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ORIGINAL RESEARCH

Association of Vascular Aging With Cardiovascular Disease in Middle-Aged Chinese People

A Prospective Cohort Study

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ABSTRACT

BACKGROUND Whether middle-aged individuals with a greater difference between chronological age and vascular age show a lower cardiovascular disease risk remains to be clarified.

OBJECTIVES This study sought to examine whether individuals with supernormal vascular aging (VA) have a lower cardiovascular disease risk than do individuals with normal VA.

METHODS This prospective cohort study included 20,917 middle-aged (40-60 years) participants from the Kailuan Study. VA was defined as the predicted age in a multivariate regression model, including classic cardiovascular risk factors and pulsed wave velocity. The chronological age minus the VA was defined as the Δ-age, and the 10th and 90th percentiles of the Δ-age were used as cutoffs to define early VA and supernormal VA, respectively. The outcome was a composite of myocardial infarction, hospital admission for heart failure, and stroke. The study used Cox proportional hazards regression to examine the association between the VA categories and the incident cardiovascular outcome.

RESULTS During the median 4.6-year follow-up period, 584 endpoint events were observed. After adjusting for potential variables, when compared with the normal VA group, the supernormal VA group had a decreased rate of cardiovascular events (HR: 0.47; 95% CI: 0.35-0.64), and the early VA group had an increased rate (HR: 1.90; 95% CI: 1.22-2.95) of cardiovascular events.

CONCLUSIONS Individuals with supernormal VA are at a lower risk of cardiovascular events, and individuals with early VA are at a higher risk of cardiovascular events than individuals with normal VA. Further characterization may provide novel insight into future preventive strategies against cardiovascular disease. (JACC: Asia 2023;3:895-904) © 2023 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/).

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ABBREVIATIONS AND ACRONYMS

Δ-age = chronological age minus vascular age

ASCVD = atherosclerotic cardiovascular disease

baPWV = brachial-ankle pulsed wave velocity

cfPWV = carotid femoral pulsed wave velocity

HVA = healthy vascular aging

PWV = pulsed wave velocity

VA = vascular aging

Cardiovascular disease is an important global public health problem, and it is a leading cause of morbidity and mortality.[1] The Framingham Heart Study identified several risk factors for cardiovascular disease and developed the first coronary heart disease risk equations in 1976.[2] Since then, several tools that are based on the predicted risk of cardiovascular disease have been published and are used to guide clinical practice to identify individuals at low, intermediate, and high cardiovascular risk.[3-7] However, these tools were all derived from Western populations, thus limiting their applicability in Asian populations.[7,8]

Chronological age is a heavily weighted variable in most risk scores using traditional risk factors. However, there is significant heterogeneity in cardiovascular disease risk for persons of the same chronological age. In fact, young subjects with a significant elevated risk factor burden are still likely to have a low cardiovascular risk score. Vascular age is a means of expressing cardiovascular risk as an age. It is thought to improve the risk prediction of cardiovascular events and may contribute to a better understanding of cardiovascular risk, which could then be identified early in individuals who present with an abnormally high cardiovascular risk for their age and sex.

Previous studies demonstrated that vascular age is more useful than estimated cardiovascular risk score in young subjects with a low estimated cardiovascular risk score.[9,10] Furthermore, a previous study indicated that early vascular aging (VA) improves the risk prediction of cardiovascular events beyond traditional cardiovascular risk factors.[11] However, some individuals show an abnormally low cardiovascular risk for their age, and this represents the opposite extreme phenotype, recently identified as supernormal VA. Recent results from an older adult cohort study, which was the first study to validate the clinical relevance of supernormal VA, indicated that compared with patients with normal VA, patients with supernormal VA were at a lower risk of cardiovascular events; whereas patients with early VA were at a higher risk of cardiovascular events.[12] However, such investigations remain to be carried out in middle-aged populations.

In the present study, which is based on a community population in China, we examined whether, despite exposure to several cardiovascular risk factors, VA can predict cardiovascular risk. We also aimed to confirm whether patients with supernormal VA are at a lower cardiovascular risk than their chronological age and are thus protected against the deleterious effects of age and cardiovascular risk factors.

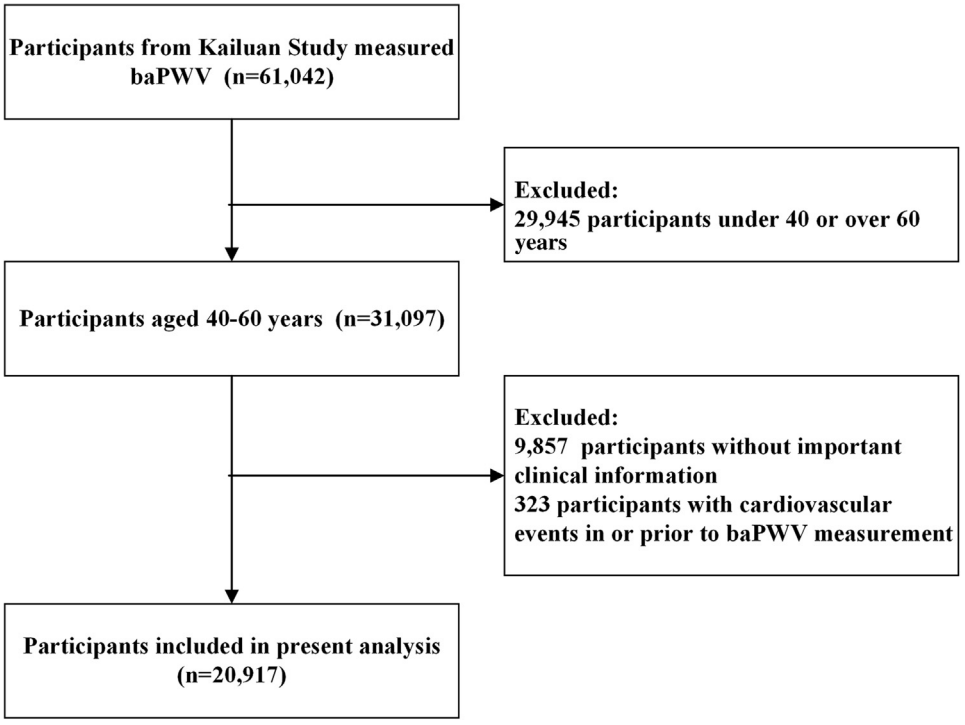
METHODS

STUDY DESIGN AND PARTICIPANTS. The Kailuan Study is an ongoing, population-based, prospective cohort study.[13] Participants aged ≥18 years were included in the first survey (2006) from the Kailuan community in Tangshan, China.[13] The details of the Kailuan Study design have been described previously.[14] The participants have undergone face-to-face questionnaires, physical examinations, and laboratory assessments at the 11 local hospitals every 2 years since the first survey. Since the third survey in 2010, the participants who consented to join nested studies on vascular health underwent brachial-ankle pulsed wave velocity (baPWV) measurements to assess the health status of their artery walls.[15,16] A total of 31,097 participants aged 40 to 60 years who underwent at least 1 baPWV survey from March 1, 2010 to December 31, 2019 were included. After excluding 1,937 participants without synchronized clinical data and 8,243 participants with previous cardiovascular disease before baPWV measurement, a total of 20,917 participants were enrolled in the final analysis (**Figure 1**). All participants were followed up until their death or December 31, 2019, whichever came first. The study was approved by the Ethics Committees of both Kailuan General Hospital and Beijing Tiantan Hospital (Beijing, China), and written informed consent was obtained from all participants.

VASCULAR AGE MODELING. VA was defined as the predicted age in a multivariate regression model, including classic cardiovascular risk factors and baPWV. Variable selection was made by backward stepwise approach. Moreover, the variables showing a nonlinear relationship with age were transformed by smoothing splines (generalized additive models). The final models included waist circumference, treated or untreated systolic blood pressure, diastolic blood pressure, total cholesterol concentration, high-density lipoprotein cholesterol concentration, fasting plasma glucose concentration, and baPWV. The classic parameters of equations with coefficients of parameters for linear regression are shown in Supplemental Table 1.

EARLY VA AND SUPERNORMAL VA DEFINITIONS. The difference between chronological age and VA is denoted as Δ-age. The 10th and 90th percentiles of Δ-age were used as cutoffs to define early VA and

FIGURE 1 Study Flowchart



A total of 31,097 participants from Kailuan Study aged 40 to 60 years with at least 1 brachial-ankle pulsed wave velocity (baPWV) survey from March 1, 2010 to December 31, 2019 were included. After excluding 1,937 participants without synchronized clinical information data and 8,243 participants with previous cardiovascular disease before brachial-ankle pulsed wave velocity measurement, a total of 20,917 participants were enrolled in the final analysis.

supernormal VA, respectively.[12] Values between the 10th and 90th percentiles of Δ-age were defined as normal VA. The proportions of healthy VA (HVA)[17] and the atherosclerotic cardiovascular disease (ASCVD) score[3] were compared among the 3 VA groups (normal VA, early VA, supernormal VA). On the basis of previous research in this population, HVA was defined as a low baPWV (baPWV lower than the upper quartile value) and normotensive blood pressure (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, and absence of antihypertensive drugs). The ASCVD risk prediction equations were developed from sex-specific Cox proportional hazards models that included the covariates of age, waist circumference, geographic region, urbanization, family history of ASCVD, treated or untreated systolic blood pressure, total cholesterol concentration, high-density lipoprotein cholesterol concentration, current smoking status, and history of diabetes mellitus. The foregoing values were multiplied by the coefficients from the sex-specific equations, and the sum of coefficient × value was calculated for the individual sum. The individual sum was included in the sex formula to calculate the individual ASCVD risk score.

OUTCOME ASCERTAINMENT. The primary outcome in the present study was a composite cardiovascular endpoint consisting of myocardial infarction, hospital admission for heart failure, and stroke.[18,19] The outcome adjudication was available from baseline through December 31, 2019. To retrieve potential events, the subjects were linked to the Municipal Social Insurance and Hospital Discharge Register. All medical records, including from emergency department visits and local hospitalizations, were collected and adjudicated centrally. Stroke was defined according to the World Health Organization's criteria on the basis of clinical symptoms, images obtained by computed tomography or magnetic resonance imaging, and other diagnostic reports.[20]

Stroke included ischemic stroke, hemorrhagic stroke, and unspecified stroke. Myocardial infarction was defined on the basis of cardiac enzyme concentrations, symptoms, electrocardiographic signs, and necropsy.[21] Hospital admission for heart failure was defined in accordance with the criteria of the European Society of Cardiology on the basis of clinical symptoms, echocardiography, chest radiography, and electrocardiography.[22] The composite cardiac events included myocardial infarction and hospital admission for heart failure. All-cause mortality was confirmed by certificates reviewed by the study clinicians from vital statistics offices.[23] The secondary outcomes included stroke, cardiac events, all-cause mortality, ischemic stroke, hemorrhagic stroke, myocardial infarction, and hospital admission for heart failure.

DATA COLLECTION. In the Kailuan Study, all participants completed a questionnaire to evaluate demographics, socioeconomic parameters, lifestyle habits, and medical history. Current smoking was defined as smoking for at least the past year. Current alcohol intake was defined as consumption of an alcoholic beverage once or more in the past year. Physical activity was classified as inactive (0 min), moderately active (1-79 minutes), or very active (≥80 minutes) according to the duration of moderate or vigorous activity per week. The use of medication within the 2 weeks before the baseline interview was collected by self-reporting. The anthropometric measurements included height and weight, and body mass index was calculated as weight in kilograms divided by height in meters squared.

Blood pressure was measured using a manual sphygmomanometer and an electronic blood pressure meter (HEM-8102A, Omron Limited).[24] At least 2 readings of systolic blood pressure and diastolic blood pressure were taken after the participants had rested in the seated position for at least 5 minutes. If the 2 measurements differed by more than 5 mm Hg, a third measurement was obtained. The average blood pressure value was used for the analysis.

baPWV was measured using the BP-203RPE III automatic waveform analyzer (Colin Co), which simultaneously records pulsed wave velocity (PWV), blood pressure, electrocardiography, and heart sounds following standard operating procedures, as detailed elsewhere.[25] Briefly, the participants were asked to lie down and keep quiet during the measurement. Electrocardiographic electrodes were placed on both wrists, a microphone was placed on the left edge of the sternum, and pneumatic cuffs were placed on the brachia and ankles. The semiconductor pressure sensor was used to measure the pulsed volume waveforms. Measurement was repeated twice for each subject, and the second measurement was used as the final reading. The maximum baPWV on the left and right sides was used for the analysis.

Fasting blood samples were collected from the antecubital vein in the morning after an overnight fast (8-12 hours). All plasma samples were analyzed using an automatic analyzer (Hitachi 747, Hitachi)[26] at the central laboratory of Kailuan Hospital. The fasting plasma glucose concentration was also measured using an automatic analyzer (Hitachi 747). The total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations were measured with the enzymatic colorimetric method.

STATISTICAL ANALYSES. The baseline characteristics of the participants are presented as the mean ± SD, median (IQR), or frequency (percentage). Missing values were not imputed in statistical analyses. The baseline characteristics were compared among the 3 VA categories (early VA, normal VA, and supernormal VA) by using the analysis of variance or Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables. To evaluate the balance of baseline characteristics among the 3 VA categories, the maximum absolute standardized difference was calculated for each covariate. An absolute standardized difference of ≤0.1 indicated a negligible difference in a certain covariate among the 3 groups.

We performed progressively adjusted Cox proportional hazards regression to examine the hazard for incident cardiovascular events by VA category, with normal VA as the reference group. The validity of the proportionality assumption was verified by scaled Schoenfeld residuals for the VA category, the results of which suggested that the assumptions were not violated (Supplemental Table 2). We fitted 3 models to systematically adjust for potential confounding variables. Model 1 included adjustment for chronological age (continuous) and sex (categorical; male vs female). Model 2 included adjustment for all of the covariates in model 1 in addition to current alcohol consumption (categorical; current drinker vs not), physical activity (categorical; inactive vs active), body mass index (continuous), and low-density lipoprotein cholesterol (continuous; mmol/L). Model 3 was further adjusted for model 1 in addition to the ASCVD risk score (continuous; from the China-PAR Project [Prediction for ASCVD Risk in China]).

To examine the association between Δ-age and cardiovascular disease further, we performed a

TABLE 1 Characteristics of Groups With Early, Normal, or Supernormal VA

	Overall Population (N = 20,917)	Early VA (n = 2,091, 10.0%)	Normal VA (n = 16,734, 80.0%)	Supernormal VA (n = 2,092 (10.0%)	*P* Value	ASD
Chronological age, y	49.0 (45.0-53.0)	41.0 (40.0-42.0)	49.0 (46.0-52.0)	57.0 (56.0-59.0)	<0.001	4.825
Vascular age, y	48.8 (47.8-50.0)	49.1 (48.2-50.2)	48.8 (47.7-50.0)	48.8 (47.8-50.0)	<0.001	0.194
Δ-age, y	−0.05 (−3.6 to 3.6)	−7.6 (−8.5 to −6.9)	−0.05 (−2.8 to 2.8)	7.9 (7.0-9.1)	<0.001	6.195
baPWV, m/s	14.4 (12.9-16.2)	14.8 (13.4-16.4)	14.3 (12.8-16.2)	14.2 (12.8-15.9)	<0.001	0.158
Male	15,195 (72.6)	1,729 (82.7)	11,974 (71.6)	1,492 (71.3)	<0.001	0.182
Current smoker	6,960 (33.3)	738 (35.3)	5,572 (33.3)	650 (31.1)	0.01	0.060
Current alcohol use	6,833 (32.7)	728 (34.8)	5,498 (32.9)	607 (29.0)	<0.001	0.083
Physical activity	12,593 (60.2)	1,233 (59.0)	10,162 (60.7)	1,198 (57.3)	0.005	0.047
BMI, kg/m^2	24.8 (22.9-27.2)	25.4 (23.4-27.7)	24.8 (22.9-27.1)	24.8 (22.6-27.0)	<0.001	0.153
WC, cm	87.0 (80.0-93.0)	88.0 (83.0-94.0)	87.0 (80.0-93.0)	87.0 (80.0-93.0)	<0.001	0.147
SBP, mm Hg	130.0 (120.0-140.7)	131.7 (121.7-142.7)	130.0 (120.0-140.7)	130.0 (120.0-140.0)	<0.001	0.128
DBP, mm Hg	82.0 (76.7-90.0)	83.0 (78.0-90.0)	82.0 (76.7-90.0)	81.7 (76.0-90.0)	<0.001	0.080
FBG, mmol/L	5.4 (4.9-5.9)	5.4 (5.0-6.0)	5.4 (4.9-5.9)	5.3 (4.9-5.8)	<0.001	0.085
LDL-C, mmol/L	2.7 (2.3-3.3)	2.9 (2.4-3.4)	2.7 (2.3-3.3)	2.7 (2.2-3.3)	<0.001	0.076
HDL-C, mmol/L	1.4 (1.2-1.7)	1.4 (1.2-1.6)	1.4 (1.2-1.7)	1.4 (1.2-1.7)	<0.001	0.032
TG, mmol/L	1.4 (0.9-2.1)	1.5 (1.0-2.4)	1.3 (0.9-2.1)	1.3 (0.9-1.9)	<0.001	0.139
TC, mmol/L	5.0 (4.4-5.6)	5.1 (4.4-5.7)	5.0 (4.4-5.6)	5.0 (4.4-5.6)	<0.001	0.043
Hypoglycemic medication	531 (2.5)	70 (3.3)	428 (2.6)	33 (1.6)	0.001	0.077
Antihypertensive medication	1,897 (9.1)	202 (9.7)	1,536 (9.2)	159 (7.6)	0.04	0.049
Lipid-lowering medication	163 (0.8)	24 (1.1)	119 (0.7)	20 (1.0)	0.06	0.030
HVA	3,900 (18.7)	215 (10.3)	3,314 (19.8)	371 (17.7)	<0.001	0.179
ASCVD score, %	3.6 (1.8-6.4)	2.3 (1.3-3.9)	3.5 (1.8-6.3)	5.9 (3.8-8.6)	<0.001	0.523

Values are median (IQR) or n (%).

Δ-age = chronological age minus vascular age; ASCVD = atherosclerotic cardiovascular disease; ASD = absolute standard difference; baPWV = brachial-ankle pulsed wave velocity; BMI = body mass index; DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; HVA = healthy vascular aging; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride, VA = vascular aging; WC = waist circumference.

restricted cubic spline with 5 knots (at the 5th, 25th, 50th, 75th, and 95th percentiles). This restricted cubic spline was adjusted for age and sex. As an additional analysis, the associations between Δ-age as a continuous variable and outcomes were computed by Cox proportional hazards regression using the same set of covariates.

Finally, we used the C-statistic, integrated discrimination improvement, and net reclassification index to evaluate the incremental predictive value of VA and baPWV beyond the ASCVD risk score.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc). Statistical significance was defined as a 2-sided *P* value of <0.05.

RESULTS

BASELINE CHARACTERISTICS. Early VA was defined when the vascular age was greater than the chronological age of 5.7 years or more (Δ-age <-5.7 years), and supernormal VA was defined when the vascular age was lower than the chronological age of 6.2 years or more (Δ-age >6.2 years). The clinical characteristics of the patients in the 3 VA categories (early VA, normal VA, and supernormal VA) are shown in Table 1. Individuals with early VA were significantly younger and individuals with supernormal VA were significantly older than individuals with normal VA. Participants in the early VA group tended to be male, more frequently current smokers and drinkers, and more frequently obese with a higher body mass index and a larger waist circumference. Similarly, individuals in the early VA group had higher baPWV, systolic blood pressure, and diastolic blood pressure, as well as less blood pressure-lowering drug use, than the normal VA group and the supernormal VA group. Furthermore, the percentage of individuals with HVA and an ASCVD risk score was lower in the early VA group and higher in the supernormal VA group than in the normal VA group, and this finding was driven by differences in chronological age among the groups.

RISK OF CARDIOVASCULAR EVENTS IN THE EARLY VA AND SUPERNORMAL VA GROUPS. During the median follow-up period of 4.6 years (IQR: 2.6-8.01 years), 584 (2.8%) incident cardiovascular events were identified, of which 390 (1.9%) were total stroke (353 ischemic stroke, 34 hemorrhagic stroke) and 206 (1.0%) were cardiac events (88 myocardial infarction, 131 heart failure), and 236 participants (1.1%) died.

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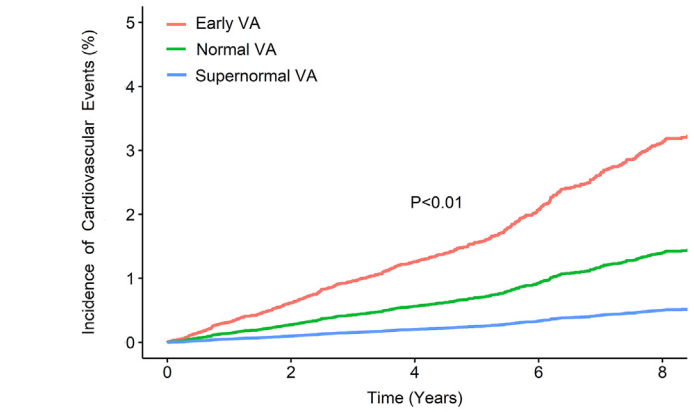
DECEMBER 2023:895–904

FIGURE 2 Cumulative Incidence of Cardiovascular Events Stratified by Vascular Aging Categories



Early VA	2091	1704	1009	451	309
Normal VA	16734	14701	10246	6530	4326
Supernormal VA	2092	1767	1243	891	649

The endpoint of cardiovascular events was a composite of myocardial infarction, hospital admission for heart failure, and stroke. Estimated cumulative cardiovascular events were stratified by vascular aging (VA) categories from multivariable Cox proportional hazards regressions after adjustments for age and sex.

The participants in the early VA group experienced a higher risk of cardiovascular events than the participants in the other groups during the follow-up period ($P < 0.01$) (**Figure 2**). After adjusting for potential confounding variables, when compared with the normal VA group, the participants in the supernormal VA group had a decreased rate of cardiovascular events (HR: 0.47; 95% CI: 0.35-0.64), and the early VA group had an increased rate of cardiovascular events (HR: 1.90; 95% CI: 1.22-2.95) (**Table 2**). After multivariate adjustment, the HRs for stroke were 0.43 (95% CI: 0.30-0.62) for supernormal VA and 1.96 (95% CI: 1.19-3.22) for early VA. Similar results were observed for ischemic stroke and hemorrhagic stroke (Supplemental Table 3).

After multivariate adjustment, the HRs for cardiac events were 0.52 (95% CI: 0.32-0.86) for supernormal VA and 1.65 (95% CI: 0.65-4.19) for early VA. In the multivariate model, the HRs for all-cause mortality were 0.65 (95% CI: 0.42-0.99) for supernormal VA and 1.30 (95% CI: 0.63-2.68) for early VA (**Table 2**). A similar pattern was observed for the outcomes of myocardial infarction and heart failure (Supplemental Table 3). Sensitivity analyses excluding incident cardiovascular events within the first 2 visits (n = 2,805) with the Cox proportional hazards model yielded similar results (Supplemental Table 4).

ADDITIONAL ANALYSES. As a continuous variable, Δ-age was significantly associated with the main outcome of cardiovascular events in the fully adjusted model (HR: 0.74; 95% CI: 0.71-0.78). A 1-year difference between chronological age and vascular age (Δ-age) was associated with 26% fewer total strokes, 23% fewer cardiac events, and 18% fewer all-cause mortalities (Supplemental Table 5). The results did not change for the other secondary outcomes (Supplemental Table 6).

Using the restricted cubic spline analysis, an L-shaped association was observed between Δ-age and cardiovascular events. A chronological age greater than the vascular age decreased the cardiovascular risk, whereas a chronological age less than the vascular age increased the cardiovascular risk (Supplemental Figure 1).

INCREMENTAL PREDICTIVE VALUE OF VASCULAR AGE. We evaluated whether vascular age would increase the predictive value of conventional risk factors (**Table 3**). With cardiovascular events as the outcome of interest, the C-statistic of the conventional model did significantly improve with the addition of baPWV (difference in C-statistic: 0.045; 95% CI: 0.033-0.058; $P < 0.001$) and vascular age (difference in C-statistic: 0.048; 95% CI: 0.033-0.062; $P < 0.001$). The discriminatory power and risk reclassification were substantially better with the addition of vascular age (integrated discrimination improvement: 0.84%; $P < 0.001$; continuous net reclassification index: 41.64%; $P < 0.001$). Similar results were observed for the secondary outcomes.

DISCUSSION

This prospective study showed that compared with individuals with normal VA, those with supernormal VA had a decreased cardiovascular risk and those with early VA had an increased cardiovascular risk (**Central Illustration**). A vascular age 1 year lower than the chronological age was associated with a 26% reduction in the age- and sex-adjusted rate of cardiovascular events. Further analysis showed that conventional risk factors with the addition of vascular age had higher predictive value for cardiovascular events. This study is the first to validate the clinical risk of cardiovascular disease in individuals with early VA and individuals with supernormal VA in a middle-aged population on the basis of prospective data.

TABLE 2 HRs for VA Categories for Clinical Events

	VA Categories	Model 1	Model 2	Model 3
Cardiovascular events	Supernormal VA	0.42 (0.32-0.57)	0.45 (0.34-0.60)	0.47 (0.35-0.64)
	Normal VA	Reference	Reference	Reference
	Early VA	2.12 (1.37-3.30)	1.94 (1.25-3.01)	1.90 (1.22-2.95)
Stroke	Supernormal VA	0.38 (0.27-0.55)	0.41 (0.28-0.58)	0.43 (0.30-0.62)
	Normal VA	Reference	Reference	Reference
	Early VA	2.19 (1.33-3.61)	2.02 (1.23-3.32)	1.96 (1.19-3.22)
Cardiac events	Supernormal VA	0.48 (0.29-0.78)	0.51 (0.31-0.84)	0.52 (0.32-0.86)
	Normal VA	Reference	Reference	Reference
	Early VA	1.82 (0.72-4.63)	1.64 (0.64-4.16)	1.65 (0.65-4.19)
All-cause mortality	Supernormal VA	0.57 (0.37-0.86)	0.58 (0.38-0.89)	0.65 (0.42-0.99)
	Normal VA	Reference	Reference	Reference
	Early VA	1.48 (0.72-3.07)	1.43 (0.69-2.95)	1.30 (0.63-2.68)

Values are HR (95% CI). Model 1: Adjusted for age and sex. Model 2: Model 1 plus body mass index, alcohol consumption, physical activity, and low-density lipoprotein cholesterol at baseline. Model 3: Model 1 plus atherosclerotic cardiovascular disease score at baseline.

VA = vascular aging.

Cardiovascular disease and mortality increase exponentially with age, yet substantial heterogeneity exists among individuals in terms of the extent to which age affects outcomes. Thus, vascular age needs to be defined in a way that encompasses the complex processes that occur with age at the organ, tissue, and cellular levels. Vascular age more accurately reflects structural and functional changes than chronological age, thereby leading to a better understanding of the level of risk and predicting health outcomes.[27] A randomized trial showed that informing patients about their cardiovascular risk on the basis of the Heart Age tool resulted in a greater reduction in cardiovascular risk than was observed when the Framingham REGICOR risk score was used.[28] In addition, vascular age fairly reflects individual cardiovascular risk, especially in young and middle-aged individuals whose10-year risk is inherently low because of their age.

PWV is a commonly used surrogate marker of arterial stiffness and may be considered a physiologic method for quantifying VA.[29,30] PWV increases with age, and an excessive increase in PWV at any age is associated with adverse outcomes.[11,31] HVA is associated with normal blood pressure and lower carotid artery stiffness.[32] According to the definition

TABLE 3 Reclassification and Discrimination Statistics for Outcomes by baPWV and Vascular Age

	Difference in C-Statistic		IDI		NRI (Continuous)	
	Estimate (95% CI)	*P* Value	Estimate (95% CI), %	*P* Value	Estimate (95% CI), %	*P* Value
Cardiovascular events						
Conventional model[a]	Reference		Reference		Reference	
Conventional model + baPWV	0.045 (0.033-0.058)	<0.001	0.89 (0.56-1.22)	<0.001	35.78 (27.59-44.00)	<0.001
Conventional model + vascular age	0.048 (0.033-0.062)	<0.001	0.84 (0.62-1.07)	<0.001	41.64 (33.50-49.77)	<0.001
Stroke						
Conventional model	Reference		Reference		Reference	
Conventional model + baPWV	0.060 (0.043-0.077)	<0.001	0.80 (0.53-1.07)	<0.001	44.43 (34.47-54.39)	<0.001
Conventional model + vascular age	0.052 (0.034-0.071)	<0.001	0.56 (0.38-0.74)	<0.001	46.14 (36.28-56.00)	<0.001
Cardiac events						
Conventional model	Reference		Reference		Reference	
Conventional model + baPWV	0.016 (0.004-0.028)	0.007	0.20 (-0.02-0.42)	0.08	14.55 (9.00-28.21)	<0.001
Conventional model + vascular age	0.032 (0.013-0.051)	<0.001	0.33 (0.16-0.50)	<0.001	31.71 (18.03-45.39)	<0.001
All-cause mortality						
Conventional model	Reference		Reference		Reference	
Conventional model + baPWV	0.017 (−0.001 to 0.034)	0.06	0.30 (0.15-0.46)	<0.001	20.23 (7.44-33.02)	0.002
Conventional model + vascular age	0.020 (0.003-0.038)	0.02	0.14 (0.05-0.23)	0.002	26.94 (14.14-39.74)	<0.001

Values are difference in C-statistic, IDI, and NRI. [a]Conventional model: age, sex, and atherosclerotic cardiovascular disease score at baseline.

baPWV = brachial-ankle pulsed wave velocity; IDI = integrated discrimination improvement; NRI = net reclassification index.

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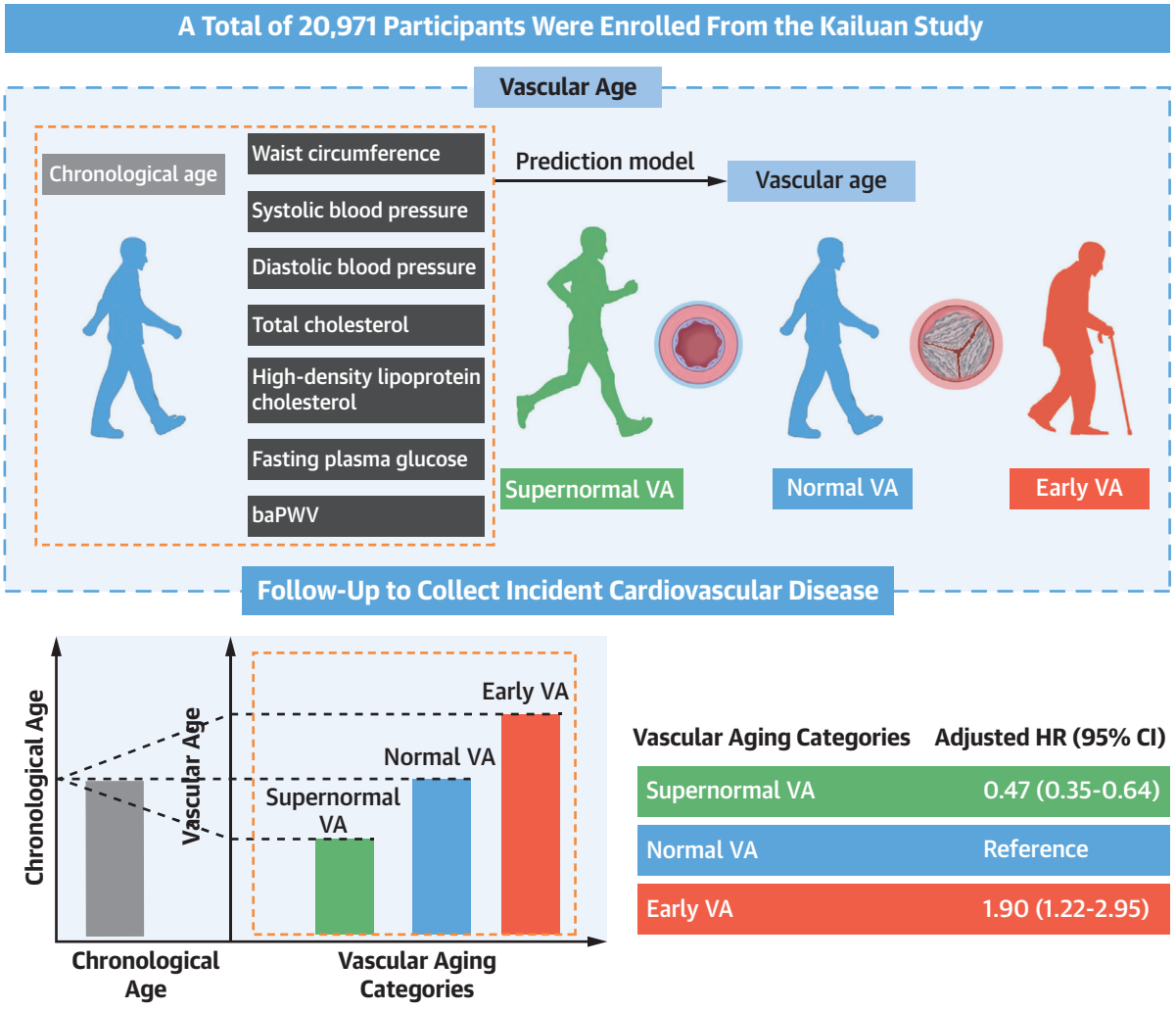
CENTRAL ILLUSTRATION Study Hypothesis



Zuo Y, et al. JACC: Asia. 2023;3(6):895-904.

Vascular age was defined as the predicted age in a multivariable regression model, including classic cardiovascular risk factors and brachial-ankle pulsed wave velocity (baPWV). For a substantially similar vascular age, individuals with early vascular aging (VA) are younger and supernormal vascular aging are older than the normal vascular aging group. Supernormal vascular aging participants had a lower rate of cardiovascular disease, and early vascular aging participants had a higher rate.

of HVA proposed in the Framingham Study, having healthy arteries and a normal blood pressure is possible, and it is the optimal cardiovascular risk profile.[33] Several studies have reported associations between HVA and a lower risk of cardiovascular events,[33] stroke,[17] and subclinical atherosclerosis.[34] Achieving HVA may be an important clinical goal for preventing age-related cardiovascular risk. However, little attention has been paid to the study of persons with very low PWV values. Very low PWV values, which are thought to be protective against cardiovascular risk, are considered supernormal VA.

Individuals with supernormal VA have abnormally healthy arteries, as identified by their chronological age and cardiovascular risk factor burden. These individuals show a reduced risk of cardiovascular events. A recent study represented the first validation of the clinical significance of the supernormal VA concept, in which determinant factors included normal blood pressure, PWV, and other lifestyle biomarkers, on the basis of data from a prospective older

adult cohort.[12] The main finding was that persons with supernormal VA showed an age- and sex-adjusted rate of cardiovascular events that was approximately 40% lower than in individuals with normal VA. However, this finding needs to be verified in other populations to broaden the applicability of this concept. Indeed, our study, which was performed in a large Chinese middle-aged cohort, showed that subjects with supernormal VA had a 53% lower risk of cardiovascular events than individuals with normal VA.

STUDY STRENGTHS. First, it is a prospective study with a large sample size and a long follow-up period. Second, sociodemographic, clinical, and lifestyle factors were collected through a well-established questionnaire, whereas blood pressure and baPWV values were measured using standardized and unified methods. Finally, several sensitivity analyses were conducted, and the results of the sensitivity analyses were consistent with the main analyses, thereby strengthening the conclusions and credibility of our findings.

STUDY LIMITATIONS. First, we used the baPWV instead of the carotid-femoral PWV (cfPWV). The cfPWV is the gold standard; however, many studies have reported that baPWV is well associated with cfPWV. Second, predicting the VA phenotype may be affected by unmeasured variables or extreme values. This error was minimized by data cleaning, and outlier removal had already been performed. Third, the Kailuan Study included mostly men (72.6%). We thus did not have enough statistical power to establish a sex-stratified equation and detect sex differences. Furthermore, our findings could not be generalized to other populations because the current study included only middle-aged Chinese adults. More studies, including young adults and different ethnic groups, are needed to confirm our findings. Finally, the cutoffs for early VA and supernormal VA were defined by our middle-aged cohort. Therefore, future studies are needed to validate the findings in other middle-aged cohorts to broaden the applicability of these cutoff values.

CONCLUSIONS

Our community-based middle-aged population study showed that individuals with a vascular age ≥6 years lower than their chronological age (the supernormal VA phenotype) showed an adjusted rate of cardiovascular events that was approximately 53% lower than individuals with normal VA. In addition, VA performed better than baPWV in predicting cardiovascular disease, a finding that provides novel insight into future preventive strategies against cardiovascular disease. Furthermore, the use of VA classification may help to identify individuals who are at a premature risk of cardiovascular events as a result of nonconventional cardiovascular risk factors.

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PERSPECTIVES

COMPETENCY IN PROFESSIONALISM: Our present findings emphasized the importance of VA in the development of cardiovascular disease. Individuals who presented with an abnormally high cardiovascular risk for their age and sex were identified as having early VA, whereas persons with an abnormally low cardiovascular risk for their age and sex were identified as having supernormal VA. Compared with individuals with normal VA, individuals with supernormal VA were at a lower risk of cardiovascular events, whereas individuals with early VA were at a higher risk of cardiovascular events.

TRANSLATIONAL OUTLOOK: VA performed better than conventional cardiovascular risk factors and baPWV in predicting cardiovascular disease, and this finding provides novel insight into future preventive strategies against cardiovascular disease.

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KEY WORDS cardiovascular disease, prospective cohort study, risk factors, vascular aging

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