifuged at 3000 × g for 10 minutes before being stored at −80°C until analysis. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting blood glucose were measured using an automatic biochemical analyzer (model 7600; Hitachi, Ltd., Tokyo, Japan) as previously described[19, 25, 27, 30, 32].

Participants who reported continuous or cumulative smoking for 6 months or more during their lifetime were defined as cigarette smokers[31]. Alcohol consumption was defined as daily alcohol use (liquor, beer, or wine) for 6 month or more[32]. Hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or as the use of antihypertensive medications based on participants' clinical data or self-report[33]. Diabetes was defined as fasting blood glucose at least 7.0 mmol/L, current use of antidiabetic medications or a previous history of diabetes mellitus[34]. Hyperlipidemia was defined as the presence of any one of the following four situations: hypertriglyceridemia (TG ≥ 2.26 mmol/L), hypercholesterolemia (TC ≥ 6.22 mmol/L), high levels of LDL (≥ 4.14 mmol/L), or low levels of HDL (≤ 1.04 mmol/L)[35].

Statistical analyses

All trajectories were identified using group-based trajectory modeling within the "Traj" plugin in Stata software 14.0 (Stat Corp., College Station, Texas, USA). In this study, we constructed CVRF (SBP, BMI and HR) trajectories from childhood to middle age (≥3 times CVRF measured in 1987-2017, and excluded data only from the first three years visit or the last three years visit). To select the optimal number of groups and the shapes of trajectories, we did a 3-stage procedure which has been previously described[24]. At first step, we selected a fit model based on the distribution of the variable. In this study, SBP, BMI and HR are continuous variables, thus we choose a censored normal (cnorm) as the fit model. Then, for each trajectory, we fitted it with a different shape (0=intercept, 1=linear, 2=quadratic, and 3=cubic). Finally, we identified the best fitting trajectories of BMI, SBP and HR according to the results of step two. The Bayesian Information Criterion (BIC) was calculated and compared with various trajectory numbers, with the lowest absolute BIC value indicating a strong model fit. In addition to the BIC information, the best model should have an average posterior probability (APP) >70%, meaning that the trajectory included participants with similar patterns and distinguished the participants with distinct patterns. To ensure that each trajectory group had a certain distribution, the sample size of each group should be >5%. SBP, BMI, and HR trajectories were started with quadratic shapes. Different shape combinations in the four, three and two trajectory groups were tested for SBP, BMI and HR, respectively **(Table S1-3)**. According to the BIC, and APP of each group as well as the sample size of each group, we choose best-fitting model for SBP, BMI and HR.

Games-Howell post hoc test was conducted to investigate significant differences between trajectory groups. Linear regression analyses were used to examine the associations between CVRF trajectory groups and vascular aging in midlife. β and 95% confidence intervals (CIs) were calculated after adjusting for age, sex, smoking, drinking, total cholesterol,

triglycerides, and fasting blood glucose. According to the CVRF trajectory classification, we defined a total risk score to reflect the cumulative burden of CVRF. The association between accumulation of CVRF and vascular aging in midlife was also explored using linear regression analyses. The regression analyses were conducted with adjustment for age, sex, smoking, drinking, total cholesterol, triglycerides, and fasting blood glucose. In addition, the analyses were further adjusted for CRVF including SBP, BMI and HR in 2017. In sensitivity analysis, we repeated the analysis after excluding patients with hypertension, diabetes, or hyperlipidemia in follow-ups. We further adjusted for SBP, BMI, and HR in 1987 or 2017 assess the robustness of our estimates. $P<0.05$ was considered statistically significance. Stata software 14.0 (Stat Corp., College Station, Texas, USA) was used for all analysis.

Results

Characteristics of Study Population

The prospective cohort study included 2180 participants for trajectory analyses from childhood to middle age. Males accounted for 56.7% and the median age in 2017 was 42 (39-44) y (**Table 1**). The details for each of the SBP, BMI, HR trajectory groups over the 30 years follow-up are presented in **Table 2**. Four distinct SBP trajectories were named according to the morphological characteristics as: “low-stable” (n=266, 12.20%), “moderate-stable” (n=1302, 59.72%), “high-stable” (n=483, 22.16%), and “Persistently-increasing” (n=129, 5.92%) (**Figure 2A**). In addition, three distinct BMI trajectories were identified: “low-stable” (n=862, 39.78%), “moderate-stable” (n=1076, 46.65%), and “high-stable” (n=229, 10.47%) (**Figure 2B**). HR was divided into 2 distinct trajectories: “low-stable” (n=1622, 75.79%) and “high-stable” (n=518, 24.21%) (**Figure 2C**). The SBP, BMI and HR levels by age periods of each trajectory group are presented in **Table S4**. Distributions of SBP, BMI, HR cIMT, and baPWV in different group were presented in **Figure S1-5**, respectively.

Trajectories of CVRFs from Childhood to Midlife and baPWV in Midlife

SBP trajectories from childhood to midlife were associated with baPWV in midlife (**Table 3**). Compared with the low-stable SBP group, moderate-stable, high-stable, and persistently-increasing SBP groups were significantly associated with higher baPWV after adjustment for covariates [β=1.026 (95% CI: 0.777, 1.275) for moderate-stable group; β= 2.638 (95% CI: 2.344, 2.932) for high-stable group; β= 5.358 (95% CI: 4.958, 5.759) for persistently-increasing group]. BMI trajectory was positively associated with baPWV; the moderate-increasing and high-increasing BMI groups were associated with the higher baPWV compared with the low-increasing BMI [β= 0.375 (95% CI: 0.174, 0.576) for moderate-increasing BMI; β= 0.854 (95% CI: 0.518, 1.190) for high-increasing BMI] (**Table 3**). Furthermore, high-stable HR group was also associated baPWV compared with low-stable HR (β=0.465, 95%CI: 0.245 to 0.685 for high-stable HR) (**Table 3**).

Trajectories of CVRFs from Childhood to Midlife and cIMT in Midlife

Similar to the results for baPWV, SBP trajectory [β= 0.031 (95% CI: 0.007, 0.054), for high-stable group; β= 0.042 (95% CI: 0.010, 0.074) for high-increasing group] and BMI trajectory [β= 0.023 (95% CI: 0.010, 0.037) for moderate-increasing BMI; β= 0.031 (95% CI: 0.009, 0.053) for high-increasing BMI] also showed a positive association with cIMT. However, no associations were observed between HR and cIMT (**Table 3**).

Cumulative Burden of CVRFs from Childhood to Midlife and Vascular Aging Indicators in Midlife

The impact of the cumulative burden of CVRFs from early childhood to midlife on vascular aging was assessed. For each participant, the cumulative burden from each of the three

CVRFs (i.e., SPB, BMI and HR) was estimated by the total number of cardiovascular trajectories associated with higher baPWV and cIMT the participant belonged to. It was assigned one point if the participant was showed (1) high-stable SBP or persistently-increasing SBP groups, (2) moderate-stable BMI or high-stable BMI group, and (3) high-stable HR group. In the study, CVRF risk points were summed up to form a total score to determine a cumulative burden from childhood to midlife. As shown in **Table 2**, baPWV and cIMT increase as the total score increases. The numbers and proportions of participants were 539 (25.27%), 1076 (42.90%), 229 (25.60%), and 133 (6.24%) with 0, 1, 2 and 3 total scores, respectively. In the multivariable linear regress analyses for the total score, the CVRF free group (referred to 0) was used as the reference. For the total score, positive linear trends were found with baPWV (β= 0.656, 95%CI: 0.265 to 1.047 for 3 CVRFs), and cIMT (β= 0.045, 95%CI: 0.011 to 0.079 for 3 CVRFs) (**Table 4**). In addition, to highlight the cumulative burden of CVRFs from childhood to midlife, we also established trajectories of CVRFs from 18 years of age. The association between the cumulative burden of CVRFs from early adulthood to midlife and vascular aging was not statistically significant (**Table S5**).

Sensitivity Analyses

Several sensitivity analyses were conducted. First, we repeated analysis after excluding participants with hypertension, diabetes, or hyperlipidemia. For baPWV, the associations for SBP, BMI and HR remained similar. For cIMT, SBP and BMI were found similar to the previous analyses. Furthermore, for the total score, a positive association for baPWV and cIMT was also observed in participants excluding hypertension (**Table S6**). Next, we further adjusted for SBP, BMI, and HR in 1987. The associations with baPWV and cIMT were consistent (**Table S7**). Finally, we further adjusted for SBP, BMI, and HR in 2017. We found that the association between SBP trajectory and baPWV remained significant (**Table S8**).

Discussion

In this study, we explored the life-course from childhood, adolescence, adulthood, to middle age, and identified diverse trajectories in SBP, BMI, and HR over a 30-year follow-up, during which China began to reform and open up, and people's lifestyles have undergone tremendous changes. We observed that longitudinal exposure to high SBP, BMI, and HR since childhood are significantly associated with baPWV in midlife. Furthermore, participants with high SBP and BMI were more likely to have high cIMT. Importantly, groups with accumulation of CVRF had greater baPWV and cIMT in midlife. Our findings support the notion that trajectories of SBP, BMI and HR trends since childhood are important predictors of vascular aging, and highlight the impact of cumulative burden of longitudinal CVRF on vascular aging.

The two components of vascular aging, arterial stiffness defined by baPWV and atherosclerosis defined by cIMT can both be used as surrogate markers for CVD and mortality[36-38]. Previous epidemiological studies have shown that SBP, BMI and HR to be independently and positively associated with baPWV[39-42]. However, these studies were conducted based on a single CVRF measurement, which did not adequately reflect the continuous effects of CVRF on vascular aging and was susceptible to lifestyle factors, dietary conditions, and other factors. Group-based trajectory modeling (GBTM) takes into account variations in time to distinguish changes in CVRFs over time and heterogeneity within multiple CVRF measurements. It assigns individuals with similar CVRF development trends to the same subgroup based on multiple measurement data over a long period[43, 44]. It provides an effective approach to evaluate the effect of certain predictors on target organs over the course of a lifetime. In the present study, we used GBTM to determine the trajectory of

CVRFs changes from childhood to midlife. It was found that baPWV was positively correlated with the trajectory groups with higher SBP, higher BMI, and higher HR. Furthermore, the positive association also exists between cIMT and trajectory groups with consistently-increasing SBP and high BMI. These findings stress the importance of early identification of risk stratification and launching preventative efforts against CVRF as early as possible.

Recent studies have suggested the importance of a longitudinal burden of CVRF[20-22]. Our previous studies also demonstrated the important role of high-increasing BMI on arterial stiffness[19]. Furthermore, the Young Finns Study has pointed out that BMI accumulation may be associated with increase in cIMT in participants aged 34-49 years[22]. Consistent with these results, the Bogalusa Heart Study also showed the adverse effects of cumulative burden of BMI and SBP on arterial wall stiffening and thickening by calculating the area under the curve (AUC) to measure the long-term burden of the risk factors[45]. In addition, in the Kailuan study, heart rate trajectory pattern has been recognized as an independent risk factor for accelerated arterial stiffness[23]. Consistent with previous findings, we showed that the more adverse CVRFs were accumulated from childhood to midlife, the higher vascular aging was observed in later life. Vascular aging processes are known to be ongoing already years or decades before manifesting clinical symptoms. Therefore, exploring the long-term cumulative effects of CVRF since childhood can provide a basis for primary or primordial prevention for CVD.

Marked increasing changes in SBP and BMI in adolescence (<20 years) was observed, which were then maintained stable at this level (Figure 2). The robust positive associations with baPWV and cIMT were observed for SBP and BMI trajectory group, and the findings suggest

that adolescence risk status may be modifiable and could alter arterial structure. Adolescence status is an important period that influences arterial properties, and there is a developmental adaptation in arterial compliance during this period under the influence of hormones[46]. Thus, it should be caution to disassociate the normal adaptations that occur with growth from the accumulation effects of CVRFs on vascular aging during adolescence. However, it should be noted that the properties of the arterial wall are affected by many endogenous and environmental influences throughout life, not just adolescence period alone. Only by understanding trajectory of CVRFs across life and the characteristics associated with deviation from 'normal' age-related change, can individuals at high risk of disease be understood and identified[47].

These innovative findings highlight the impact of longitudinal accumulation of CVRF trajectory beginning in childhood on vascular aging. It should be noted that midlife has been identified as an essential period of accelerated vascular aging[9]. Therefore, it would be important to investigate the cumulative effect of CVRF before midlife on vascular aging. Importantly, the previous longitudinal studies on CVRF have generally considered the effect of a single risk factor. To our knowledge, the present study is the first population-based study to simultaneously examine the association between cumulative burden from multiple CVRF trajectory accumulation from childhood to midlife and vascular aging in midlife. The number of CVRF accumulation components defined by different trajectories from childhood through midlife was longitudinally associated with vascular aging. As highlighted in current study, we encouraged to increase recognition of the importance of changes in CVRFs throughout life. The preventative measures to improve lifestyle at all stages of life-course to decrease CVD risk in later life is important. The underlying mechanisms how different CVRFs contributed differently to the progression of vascular aging in various stages of life remains unclear and

deserves further research.

The key strengths of our study are the regular visits over a 30-year follow-up, and a thorough collection of vascular aging assessments. This cohort included children and adolescents at baseline who have regularly undergone several follow-ups, allowing us to investigate the effect of early-life course of multiple risk factor exposure on vascular damage in midlife. Our findings highlight the subclinical effects of CVRF before midlife. It has important implications for the need for early interventions when exposure is likely to be easier to control and adverse CVD manifestation may be reversible. However, our study also has some limitations. Firstly, although carotid-femoral PWV (cfPWV) is the gold standard for measuring arterial stiffness, the baPWV has been shown to be a substantial and independent predictor of cardiovascular morbidity and mortality[48, 49]. Secondly, since all of the recruited participants were Han Chinese from northern China, the trajectories identified in this cohort may not be generalizable to other populations. However, the homogeneous character of our sample, on the other hand, may assist eliminate potential confounding factors such as racial and healthcare disparities, hence improving internal validity. Thirdly, the associations between different trajectories and vascular aging do not suggest a causal relationship because of the limitation of observational study. Nevertheless, our study still provides a clue that previous history of CVRFs is closely associated with vascular aging after adjusted by CVRFs in 2017. Fourthly, while the trajectory groups reflect a general trend of CVRF through time, they may not precisely define each individual's CVRF trajectory. Finally, we could not explore whether changes in SBP or other risk factors precede changes in vascular aging, because the vascular data was only available in 2017. Thus, it’s immature to elucidate the causal effect of CVRF accumulation on vascular aging before midlife. In addition, we could not conduct our analyses stratified by sex as our sample size will not

provide sufficient power for such analyses, although we have adjusted for sex in all analyses. Ongoing longer-term follow-up will continue and further studies are required to address these important questions.

Perspectives

Our study showed that maintaining high SBP, high BMI and high HR from childhood onward was associated with a higher risk of vascular aging in midlife. Additionally, the longitudinal exposure to an increasing number of risk factors was associated with greater risk of vascular aging in midlife. Monitoring CVRF trajectories from childhood may be an important approach to identify individuals at higher risk of developing CVD. Early prevention and intervention in this population to decrease CVRF accumulation may effectively reduce cardiovascular risks in later life.

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Disclosures

The authors have no potential conflicts of interest to disclose.

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Novelty and Relevance

1. What Is New?

Longitudinal exposure to individual cardiovascular risk factors from childhood to midlife and cardiovascular risk factor accumulation were associated with an increased risk of vascular aging in midlife.

2. What Is Relevant?

Vascular aging represents the decline in function and structure of arteries is a major contributor to cardiovascular outcomes.

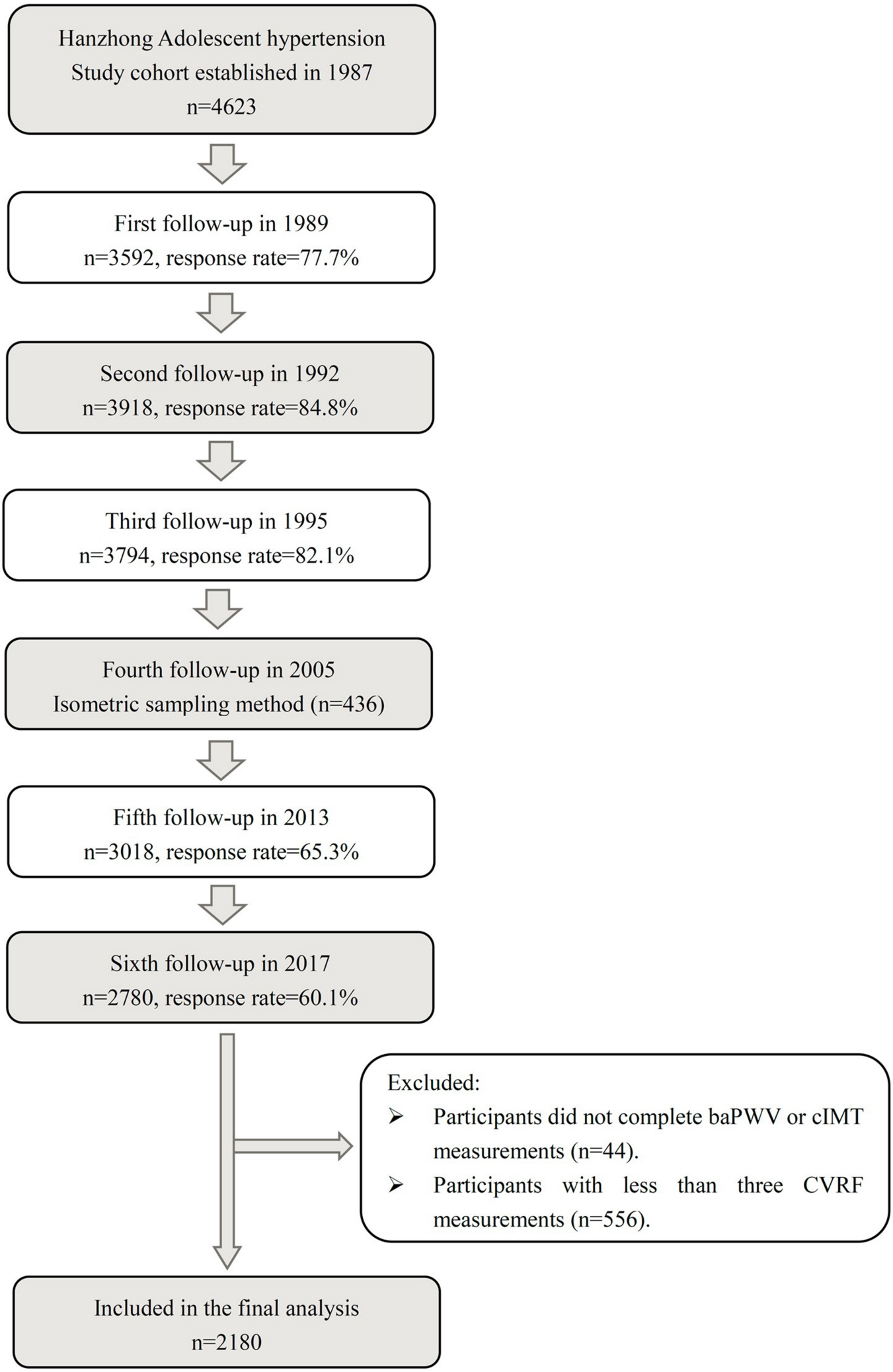
3. Clinical/Pathophysiological Implications?

Monitoring CVRF trajectories from childhood may be an important approach to identify individuals at higher risk of developing CVD. Early prevention and intervention in this population to decrease CVRF accumulation may effectively reduce cardiovascular risks in later life.

Figure legends

Figure 1. Flow diagram showing the selection of study population. baPWV, brachial–ankle pulse wave velocity; cIMT, carotid intima–media thickness; CVRF, cardiovascular risk factor.

Figure 2. Long-term SBP, BMI, HR trajectories from childhood to middle age. SBP, systolic blood pressure; BMI, body mass index; HR, heart rate.


Hanzhong Adolescent hypertension Study cohort established in 1987 n=4623
First follow-up in 1989 n=3592, response rate=77.7%
Second follow-up in 1992 n=3918, response rate=84.8%
Third follow-up in 1995 n=3794, response rate=82.1%
Fourth follow-up in 2005 Isometric sampling method (n=436)
Fifth follow-up in 2013 n=3018, response rate=65.3%
Sixth follow-up in 2017 n=2780, response rate=60.1%
Excluded:
Participants did not complete baPWV or cIMT measurements (n=44).
Participants with less than three CVRF measurements (n=556).
Included in the final analysis n=2180

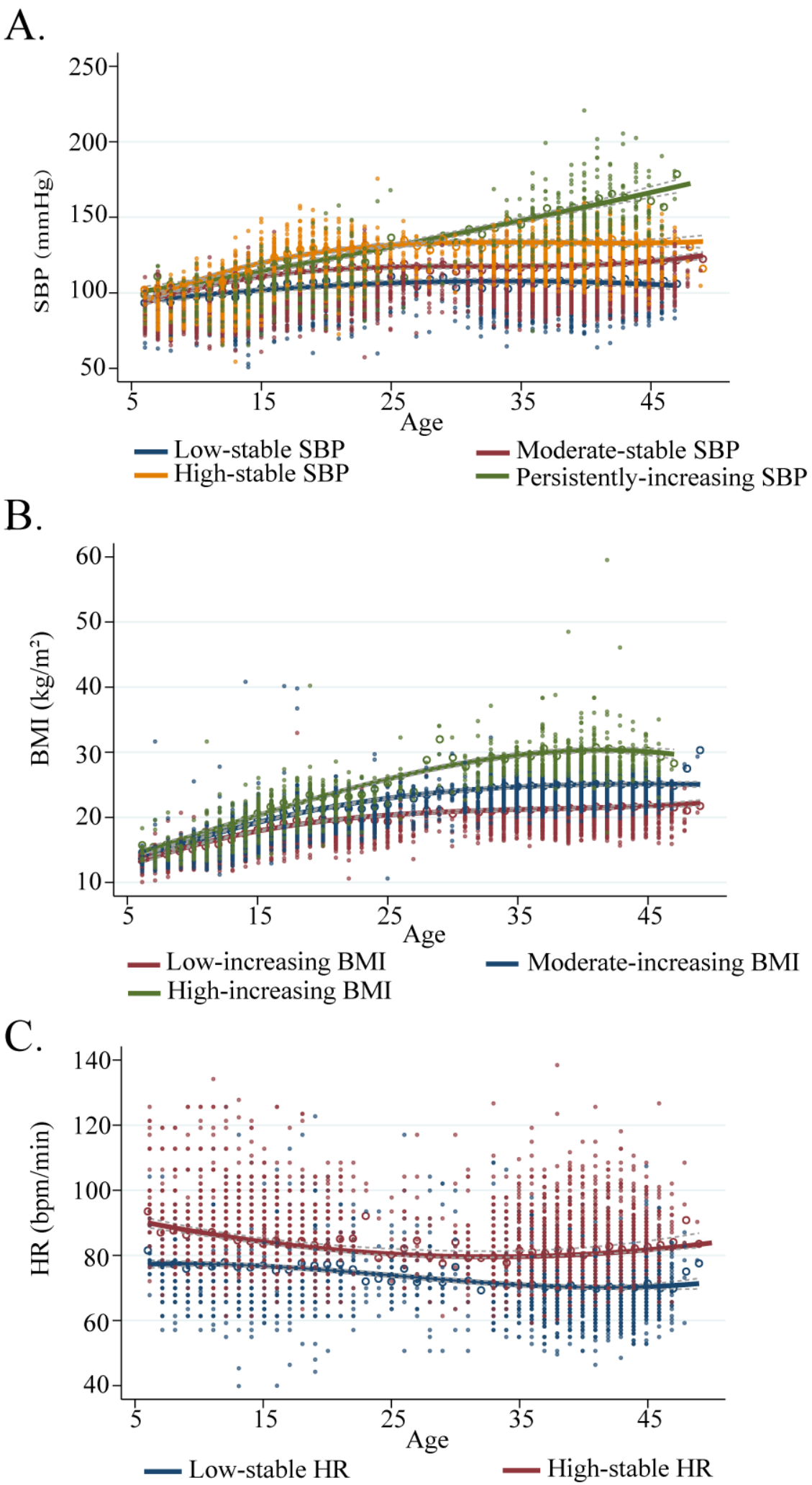

A.
SBP (mmHg)
250
200
150
100
50
5
15
25
35
45
Age
Low-stable SBP
High-stable SBP
Moderate-stable SBP
Persistently-increasing SBP
B.
BMI (kg/m²)
60
50
40
30
20
10
5
15
25
35
45
Age
Low-increasing BMI
High-increasing BMI
Moderate-increasing BMI
C.
HR (bpm/min)
140
120
100
80
60
40
5
15
25
35
45
Age
Low-stable HR
High-stable HR

Table 1. Demographic characteristics and cardiovascular risk factors.

Parameter	Value
Baseline in 1987	
Age (years)	12(9-14)
SBP (mmHg)	104(97-111)
DBP (mmHg)	65(60-71)
HR (bpm/min)	16.26(14.93-18.26)
BMI (kg/m^2)	78(72-84)
Follow-up in 2017	
Age (years)	42(39-44)
Sex (female, %)	944(43.43%)
Smoking (%)	992(43.57%)
Drinking (%)	675(29.64%)
Diabetes (%)	481(21.12%)
Hypertension (%)	398(27.48%)
baPWV (m/s)	12.20(10.95-13.74)
cIMT(mm)	0.62(0.53-0.75)
SBP (mmHg)	121(112-131)
DBP (mmHg)	76(69-84)
HR (bpm/min)	73(67-80)
BMI (kg/m^2)	23.81(21.86-26.05)
Fasting glucose (mmol/l)	4.57(4.27-4.90)
Triglycerides (mmol/l)	1.35(0.96-1.95)
Total cholesterol (mmol/l)	4.50(4.04-4.99)
HDL (mmol/l)	1.14(0.99-1.33)
LDL (mmol/l)	2.50(2.13-2.90)

baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein. Data were presented as median (interquartile range, IQR) for continuous variables and percentage for dichotomous variables.

Table 2. Descriptive characteristics for the cardiovascular risk factor trajectory and risk score groups.

Variable	N	SBP in 2017 (mmHg)	BMI in 2017 (kg/m^2)	HR in 2017 (bpm/min)	baPWV in 2017 (m/s)	cIMT in 2017 (mm)
SBP (n=2180)						
Low-stable	266	104(100-109)	22.25(20.29-23.87)	73(66-80)	10.51 (9.76-11.57)	0.60 (0.50-0.70)
Moderate-stable	1302	119(113-126)	23.49(21.70-25.55)	73(66-79)	12.82 (10.84-13.02)	0.60 (0.53-0.73)
High-stable	483	134(127-141)	25.10(23.11-26.79)	74(68-80)	13.52 (12.56-15.01)	0.65 (0.55-0.77)
Persistently-increasing	129	159(152-172)	26.72(24.27-29.22)	76(70-86)	16.10 (14.72-17.99)	0.65 (0.57-0.78)
BMI (n=2167)						
Low-increasing	862	117(109-126)	21.44(20.23-22.59）	73(66-81)	11.96 (10.71-13.20)	0.60 (0.50-0.70)
Moderate-increasing	1076	123(115-133)	25.02(23.79-26.32)	73(66-79)	12.33 (11.09-13.90)	0.65 (0.55-0.75)
High-increasing	229	129(119-144)	29.51(28.39-31.04)	75(69-82)	12.84 (11.27-14.49)	0.65 (0.57-0.75)
HR (n=2140)						
Low-stable	1622	121(112-131)	23.84(21.88-26.11)	70(65-75)	12.16 (10.98-13.56)	0.62 (0.53-0.75)
High-stable	518	123(114-133)	23.62(21.73-25.92)	84(78-89)	12.45 (10.95-14.02)	0.75 (0.62-0.75）
Risk factor Score (n=2133)						
0	539	115(108-122)	21.42(20.18-22.60)	70(64-75)	11.84 (10.73-13.17)	0.62 (0.53-0.75)
1	915	119(111-127)	24.13(22.45-26.10)	73(67-79)	12.45 (10.95-14.02)	0.62 (0.53-0.75)
2	546	131(122-144)	25.61(23.85-27.58)	75(69-83)	13.20 (11.74-15.09)	0.65 (0.55-0.75)
3	133	138(123-151)	25.91(24.48-27.50)	84(77-89)	14.08 (12.67-15.99)	0.65 (0.57-0.78)

SBP, systolic blood pressure; BMI, body mass index; HR, heart rate; baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness. Data were presented as median (interquartile range, IQR).

Table 3. Associations between cardiovascular risk factor trajectories from childhood to midlife and vascular aging in midlife.

Variable	baPWV		cIMT	
	β (95%CI)	P value	*β* (95%CI)	P value
SBP				
Low-stable	Reference		Reference	
Moderate-stable	1.026(0.777-1.275)	<0.001	0.015(-0.005-0.035)	0.149
High-stable	2.638(2.344-2.932)	<0.001	0.031(0.007-0.054)	0.010
Persistently-increasing	5.358(4.958-5.759)	<0.001	0.042(0.010-0.074)	0.010
BMI				
Low-increasing	Reference		Reference	
Moderate-increasing	0.375(0.174-0.576)	<0.001	0.023(0.010-0.037)	<0.001
High-increasing	0.854(0.518-1.190)	<0.001	0.031(0.009-0.053)	0.009
HR				
Low-stable	Reference		Reference	
High-stable	0.465(0.245-0.685)	<0.001	0.006(-0.008-0.021)	0.392

baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; SBP, systolic blood pressure; BMI, body mass index; HR, heart rate. Model was adjusted with age, sex, smoking, drinking, total cholesterol, triglycerides, and fasting blood glucose in 2017.

Table 4. Association between cardiovascular risk factor score and vascular aging in midlife.

Outcome	0	1		2		3	
		***β* (95%CI)**	***P* value**	***β* (95%CI)**	***P* value**	***β* (95%CI)**	***P* value**
baPWV (n=1947)							
Model 1	Reference	0.396(0.168-0.625)	0.001	1.896(1.640-2.152)	<0.001	3.086(2.674-3.498)	<0.001
Model 2	Reference	0.308(0.085-0.530)	0.007	1.595(1.343-1.847)	<0.001	2.648(2.246-3.049)	<0.001
Model 3	Reference	0.125(-0.073-0.323)	0.215	0.262(0.004-0.519)	0.046	0.656(0.265-1.047)	0.001
cIMT (n=1949)							
Model 1	Reference	0.021(0.005-0.037)	0.009	0.036(0.018-0.054)	<0.001	0.063(0.035-0.091)	<0.001
Model 2	Reference	0.020(0.004-0.036)	0.015	0.025(0.007-0.043)	0.006	0.055(0.026-0.083)	<0.001
Model 3	Reference	0.012(-0.006-0.03)	0.180	0.014(-0.009-0.037)	0.226	0.045(0.011-0.079)	0.010

baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness. Model 1: unadjusted; Model2: adjusted with age in 2017, sex, smoking, drinking, total cholesterol, triglycerides and fasting blood glucose in 2017; Model 3: Model 2 + systolic blood pressure, body mass index, heart rate in 2017.

Early life cardiovascular risk factor trajectories and vascular aging in midlife: a 30-year prospective cohort study

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Table S1. Comparison of four group trajectory model shapes in SBP.

Trajectory	BIC	group_APP1	group_APP2	group_APP3	group_APP4
4 traj - (2,2,2,2)	-40318.53	0.8082224	0.8517075	0.7934566	0.7947865
4 traj - (2,2,2,3)	NA				
4 traj - (2,2,3,2)	-40303.95	0.7794747	0.780143	0.7988946	0.8738685
4 traj - (2,2,3,3)	-40304.33	0.779587	0.7845499	0.8024119	0.8863101
4 traj - (2,3,2,2)	-40263.84	0.7830153	0.8132789	0.7992547	0.8518024
4 traj - (2,3,2,3)	**-40254.52**	**0.7719861**	**0.8153033**	**0.8663028**	**0.8059779**
4 traj - (2,3,3,2)	-40264.3	0.7833028	0.8140121	0.8626873	0.8058093
4 traj - (2,3,3,3)	-40307.88	0.8774009	0.8409359	0.9633505	0.8946124
4 traj - (3,2,2,2)	-40263.84	0.8132799	0.7829625	0.7992874	0.8518378
4 traj - (3,2,2,3)	-40264.3	0.814006	0.7833186	0.8058032	0.8626916
4 traj - (3,2,3,2)	-40279.41	0.8341061	0.7734396	0.8581944	0.7857577
4 traj - (3,2,3,3)	-40254.88	0.8176923	0.7709865	0.8724745	0.8106994
4 traj - (3,3,2,2)	-40280.57	0.9045643	0.8645706	0.8433827	0.9278683
4 traj - (3,3,2,3)	-40242.64	0.8313313	0.7932228	0.7977772	0.8397555
4 traj - (3,3,3,2)	-40242.64	0.8313336	0.7932238	0.8397609	0.7977667
4 traj - (3,3,3,3)	-40257.05	0.8946042	0.8405425	0.9620246	0.886591

SBP, systolic blood pressure; BIC, the Bayesian Information Criteria; APP, average posterior probability.

Table S2. Comparison of three group trajectory model shapes in BMI.

Trajectory	BIC	group_APP1	group_APP2	group_APP3
3 traj-(2,2,2)	-23118.6	0.9495893	0.8962829	0.9230917
3 traj-(2,2,3)	NA			
3 traj-(2,3,2)	NA			
3 traj-(2,3,3)	-22723.84	0.8883979	0.8953528	0.8809125
3 traj-(3,2,2)	-22727.78	0.8965234	0.8866614	0.882311
3 traj-(3,2,3)	-22748.04	0.8862281	0.8863115	0.9082082
3 traj-(3,3,2)	-22723.67	0.8865743	0.8908348	0.8960705
3 traj-(3,3,3)	**-22719.9**	**0.8869868**	**0.8911144**	**0.8969666**

BMI, body mass index; BIC, Bayesian Information Criteria; APP, average posterior probability.

Table S3. Comparison of two group trajectory model shapes in HR.

Trajectory	BIC	group_APP1	group_APP2
2 traj-(2,2)	-30413.78	0.8946813	0.7972088
2 traj-(2,3)	-30417.55	0.895188	0.7974365
2 traj-(3,2)	**-30410.08**	**0.8953658**	**0.8037998**
2 traj-(3,3)	-30413.77	0.8961014	0.8038007

HR, heart rate; BIC, Bayesian Information Criteria; APP, average posterior probability.

Table S4. SBP (mmHg), BMI (kg/m^2) levels and HR (bpm/min) levels by age periods in trajectory groups from childhood to middle age.

Groups	SBP trajectory	BMI trajectory	HR trajectory
Age range	**Low-stable**	**Low-increasing**	**Low-stable**
5-10 y	96(90-102)	14.35(13.79-15.08)	78(72-84)
11-20 y	101(93-107)	18.09(16.51-19.39)	76(72-82)
21-30 y	105(99-109)	19.68(18.66-20.71)	76(68-80)
31-40 y	102(98-108)	21.35(20.15-22.44)	70(64-76)
41-50 y	104(100-109)	21.56(20.45-22.75)	70(64-75)
Age range	**Moderate-stable**	**Moderate-increasing**	**High-stable**
5-10 y	100(94-106)	15.14(14.43-15.83)	88(82-96)
11-20 y	110(102-118)	19.48(17.91-21.09)	84(80-90)
21-30 y	117(110-123)	21.54(20.45-22.91)	82(76-90)
31-40 y	117(110,123)	24.99(23.67-26.14)	82(76-88)
41-50 y	120(114-126)	25.07(23.74-26.40)	84(78-90)
Age range	**High-stable**	**Moderate-increasing**	
5-10 y	105(98-112)	15.38(14.83-16.14)	
11-20 y	121(113-130)	20.58(18.68-22.58)	
21-30 y	131(124-139)	23.90(22.66-26.06)	
31-40 y	133(127-140)	29.30(28.37-30.75)	
41-50 y	134(127,141)	29.66(28.39-31.33)	
Age range	**Persistently-increasing**		
5-10 y	107(100-114)		
11-20 y	115(108-121)		
21-30 y	122(117-131)		
31-40 y	153(143-164)		
41-50 y	159(152-177)		

SBP indicates systolic blood pressure; BMI indicates body mass index; HR indicates heart rate. Data were presented as median (interquartile range, IQR).

Table S5. Association between cardiovascular risk factor score since 18 years and vascular aging in midlife.

Outcome	0	1		2		3	
		***β* (95%CI)**	***P* value**	***β* (95%CI)**	***P* value**	***β* (95%CI)**	***P* value**
baPWV							
Model 1	Reference	0.177 (-0.269-0.623)	0.436	1.488 (1.015-1.961)	<0.001	2.767 (2.145- 3.390)	<0.001
Model 2	Reference	0.163 (-0.272-0.599)	0.462	1.405 (0.935-1.876)	<0.001	2.397 (1.781-3.013)	<0.001
Model 3	Reference	0.013 (-0.372-0.397)	0.948	0.132 (-0.347-0.611)	0.588	0.304 (-0.326-0.934)	0.344
cIMT							
Model 1	Reference	0.050 (0.020-0.080)	0.001	0.047 (0.015-0.079)	0.004	0.047 (0.005-0.088)	0.028
Model 2	Reference	0.051 (0.021-0.081)	0.001	0.047 (0.015-0.080)	0.004	0.042 (0.000-0.084)	0.051
Model 3	Reference	0.044 (0.011-0.077)	0.009	0.035 (-0.006-0.076)	0.095	0.025 (-0.029-0.079)	0.368

baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness. Model 1: unadjusted; Model2: adjusted for age in 2017, sex, smoking, drinking, total cholesterol, triglycerides and fasting blood glucose in 2017; Model 3: Model 2 + systolic blood pressure, body mass index, heart rate in 2017.

Table S6. Association between risk factor trajectories and vascular aging index in midlife in participants excluding hypertension, diabetes, and hyperlipidemia.

Variable	Exclude hypertension		Exclude diabetes		Exclude hyperlipidemia	
	β (95%CI)	*P* value	*β* (95%CI)	*P* value	*β* (95%CI)	*P* value
baPWV						
SBP						
Low-stable	Reference		Reference		Reference	
Moderate-stable	0.982(0.746,1.217)	<0.001	1.036(0.767,1.304)	<0.001	1.014(0.733,1.295)	<0.001
High-stable	2.427(2.129,2.726)	<0.001	2.626(2.302,2.951)	<0.001	2.566(2.223,2.910)	<0.001
Persistently-increasing	5.092(4.500,5.684)	<0.001	5.698(5.226,6.170)	<0.001	5.665(5.133,6.196)	<0.001
BMI						
Low-increasing	Reference		Reference		Reference	
Moderate-increasing	0.157(-0.034,0.348)	0.108	0.372(0.147,0.597)	0.001	0.367(0.135,0.599)	0.002
High-increasing	0.421(0.079,0.762)	0.016	0.804(0.421,1.188)	<0.001	1.001(0.575,1.427)	<0.001
HR						
Low stable	Reference		Reference		Reference	
High stable	0.316(0.104,0.527)	<0.001	0.356(0.110,0.601)	0.325	0.316(0.059,0.573)	0.016
Total Score*						
0	Reference		Reference		Reference	
1	0.136(-0.062,0.334)	0.179	0.101(-0.116,0.101)	0.362	0.113(-0.117,0.342)	0.337
2	0.175(-0.093,0.444)	0.201	0.211(-0.077,0.211)	0.151	0.292(-0.013,0.597)	0.061

	3	0.515(0.069,0.960)	0.024	0.433(-0.003,0.433)	0.052	0.223(-0.261,0.708)	0.3
	cIMT						
	SBP						
	Low-stable	Reference		Reference		Reference	
	Moderate-stable	0.015(-0.005,0.036)	0.139	0.020(-0.002,0.042)	0.080	0.023(0.0001,0.046)	0.0
	High-stable	0.026(0.001,0.052)	0.046	0.038(0.012,0.065)	0.005	0.034(0.006,0.062)	0.0
	Persistently-increasing	0.026(-0.024,0.076)	0.310	0.046(0.008,0.084)	0.017	0.040(-0.003,0.083)	0.0
	BMI						
	Low-increasing	Reference		Reference		Reference	
	Moderate-increasing	0.026(0.012,0.041)	<0.001	0.015(-0.0005,0.03)	0.057	0.017(0.001,0.033)	0.0
	High-increasing	0.03(0.004,0.055)	0.026	0.031(0.005,0.057)	0.019	0.024(-0.006,0.053)	0.1
	HR						
	Low-stable	Reference		Reference		Reference	
	High-stable	0.006(-0.010,0.022)	0.485	0.004(-0.012,0.021)	0.617	-0.002(-0.020,0.016)	0.8
	Total Score*						
	0	Reference		Reference		Reference	
	1	0.017(-0.002,0.035)	0.080	0.009(0.009,-0.011)	0.398	0.004(-0.017,0.025)	0.7
	2	0.019(-0.006,0.044)	0.137	0.010(0.010,-0.016)	0.453	0.003(-0.025,0.030)	0.8
	3	0.047(0.005,0.088)	0.037	0.028(0.028,-0.010)	0.152	0.024(-0.020,0.068)	0.2

Model was adjusted for age, sex, smoking, drinking, total cholesterol, triglycerides, and serum glucose. *Model was further adjusted for SBP, BMI and HR in 2017. cIMT, carotid intima-media thickness; baPWV, brachial-ankle pulse wave velocity; SBP, systolic blood pressure; BMI, body mass index; HR, heart rate.

Table S7. Association between risk factor trajectories and vascular aging index in midlife.

Variable	*β* (95%CI)	*P* value
baPWV		
SBP		
Low-stable	Reference	
Moderate-stable	1.054 (0.796, 1.311)	<0.001
High-stable	2.683 (2.365, 3.002)	<0.001
Persistently-increasing	5.342 (4.920, 5.765)	<0.001
BMI		
Low-increasing	Reference	
Moderate-increasing	0.449 (0.241, 0.658)	<0.001
High-increasing	1.033 (0.683, 1.382)	<0.001
HR		
Low stable	Reference	
High stable	0.427 (0.187, 0.667)	<0.001
Total Score		
0	Reference	
1	0.398 (0.173, 0.623)	0.001
2	1.633 (1.369, 1.898)	<0.001
3	2.784 (2.365, 3.203)	<0.001
cIMT		
SBP		
Low-stable	Reference	
Moderate-stable	0.017 (-0.004, 0.038)	0.111
High-stable	0.033 (0.007, 0.058)	0.013
Persistently-increasing	0.045 (0.011, 0.079)	0.009
BMI		
Low-increasing	Reference	
Moderate-increasing	0.024 (0.010, 0.038)	0.001
High-increasing	0.032 (0.008, 0.056)	0.009
HR		
Low-stable	Reference	
High-stable	-0.006 (-0.022, 0.011)	0.486
Total Score		
0	Reference	
1	0.018 (0.001, 0.034)	0.037
2	0.021 (0.002, 0.040)	0.031
3	0.042 (0.012, 0.072)	0.007

Model was adjusted for age in 2017, sex, smoking, drinking, total cholesterol, triglycerides and fasting blood glucose in 2017, SBP, BMI, and HR in 1987. baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; SBP, systolic blood pressure; BMI, body mass index; HR, heart rate.

Table S8. Association between risk factor trajectories and vascular aging index in midlife.

Variable	*β* (95%CI)	*P* value
baPWV		
SBP		
Low-stable	Reference	
Moderate-stable	0.014 (-0.232, 0.260)	0.911
High-stable	0.530 (0.194, 0.866)	0.002
Persistently-increasing	1.148 (0.604, 1.693)	<0.001
BMI		
Low-increasing	Reference	
Moderate-increasing	0.129 (-0.079, 0.338)	0.224
High-increasing	0.384 (-0.031, 0.799)	0.070
HR		
Low stable	Reference	
High stable	0.009 (-0.194, 0.213)	0.928
cIMT		
SBP		
Low-stable	Reference	
Moderate-stable	0.015 (-0.007, 0.037)	0.181
High-stable	0.033 (0.003, 0.063)	0.032
Persistently-increasing	0.048 (-0.0004, 0.096)	0.052
BMI		
Low-increasing	Reference	
Moderate-increasing	0.008 (-0.011, 0.026)	0.402
High-increasing	-0.007 (-0.043, 0.030)	0.729
HR		
Low-stable	Reference	
High-stable	0.004 (-0.013, 0.022)	0.623

Model was adjusted for age, sex, smoking, drinking, total cholesterol, triglycerides, fasting blood glucose, SBP, BMI, and HR in 2017. baPWV, brachial-ankle pulse wave velocity; cIMT, carotid intima-media thickness; SBP, systolic blood pressure; BMI, body mass index; HR, heart rate.

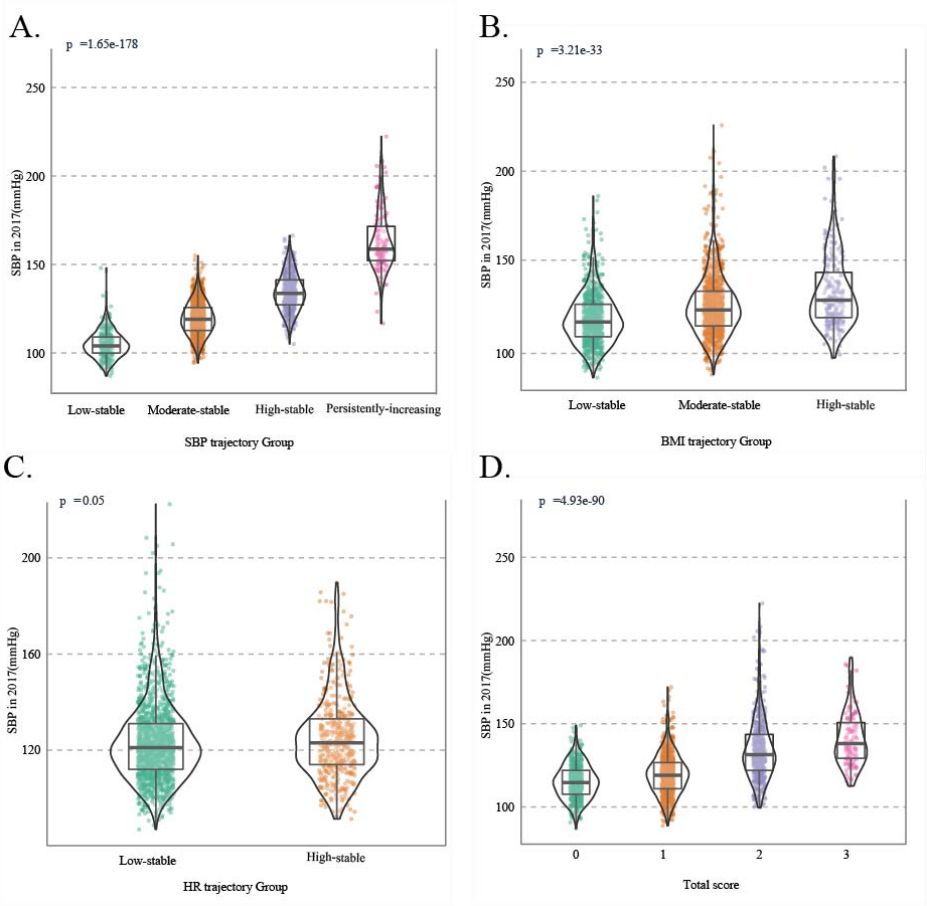

Figure S1. Distribution of SBP in 2017 among different trajectory and risk score groups. (A, SBP trajectory group; B, BMI trajectory group; C, HR trajectory group; D, Total score group) SBP, systolic blood pressure; BMI, body mass index; HR, heart rate. Boxplots indicate the median, first, and third quartiles.

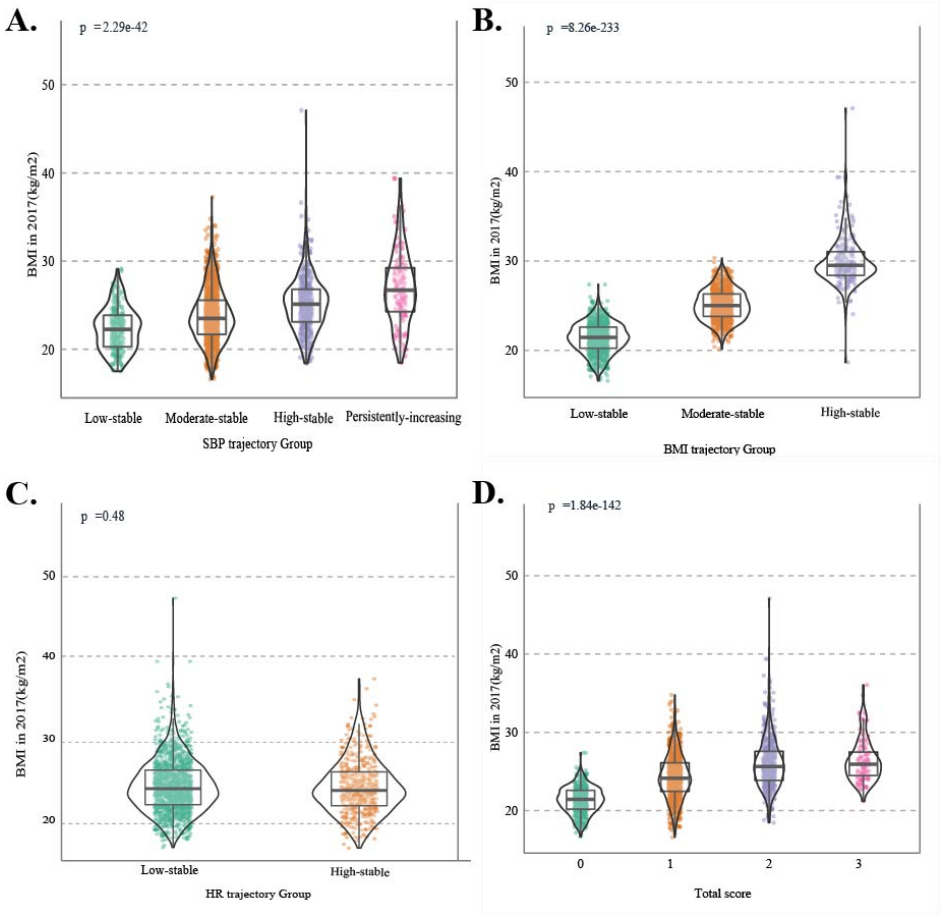

Figure S2. Distribution of BMI in 2017 among different trajectory and risk score groups. (A, SBP trajectory group; B, BMI trajectory group; C, HR trajectory group; D, Total score group) SBP, systolic blood pressure; BMI, body mass index; HR, heart rate. Boxplots indicate the median, first, and third quartiles.

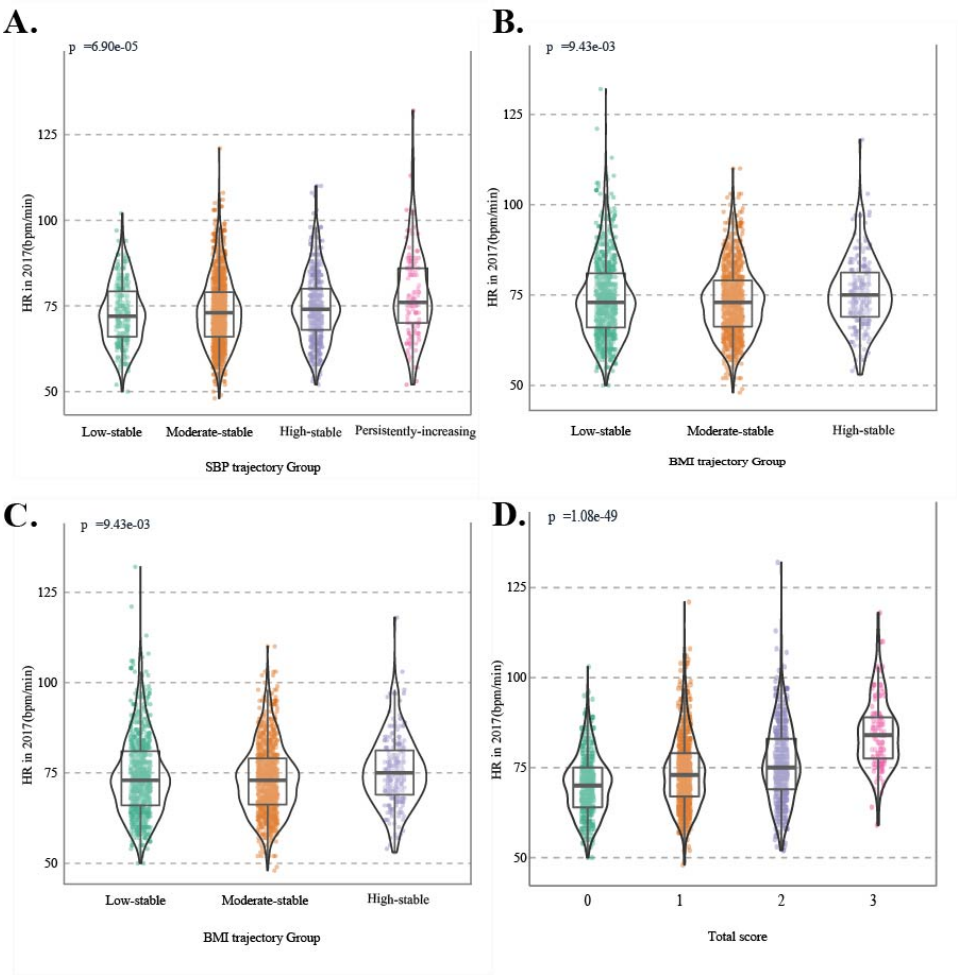

Figure S3. Distribution of HR in 2017 among different trajectory and risk score groups. (A, SBP trajectory group; B, BMI trajectory group; C, HR trajectory group; D, Total score group) SBP, systolic blood pressure; BMI, body mass index; HR, heart rate. Boxplots indicate the median, first, and third quartiles.

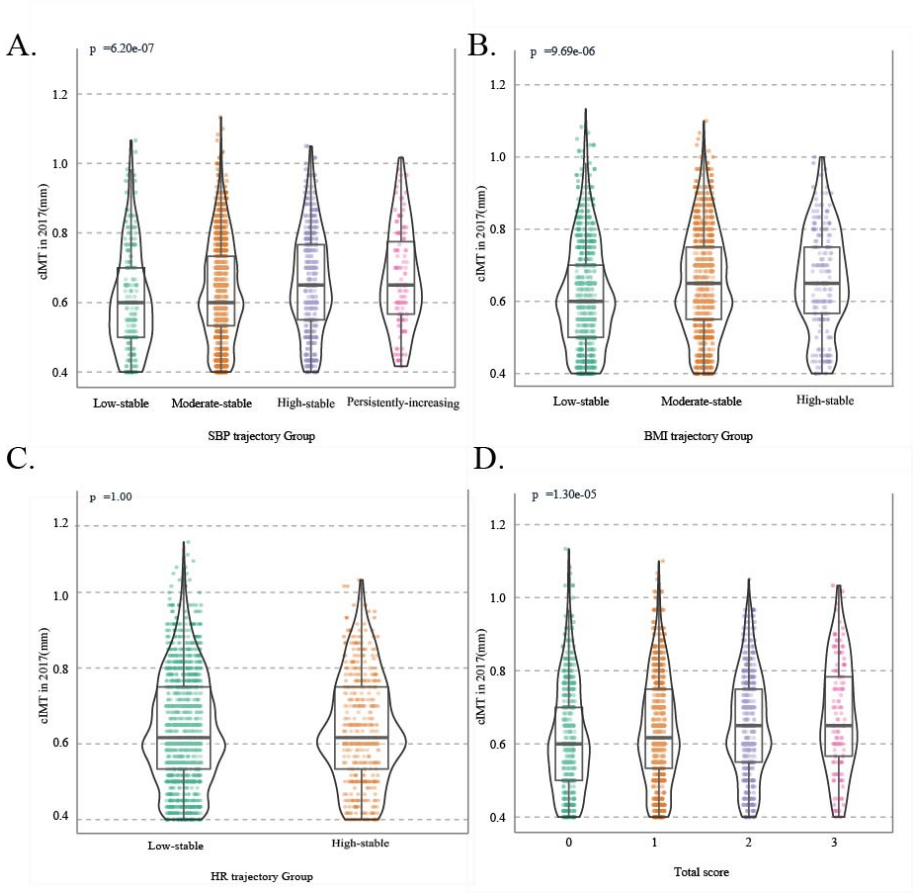

Figure S4. Distribution of cIMT in 2017 among different trajectory and risk score groups. (A, SBP trajectory group; B, BMI trajectory group; C, HR trajectory group; D, Total score group) SBP, systolic blood pressure; BMI, body mass index; HR, heart rate; cIMT, carotid intima-media thickness. Boxplots indicate the median, first, and third quartiles.

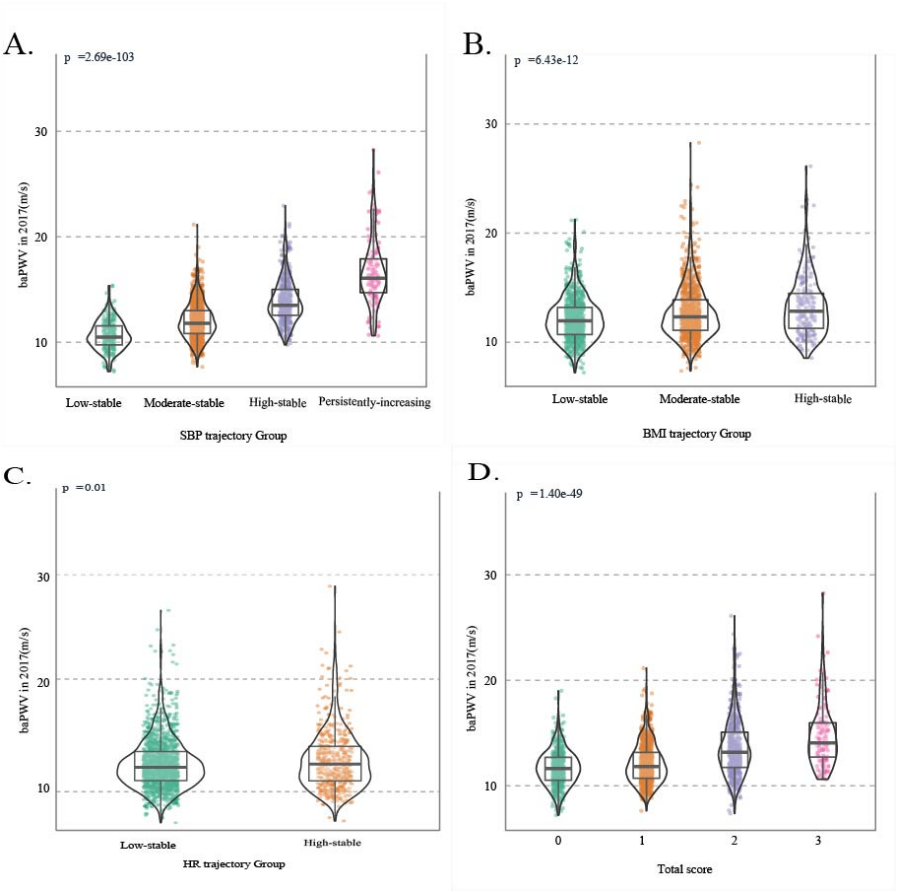

Figure S5. Distribution of baPWV in 2017 among different trajectory and risk score groups. (A, SBP trajectory group; B, BMI trajectory group; C, HR trajectory group; D, Total score group) SBP, systolic blood pressure; BMI, body mass index; HR, heart rate; baPWV, brachial-ankle pulse wave velocity. Boxplots indicate the median, first, and third quartiles.