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ORIGINAL RESEARCH

Association of Vascular Aging Phenotypes with Adverse Clinical Outcomes in the Chinese Population: A Multicentre Study

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Purpose: This study aimed to investigate the clinical implications of vascular aging (VAg) phenotypes based on the difference between chronological age (CA) and vascular age (VA).

Patients and Methods: We defined VA as the predicted age in a multivariable linear regression model including structural and functional parameters of arteries and conventional risk factors, in a multicentric, cross-sectional cohort (n=15580). According to the 10th and 90th percentiles of Δ-age (CA minus VA), we then classified the status of VAg into 3 phenotypes: the early VAg (EVA), the Normal VAg and the supernormal VAg (SUPERNOVA). We used Cox survival analysis to investigate the association between VAg phenotypes and the risk for adverse clinical outcomes (including all-cause death and cardiovascular disease) in an independent, prospective cohort (n=5316).

Results: In the prospective cohort (11.07 years, 927 events), when compared to the Normal VAg phenotype, EVA had an increased risk (HR: 2.43; 95% CI: 1.80–3.27) and SUPERNOVA had a decrease risk (HR: 0.75; 95% CI: 0.64–0.90) of adverse clinical outcomes, in particular stroke events. EVA also showed a higher risk of myocardial infarction (HR: 3.21, 95% CI: 1.56–6.62) and all-cause death (HR: 1.79, 95% CI: 1.12–2.85). The associations were independent of the atherosclerotic cardiovascular disease risk score. Further, the C-statistics increased 0.010 ($P < 0.001$), 0.013 ($P < 0.001$) and 0.016 ($P < 0.001$) separately when adding baPWV, adding the combination of baPWV and CIMT, and adding the VAg phenotypes to a model of conventional risk factors in predicting cardiovascular events.

Conclusion: This is the first study to evaluate the clinical implications of VAg phenotypes using multicentric data and undergone external validation in China. Our results emphasized that the classification of VAg phenotypes may be a potential tool to identify individuals who were susceptible to or resilient to VAg.

Keywords: age-related disease, carotid intima-media thickness, pulse wave velocity, risk assessment, vascular age, vascular aging

Introduction

Vascular aging (VAg) is characterized by accumulation of age-dependent structural and functional changes of vessels over the life course[1,2] and is a driver of age-related disease and mortality.[3] It is considered that the deteriorations of vascular system over time lead to the genesis of microvascular and macrovascular pathologies, which have deleterious effects on multiple organ functions, and ultimately contribute to many age-related chronic diseases (eg, cardiovascular disease [CVD], vascular cognitive impairment, sarcopenia, age-related macular degeneration and Alzheimer's disease).[4] With the aging population increases progressively,[5] the need to accurately evaluate the status of VAg has become urgent.

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It has been widely accepted that vascular age (VA) more accurately reflects the status of individual VAg than their chronological age (CA).[6] But there is little consensus on the measurement of VA.[7] The most commonly used method for VA calculation was derived from the estimation of individual's cardiovascular risk using the classical risk prediction model such as the Framingham Risk Score (FRS) or the Systematic Coronary Risk Evaluation.[7–9] This method may fail at young individuals with high cardiovascular risk burden or older individuals protected against the conventional cardiovascular risk factors, since CA is the most heavily weighted variable in those classical risk prediction models.[8–10] And this method may also fail at individuals who were affected by unknown risk factors.[1,2,11] Therefore, VA calculation based on the method that represents the actual damage integrating all effects of risk factors on the arterial wall may be better.[11,12]

Recent studies now indicate that it is more important to know whether the patient's VA is higher or lower than his/her CA rather than to know the absolute value of their estimating VA in clinical practice.[2,12,13] According the difference between CA and VA (Δ-age), the status of VAg could be classified into 3 phenotypes: the early VAg (EVA, individuals with the lowest deciles of Δ-age), the Normal VAg and the supernormal VAg (SUPERNOVA, individuals with the highest deciles of Δ-age).[2,12,14] The concept of VAg phenotypes offers new insights for identifying individuals who were susceptible to or resilient to the course of VAg.[2,12,14]

However, the clinical implications of VAg phenotypes have been rarely investigated. So far, only two single-centre studies have investigated it in China but lack of external validation.[15,16] In addition, the calculations of VA in previous studies were all derived from the functional parameters, while the structural parameters were not involved.[12,15,16] Emerging evidences show that the alterations of functional and structural properties of the vasculature may reflect different aspects of the VAg,[11,17,18] and integrating the two parameters may improve the measurement of VA.[11]

Therefore, we integrated measures of structural (carotid intima-media thickness, CIMT)[1,19] and functional (brachial-ankle pulse wave velocity, baPWV)[1,20] properties of the arterials to estimate VA using multicentric data from three hospitals geographically dispersed throughout China. The validation of the VA calculation model and the clinical implications of VAg phenotypes were investigated on the basis of prospective data from an independent community-based cohort.

Methods

Study Population

As shown in the flowchart in Figure 1A, the study population (n=15580, the training set) for VA calculation and definition of VAg phenotypes was consecutively and retrospectively enrolled from three large medical centres from 2019 to 2022 in the central and southern region of China, including the Tongji Hospital of Huazhong University of Science and Technology (n=214, Wuhan city, central China), the Sinopharm Dongfeng Central Hospital (n=1890, Shiyan city, central China) and the Sichuan Provincial People's Hospital (n=13476, Chengdu city, southern China). Participants less than 18 years old or with previous CVD events or cancer and those with missing variables were excluded from the present analysis.

The study population (n=5316, the validation set) for external validation of calculating VA model and clinical evaluation of VAg phenotypes was selected from the Kailuan cohort between 2010 and 2011, which is a large, community-based cohort study with long-term follow-up (Tangshan city, northern China).[21] The same exclusion criteria used in the training set were applied for the present analysis, as shown in Figure 1B.

The present study complies with the Declaration of Helsinki. The retrospective multicentre cross-sectional cohort (the training set) was approved by Ethics Review Board of the Tongji Hospital of Huazhong University of Science and Technology, the Sinopharm Dongfeng Central Hospital and the Sichuan Provincial People's Hospital. The requirement of written informed consent was waived by the Review Boards since all data were retrospectively collected and individual information was not disclosed. The prospective community-based cohort (the validation set) was approved by the Kailuan General Hospital Ethics Committee, and written informed consent was obtained from all participants.

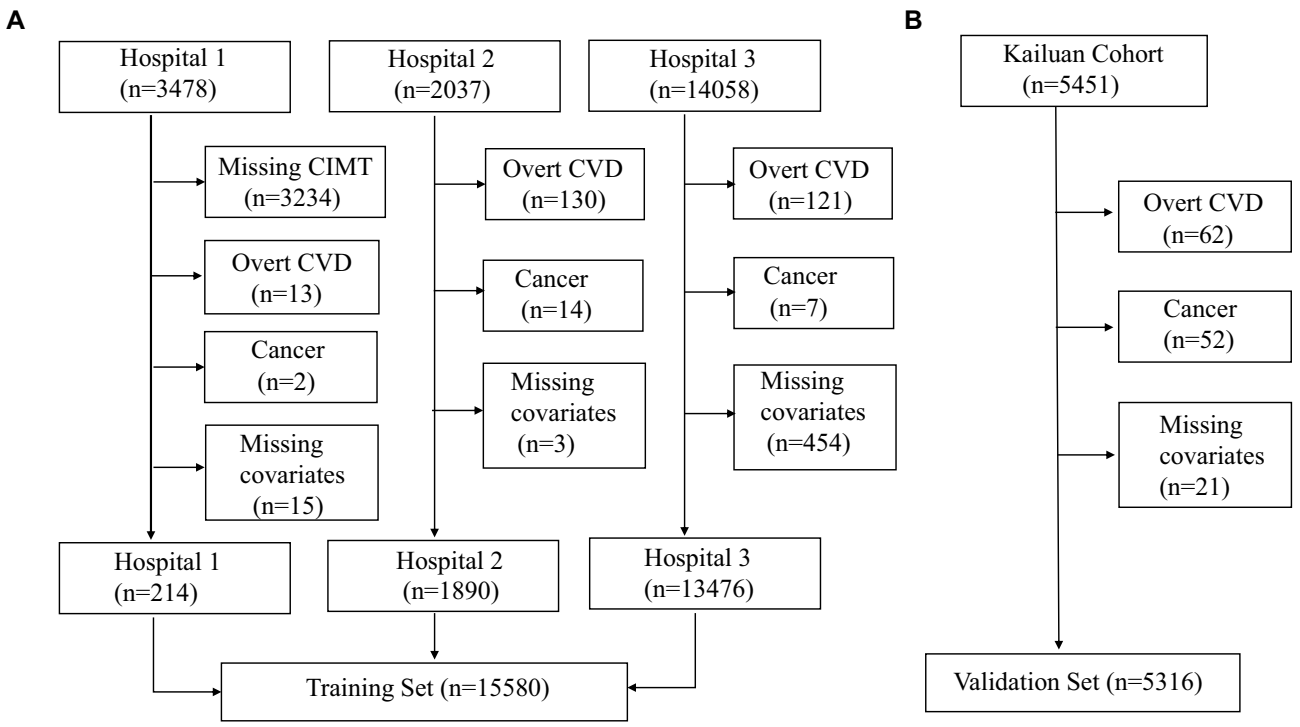

Figure 1 Flowchart of the Study Populations for the Training Set (**A**) and the Validation Set (**B**).
Notes: Hospital 1 indicates the Tongji Hospital of Huazhong University of Science and Technology; Hospital 2, the Sinopharm Dongfeng Central Hospital;Hospital 3, the Sichuan Provincial People's Hospital.
Abbreviations: CIMT, carotid artery intima-media thickness; CVD, cardiovascular disease.

Data Collection

Demographic and Laboratory Measurements

For the training set, the characteristics and clinical features of the participants were retrospectively obtained from the periodic health screening medical records including demographic information (including age, sex), physical measurements (including height, weight, body mass index (BMI), systolic blood pressure [SBP], diastolic blood pressure [DBP], mean blood pressure [MAP] and heart rates [HR]), lifestyle habits (including smoking status and alcohol consumption status), medical history (including hypertension, diabetes mellitus and hyperlipidemia) and laboratory data (including total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C] and fasting blood glucose [FBG]).

For the validation set, data on demographic characteristics, lifestyle habits and medical history was collected using a standardized questionnaire by face-to-face interview. Physical examinations were conducted by trained nurses after the participants were taken a rest of 5-minute. Blood samples were drawn from the participants after an overnight fast. All routine laboratory measurements including TC, TG, HDL-C, LDL-C, and FBG that were tested by automated analyzers in accordance with the manufacturer's instructions. The details of the measurement protocols have been described previously.[21]

In both sets, current smoker was defined as smoking for at least six months with at least seven cigarettes per week. Current drinker was defined as consuming alcohol at least once a week for at least six months. Hypertension was considered if there was a prior diagnosis of hypertension, or self-reported hypertension, or if SBP ≥140 mmHg or DBP ≥90 mmHg.[22] Diabetes mellitus was considered if FBG ≥7.0mmol/L, or if there was a prior diagnosis of diabetes or self-reported diabetes.[23] Hyperlipidemia was defined as fasting serum TC ≥ 6.2 mmol/L, LDL-C ≥ 4.1mmol/L, TG ≥ 2.3mmol/L, or if there was a prior diagnosis of hyperlipidemia or self-reported hyperlipidemia.[24]

Measurement of CIMT

In both sets, CIMT was measured according to the Mannheim consensus[25] by trained sonographers using carotid Color Doppler ultrasound diagnostic instruments (Mindray-Resona 7 for the training set; Philips-HD15 for the validation set).

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After resting for at least 5 minutes, the participants were asked to take a supine position with the head turned to the opposite side of the examination side. CIMT was measured on the far wall of the left and right common carotid artery at a distance of 10mm below its end, avoiding the region of plaque.[25] CIMT was defined as the distance between the inner surface of the intima and the outer surface of the media.[25] The maximum value of bilateral CIMT was adopted for the present analysis.[26]

Measurement of baPWV

In both sets, baPWV was measured by trained nurses using the BP-203RPE III automatic waveform analyzer (Colin-Omron, Komaki, Japan) according standardized operating procedures, as described elsewhere.[27] Briefly, the participants were asked to avoid tobacco, alcohol, and caffeine for at least 30 minutes, and take a quiet rest for 5 minutes before the measurement. Next, trained operator tied the device's cuffs to the upper and lower limbs of the participant in a supine position, and then started the device. The participant's pulse waves were then recorded automatically by the device. Each participant underwent the measurement twice, and the results of the second measurement were saved. The larger value of bilateral baPWV was used for the present analysis.

Outcomes

For the prospective cohort (the validation set), all participants were monitored biennially until 31 December 2021. The primary outcome in the current study was a composite adverse clinical outcome consisting of all-cause death and CVD event (including hemorrhagic or ischemic stroke, myocardial infarction [MI]). Additional outcomes were CVD, MI, stroke and all-cause death. For the participants with multiple adverse clinical events, the first occurrence of clinical event was recorded. The follow-up methods and the assessment of all-cause death and CVD events has been previously described in detail.[21]

Statistical Analyses

We performed data cleaning by checking raw records of absurd data that violated logic or out of measurement range and deleting the still outliers to eliminate the impacts of measurement errors. As shown in Figure 1 and the detailed exclusions are listed in the following: A total of fifteen participants were excluded in Hospital 1 due to the lack of drinking or smoking variable (n=11) and the extreme value of blood pressure variable (n=4). A total of three participants were excluded in Hospital 2 due to the extreme value of TG or FBG variable (n=3). A total of 454 participants were excluded in Hospital 3 due to the lack of drinking or smoking variable (n=24), the lack of CIMT variable (n=55), the lack of height or weight variable (n=330), the extreme value of blood pressure variable (n=1), the extreme value of FBG variable (n=7) and the extreme value of LDL or TG or TC variable (n=37). A total of 21 participants were excluded in Kailuan Cohort due to the lack of CIMT variable (n=18) and the extreme value of blood pressure variable (n=3).

The data distribution was assessed by Kolmogorov–Smirnov test. The participant's baseline characteristics were presented as median (interquartile range [IQR]) for continuous variables, whereas frequency (percentage) for categorical variables. The baseline characteristics were compared among the training set and the validation set were examined by Mann–Whitney *U*-test (for continuous variables) and chi-square test (for categorical variables). The clinical characteristics of the three VAg phenotypes (EVA, the normal VA and SUPERNOVA) were compared by Kruskal–Wallis test (for continuous variables) and chi-square test (for categorical variables), and the size of differences were compared by effect size calculation. All statistical analyses were performed by R software (Version 4.1) and the Statistical Package for Social Sciences software (IBM SPSS Statistics Version 26.0, IBM Corp, Armonk, NY, USA). Statistical significance was considered as a 2-sided *P*-value of <0.05.

Calculation of VA and Definition of VAg Phenotypes

Those steps were conducted in the training set. VA was defined as the predicted age in a multivariable regression model,[12] including traditional cardiovascular risk factors, baPWV and CIMT. Variable selection was made by backward stepwise approach, with multicollinearity checked by variable inflation factor (VIF, variables excluded when sqrtVIF >2). The final selected variables were sex, alcohol consumption status, BMI, MAP, HR, TC, TG, FBG, diagnosis of hypertension, diagnosis of diabetes mellitus, baPWV and CIMT. Most of those continuous variables showed a non-

linear relationship with age. Therefore, the following transformations were performed to improve the prediction performance of the VA calculation model: log-transformed, 2nd-degree polynomials, or Generalized Additive Models. Those models were compared based on the R^2 and the Akaike Information Criterion (AIC),[12] with log-transformed giving the best fitting. The detailed parameters of equations with coefficients of the parameters for the final model are shown in Table S1. And the precise formula for VA calculation is listed as the following:

Vascular age = 39.543–2.670 (if male) +0.0 (if female) −1.124 (if drinker) +0.0 (if not drinker)-0.639×log (BMI) −4.533×log (MAP) −12.826×log (HR) +3.679×log (TC) −1.216×log (TG) +4.695×log (FBG) +2.600 (if hypertension present) +0.0 (if hypertension not present) +0.873 (if diabetes present) +0.0 (if diabetes not present) +29.911×log (baPWV) +9.511×log (CIMT).

The classification of VAg phenotypes was defined according to the percentiles of Δ-age (the difference between the CA and VA).[12] And the distribution of Δ-age was checked for normality using Kolmogorov–Smirnov test. Following the previous studies,[12,15,16] we defined the 10th and 90th percentiles of Δ-age as the cutoffs of EVA and SUPERNOVA respectively. In detail, the EVA individuals were considered when their VA was extremely higher than CA, thus his/her Δ-age was lower than 10th of the whole population's Δ-age. Accordingly, the SUPERNOVA phenotype was the other extreme of Δ-age distribution (over than 90th percentiles). Individuals with the Δ-age between the two extremes were considered as the Normal VAg phenotype. Clinical characteristics and atherosclerotic cardiovascular disease (ASCVD) risk score (continuous variable); from the Framingham Heart Study[8] were compared between the 3 VAg phenotypes (EVA, Normal VAg, and SUPERNOVA).

Association of VAg Phenotypes with Adverse Clinical Outcomes Risk

This step was conducted in the validation set. VA and VAg phenotypes for the validation set were calculated using the equation and cutoffs obtained from the training set. After checking the assumption of proportional hazards by Schoenfeld residuals and found to be met, a progressively adjusted Cox survival analysis was performed to test the association of VAg phenotypes with clinical outcomes risk, with the Normal VAg as the reference group. Model 1 included adjustment for age and sex. Model 2 additionally adjusted for ASCVD risk score. And we further performed the analysis in sex subgroups.

Additional Analyses

This step was also conducted in the validation set. First, we further investigated the association between clinical outcomes and Δ-age as a continuous variable rather than category variable (VAg phenotypes) in Cox survival analysis, adjusted for the same set of covariates. And we also performed the restricted cubic spline (RCS) analysis to further display the association between clinical outcomes with Δ-age as a continuous variable. The RCS analysis was adjusted for age and sex. In addition, we further evaluated the incremental predictive value of baPWV, CIMT and VAg phenotypes beyond the basic/conventional model on clinical outcomes using the Harre's C-statistic, integrated discrimination improvement (INI) and net reclassification index (NRI).

Result

Baseline Characteristics

Based on the definition of VAg phenotypes mentioned before, EVA was defined when individual's VA was greater than his/her CA of 10.5 years or more (Δ-age < −10.5 years), and SUPERNOVA was defined when the VA was lower than the CA of 10.2 years or more ((Δ-age >10.2 years). Therefore, the proportion of individuals with EVA, normal VAg, and SUPERNOVA in the training set was 10%, 80%, and 10%, respectively. And the proportion of individuals with EVA, normal VAg, and SUPERNOVA in the validation set was 5.5%, 79%, and 15.5%, respectively. The clinical characteristics of the training set and the validation set and according to VAg phenotypes are shown in Tables 1 and 2, respectively.

In the training set, the three VAg phenotypes had similar cardiovascular risk burden and VA but different CA, with the EVA individuals being the youngest group and the SUPERNOVA being the oldest group (Table 1). Minor differences (statistically significant but with small effect size) were shown for the cardiovascular risk variables among the three VAg

Table 1 Clinical Characteristics of the Training Set Grouped with VAg Phenotypes

	Overall (N=15580)	EVA (N=1544)	Normal VAg (N=12481)	SUPERNOVA (N=1555)	*P*-value	Effect Size
Chronological age (y)	51.0 (45.0–57.0)	34.0 (30.0–41.0)	50.0 (46.0–56.0)	65.0 (60.0–72.0)	< 0.001	0.329
Vascular age (y)	50.1 (46.3–54.7)	49.3 (45.5–54.7)	50.1 (46.4–54.6)	50.9 (46.2–56.4)	< 0.001	0.002
Δ-age (y)	0.1 (−5.2 to 5.2)	−13.9 (−16.7 to −12.0)	0.1 (−3.9 to 4.1)	13.5 (11.7–16.3)	< 0.001	0.484
Female (%)	5635 (36.2%)	482 (31.2%)	4673 (37.4%)	480 (30.9%)	< 0.001	0.038
BMI (kg/m^2)	24.3 (22.2–26.4)	24.1 (21.6–26.6)	24.3 (22.3–26.4)	24.2 (22.3–26.1)	0.006	0.001
Systolic BP (mmHg)	122.0 (111.0–135.0)	121.0 (110.0–134.0)	122.0 (111.0–135.0)	126.0 (115.0–139.0)	< 0.001	0.004
Diastolic BP (mmHg)	75.0 (67.0–84.0)	75.0 (66.0–84.0)	75.0 (67.0–84.0)	74.0 (68.0–81.0)	< 0.001	0.001
MAP (mmHg)	91.0 (82.0–101)	90.0 (81.0–101)	91.0 (82.0–101)	92.0 (84.0–100)	0.086	< 0.001
Current smoker (%)	3669 (23.5%)	370 (24.0%)	2994 (24.0%)	305 (19.6%)	< 0.001	0.015
Current drinker (%)	2368 (15.2%)	216 (14.0%)	1944 (15.6%)	208 (13.4%)	< 0.001	0.008
Hypertension (%)	2189 (14.1%)	175 (11.3%)	1792 (14.4%)	222 (14.3%)	< 0.001	0.009
Hyperlipemia (%)	422 (2.7%)	27 (1.7%)	372 (3.0%)	23 (1.5%)	< 0.001	0.004
Diabetes (%)	779 (5.0%)	76 (4.9%)	616 (4.9%)	87 (5.6%)	< 0.001	0.002
FBG (mmol/L)	5.01 (4.66–5.48)	4.89 (4.53–5.36)	5.01 (4.67–5.49)	5.08 (4.71–5.50)	< 0.001	0.004
HDL-C (mmol/L)	1.31 (1.12–1.55)	1.27 (1.09–1.51)	1.31 (1.12–1.55)	1.31 (1.13–1.56)	< 0.001	0.001
LDL-C (mmol/L)	2.81 (2.33–3.33)	2.75 (2.25–3.31)	2.83 (2.35–3.34)	2.76 (2.23–3.27)	< 0.001	0.001
TC (mmol/L)	4.92 (4.34–5.56)	4.76 (4.21–5.46)	4.95 (4.36–5.57)	4.87 (4.24–5.54)	< 0.001	0.002
TG (mmol/L)	1.41 (0.98–2.10)	1.34 (0.86–2.13)	1.42 (0.99–2.12)	1.34 (0.98–1.96)	< 0.001	0.001
baPWV (m/s)	14.1 (12.7–15.9)	14.2 (12.8–16.0)	14.0 (12.7–15.8)	14.5 (12.8–16.8)	< 0.001	0.003
CIMT (mm)	0.70 (0.60–0.90)	0.60 (0.60–0.80)	0.70 (0.60–0.90)	0.70 (0.60–0.80)	< 0.001	0.003

Note: Δ-age indicates chronological age minus vascular age.

Abbreviations: EVA, early vascular aging; VAg, vascular aging; SUPERNOVA, supernormal vascular aging; BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; FBG, fast blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; baPWV, brachial-ankle pulse wave velocity; CIMT, carotid artery intima-media thickness.

Table 2 Clinical Characteristics of the Validation Set Grouped with VAg Phenotypes

	Overall (N=5316)	EVA (N=293)	Normal VAg (N=4198)	SUPERNOVA (N=825)	*P*-value	Effect Size
Chronological age (y)	54.0 (47.0–64.0)	45.0 (42.0–52.0)	52.0 (46.0–60.0)	73.0 (66.0–80.0)	< 0.001	0.290
Vascular age (y)	53.3 (48.4–60.0)	60.4 (56.1–67.1)	52.0 (47.9–58.2)	57.7 (51.0–62.3)	< 0.001	0.070
Δ-age (y)	1.0 (−3.8 to 7.2)	−13.8 (−16.8 to −11.7)	0.0 (−3.8 to 4.4)	14.7 (12.1–18.6)	< 0.001	0.503
Female (%)	2115 (39.8%)	131 (44.7%)	1857 (44.2%)	127 (15.4%)	< 0.001	0.165
BMI (kg/m^2)	24.8 (22.8–27.1)	25.4 (23.4–27.3)	24.8 (22.8–27.2)	24.6 (22.3–26.7)	< 0.001	0.003
Systolic BP (mmHg)	130.0 (120.0–141.0)	140.0 (123.0–159.0)	130.0 (120.0–140.0)	131.0 (120.0–149.0)	< 0.001	0.019
Diastolic BP (mmHg)	80.0 (77.0–90.0)	90.0 (80.0–100.0)	81.0 (78.0–90.0)	80.0 (71.0–88.0)	< 0.001	0.027
MAP (mmHg)	97.0 (91.0–107.0)	106 (97.0–117.0)	97.0 (91.0–107.0)	98.0 (90.0–106.0)	< 0.001	0.017
Current smoker (%)	1554 (29.2%)	95 (32.4%)	1229 (29.3%)	230 (27.9%)	< 0.001	0.012
Current drinker (%)	1629 (30.6%)	88 (30.0%)	1272 (30.3%)	269 (32.6%)	< 0.001	0.016
Hypertension (%)	1328 (25.0%)	141 (48.1%)	999 (23.8%)	188 (22.8%)	< 0.001	0.266
Hyperlipemia (%)	515 (9.7%)	52 (17.7%)	402 (9.6%)	61 (7.4%)	< 0.001	0.022
Diabetes (%)	376 (7.1%)	46 (15.7%)	284 (6.8%)	46 (5.6%)	< 0.001	0.025
FBG (mmol/L)	5.27 (4.86–5.87)	5.62 (5.10–6.78)	5.29 (4.86–5.87)	5.15 (4.79–5.67)	< 0.001	0.014
HDL-C (mmol/L)	1.60 (1.30–1.90)	1.60 (1.30–1.90)	1.60 (1.30–1.90)	1.50 (1.30–1.90)	< 0.001	0.003
LDL-C (mmol/L)	2.63 (2.18–3.09)	2.71 (2.24–3.21)	2.65 (2.20–3.10)	2.48 (2.02–3.01)	< 0.001	0.005
TC (mmol/L)	5.00 (4.40–5.70)	5.10 (4.60–5.80)	5.00 (4.40–5.70)	4.90 (4.30–5.70)	0.001	0.002
TG (mmol/L)	1.31 (0.94–1.94)	1.47 (1.01–2.20)	1.32 (0.95–1.96)	1.22 (0.88–1.73)	< 0.001	0.005
baPWV (m/s)	15.1 (13.2–18.0)	18.6 (16.3–22.3)	14.7 (13.0–17.2)	16.6 (14.2–19.3)	< 0.001	0.070
CIMT (mm)	0.80 (0.70–0.90)	0.90 (0.70–1.0)	0.80 (0.70–0.90)	0.90 (0.80–1.10)	< 0.001	0.061
ASCVD score (%)	5.35 (2.98–9.81)	5.00 (2.92–8.73)	4.66 (2.65–8.14)	11.10 (7.02–16.1)	< 0.001	0.138

Note: Δ-age indicates chronological age minus vascular age.

Abbreviations: EVA, early vascular aging; VAg, vascular aging; SUPERNOVA, supernormal vascular aging; BMI, body mass index; BP, blood pressure; MAP, mean arterial pressure; FBG, fast blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; baPWV, brachial-ankle pulse wave velocity; CIMT, carotid artery intima-media thickness; ASCVD, atherosclerosis cardiovascular disease.

phenotypes (Table 1). In parallel to what was found in the training set, the EVA individuals and SUPERNOVA individuals had similar VA in the validation set, but the EVA individuals were 28 years younger than the SUPERNOVA individuals (Table 2). With the similar cardiovascular risk profile, the SUPERNVOVA individuals were older than individuals with the Normal VAg phenotype. Although EVA individuals showed higher proportion of current smoker, higher prevalence of hypertension, hyperlipemia and diabetes, and higher BP, FBG, LDL, TC, TG and baPWV, no variable had a large effect size except for the prevalence of hypertension (Table 2). Notably, EVA individuals tended to have higher proportion of female sex and lower ASCVD risk score than SUPERNOVA individuals (Table 2).

A comparison of the training and validation set revealed statistically significant differences in many demographic characteristics, lifestyle habits, medical history, laboratory data and arterial measurements, especially in terms of the distribution of CA, the proportion of female sex, current drinker or smoker, the prevalence of hypertension, hyperlipemia and diabetes, the validation set was significantly higher. A detailed description of the clinical characteristics in two sets is presented in Table S2.

The Association of VAg Phenotypes with Adverse Clinical Outcome Risk

During a median follow-up of 11.07 years, in total 927 adverse clinical outcome events were documented, including 312 cases of stroke, 85 cases of MI and 530 all-cause deaths. After adjusting for age and sex, the EVA phenotype had an increased rate (hazard ratio [HR]: 2.43; 95% CI: 1.80–3.27) and the SUPERNOVA phenotype had a decrease rate (HR: 0.75; 95% CI: 0.64–0.90) of adverse clinical outcome as compared to the Normal VAg phenotype (Table 3 and Figure 2). The association between VAg phenotypes and adverse clinical outcome risk remained significant after adjusting for ASCVD risk score. Similar results were observed for the outcomes of CVD and stroke, but not for the MI and all-cause death (Table 3). In detail, the HRs for CVD were 2.29 (95% CI: 1.57–3.34) for EVA and 0.66 (95% CI: 0.49–0.89) for SUPERNOVA, and the HRs for stroke were 2.00 (95% CI: 1.28–3.10) for EVA and 0.59 (95% CI: 0.42–0.84) for SUPERNOVA after multivariable adjustment. EVA also showed a higher risk of myocardial infarction (HR: 3.21, 95% CI: 1.56–6.62) and all-cause death (HR: 1.79, 95% CI: 1.12–2.85) after multivariable adjustment. But we did not find any significant association between SUPERNOVA and MI or all-cause death (Table 3). Further progressively adjusted Cox survival analysis in sex subgroups showed that EVA had a stronger association with CVD, stroke and MI in women than in men. But the association between EVA and all-cause death only maintained significant in men (Tables S5 and S6).

Table 3 Hazard Ratio for VAg Phenotypes for Outcomes

Outcomes	VAg Phenotypes	Model 1	Model 2
Adverse Clinical Outcome	SUPERNOVA	0.75 (0.64–0.90)	0.82 (0.69–0.98)
	Normal VAg	Reference	Reference
	EVA	2.43 (1.80–3.27)	2.25 (1.66–3.03)
Cardiovascular Disease	SUPERNOVA	0.58 (0.43–0.78)	0.66 (0.49–0.89)
	Normal VAg	Reference	Reference
	EVA	2.59 (1.78–3.77)	2.29 (1.57–3.34)
Stroke	SUPERNOVA	0.52 (0.37–0.73)	0.59 (0.42–0.84)
	Normal VAg	Reference	Reference
	EVA	2.27 (1.46–3.52)	2.00 (1.28–3.10)
Myocardial Infarction	SUPERNOVA	0.78 (0.43–1.43)	0.88 (0.48–1.63)
	Normal VAg	Reference	Reference
	EVA	3.21 (1.56–6.62)	2.88 (1.39–5.97)
All-cause Death	SUPERNOVA	0.87 (0.71–1.06)	0.92 (0.75–1.13)
	Normal VAg	Reference	Reference
	EVA	1.79 (1.12–2.85)	1.70 (1.06–2.71)

Notes: Values are HR (95% CI). Model 1: age- and sex- adjusted; model2: +atherosclerotic cardiovascular disease risk score at baseline.
Abbreviations: VAg, vascular aging; SUPERNOVA, supernormal vascular aging; EVA, early vascular aging.

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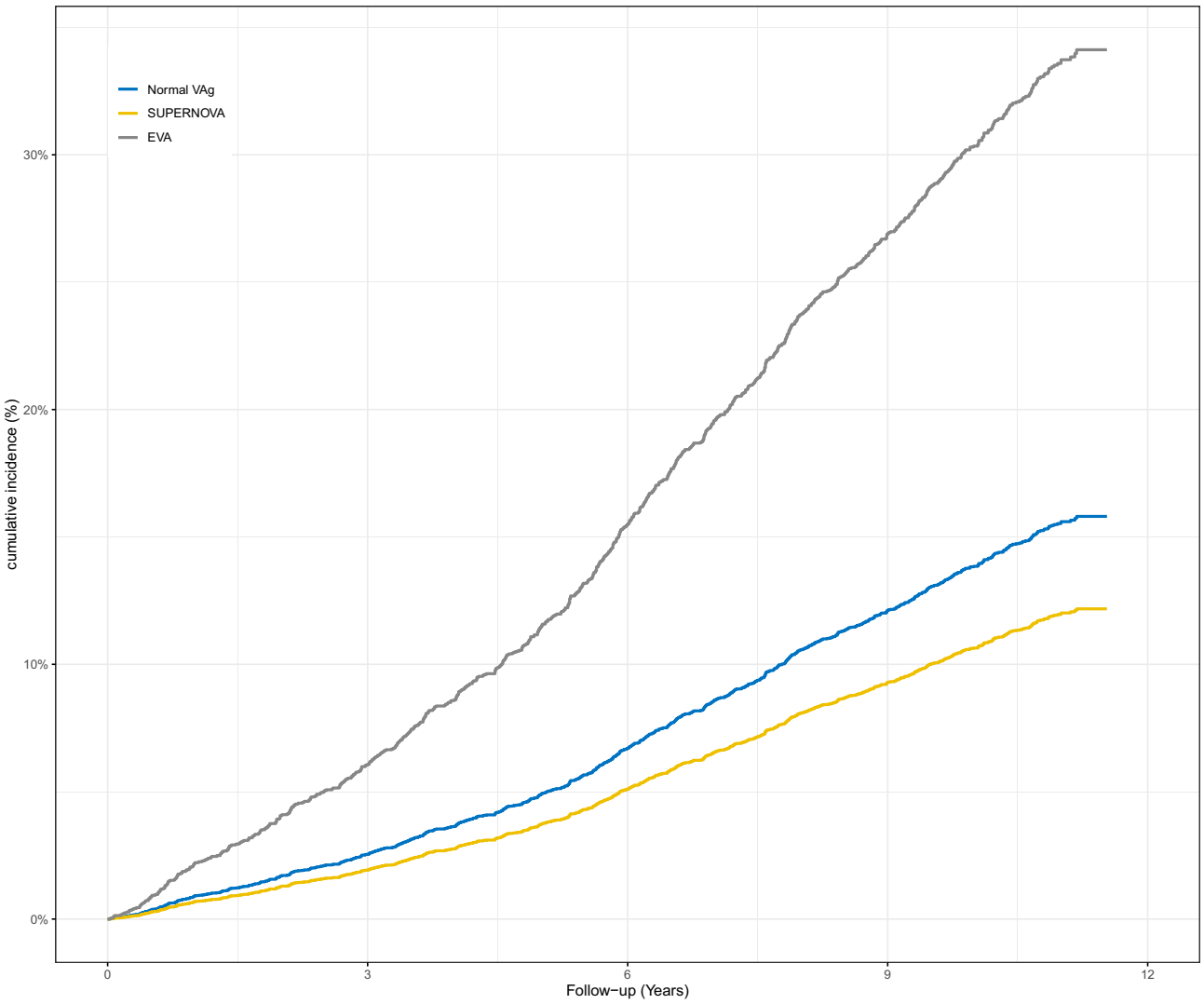

Figure 2 Cumulative Incidence of Adverse Clinical Outcome Stratified by Vascular Aging Phenotypes.
Abbreviations: VAg, indicates vascular aging; SUPERNOVA, supernormal vascular aging; EVA, early vascular aging.

Additional Analyses

As a continuous variable rather than VAg categories, Δ-age as was inversely and significantly associated with the adverse clinical outcome in the age and sex adjusted model (HR: 0.964; 95% CI: 0.955–0.973). One year difference between CA and VA (Δ-age) was associated with 3.6% less adverse clinical outcome risk, 5.5% less CVD risk, 5.4% less stroke risk, 5.3% less MI risk and 2.3% less all-cause death risk (Table S3). We also observed an L-shaped association between Δ-age and adverse clinical outcome. Individuals with CA greater than VA showed a decreased adverse clinical outcome risk, whereas individuals with CA less than VA showed an increased risk (Figure S1).

We further evaluated whether baPWV, CIMT and VAg phenotypes would increase the predictive value of basic/conventional risk factors (Table S4). With CVD as the outcome of interest, the conventional model's C-statistic did incrementally and significantly improve with the additional of baPWV (difference in C statistics [Δ-C-statistic]: 0.010; $P < 0.001$) and the combination of baPWV and CIMT (Δ-C-statistic: 0.013; $P < 0.001$) and VAg phenotypes (Δ-C-statistic: 0.016; $P < 0.001$). The discriminatory power and risk reclassification showed similar improvements when the aforementioned variables were added to the conventional model for CVD. Similar patterns were also observed for the outcomes of adverse clinical outcome and stroke (Table S4).

Discussion

In the current study, we defined the VAg phenotypes using individual data from a multicentric cross-sectional cohort in the central and southern regions of China, and their clinical implications were validated using prospective data from a community-based cohort in northern China. The main finding is that compared with individuals with the Normal VAg phenotype, those with EVA phenotype had an increased adverse clinical outcome risk whereas those with SUPERNOVA phenotype had a decreased risk. Further analysis showed that VAg phenotypes derived from the combination of structural and functional properties of vasculature have an additive effect on predicting clinical outcomes than the conventional risk factors.

Current evidence on the clinical implications of VAg phenotypes is limited. A large multicentric cohort study performed by Bruno et al[12] in the elderly Europeans represented the first validation of VAg phenotypes' clinical implications. After follow-up of 6.6 years, they found that individuals with EVA phenotype had an increased risk (HR: 2.7; 95% CI: 1.55–4.70) and those with SUPERNOVA phenotype had a decreased risk (HR: 0.59, 95% CI:0.41–0.85) of CVD as compared to the Normal VAg phenotype.[12] Followed by the European study, a community-based study included 10375 Chinese aged 40–80 years reported that CVD risk significantly increased in EVA and decreased in SUPERNOVA individuals.[15] In addition, Zuo et al conducted a middle-aged (40–60 years) cohort study in China with a follow-up period of 4.6 years and they found that SUPERNOVA individuals had a 53% lower risk than the normal group.[16]

Our results replicated the association between VAg phenotypes and clinical outcomes as found in previous researches,[12,15,16] and extends these earlier findings by several aspects. From the perspective of study design, this is the first study to evaluate the clinical implications of VAg phenotypes using multicentric data and undergone external validation in China. In addition, we included both structural and functional parameters of arterial wall to the calculation model of VA rather than only included one of the parameters. As expected, the C-statistics in our study increased 0.010 ($P < 0.001$) and 0.013 ($P < 0.001$) separately when adding baPWV, adding the combination of baPWV and CIMT to a model of conventional risk factors in predicting cardiovascular events. Our results are in line with previous evidence showing that the simultaneous use of aortic PWV and CIMT performed better for CVD prediction in a large population-based cohort.[28] In their study, they use the HRs for the risk of CVD (a change of 1m/s in aortic PWV and 0.1mm in CIMT) extracted from meta-analyses to create the vascular ageing index, and then scaled the index values to VA.[28] Differ from the previous study, we defined VA based on the integrative measurement of baPWV and CIMT plus conventional cardiovascular risk factors. With VA defined in this way, it could provide us an opportunity to measure the arterial damage that has already occurred on the basis of conventional cardiovascular risk factors,[29] and then may allow us to identify the protective or harmful mechanisms independent of conventional risk factors.[12,29]

Accordingly, VAg phenotypes based on the difference between the CA and VAs offers new insight in identifying individuals at different risk of developing CVD events. First, our study showed that individuals with SUPERNOVA phenotype had a 42% lower risk of CVD than those with Normal VAg phenotype, despite the fact that SUPERNOVA phenotype had a greater CA and a similar burden of cardiovascular risk than the Normal VAg phenotype. Thus, the SUPERNOVA phenotype identifies individuals who are resilience to the combined deleterious effects of age and conventional cardiovascular risk factors. Second, the 10-year CVD risk of individuals with EVA phenotype in our study was less than 5.1% of that in those with SUPERNOVA phenotype estimated by the ASCVD risk score, despite the fact that the EVA phenotype had a heavier cardiovascular risk burden than the SUPERNOVA phenotype. Thus, the EVA phenotype identifies individuals who are highly susceptible to conventional cardiovascular risk factors at a younger age. Last, in line with the results of the study performed by Bruno et al,[12] EVA individuals tended to have higher proportion of female sex. And EVA had a stronger association with CVD in women (HR: 3.70, 95% CI: 2.02–6.79) than in men (HR: 1.72, 95% CI:1.05–2.83) in our study. Evidence shows that the traditional models often underestimate cardiovascular risk in women, a population in which nonconventional risk factors play a major role.[30] Thus, the EVA phenotype may be particularly useful in identifying individuals who are affected by the nonconventional risk factors.

From the perspective of study population, the CA of participants in our study ranged from 18 to 106 years (the training set: 19–95 years, the validation set: 18–106 years), whereas the previous studies focused on the middle to old

age.[12,15,16] The large range of CA provided an opportunity for us to observe individuals with extremely high or low VA. Furthermore, the VA calculation model developed from recent data (from 2019 to 2022) will be more generalizable to contemporary population, since the epidemics of risk factors have dramatically changed in China during the past decade.[31] However, the incidence and mortality of stroke remained the most common cardiovascular event in China.[32] The result of our study further supports this epidemiological finding. In contrast to the foregoing observation performed in Europeans,[12] our study showed that stroke dominated over MI events as CVD outcome (11-year follow-up, 312 cases of stroke, 85 cases of MI), and the SUPERNOVA phenotype had a lower risk of stroke (HR:0.59, 95% CI: 0.42–0.84) but not for MI (HR: 0.88, 95% CI: 0.48–1.63).

From the perspective of study outcome, a composite adverse clinical outcome was defined in the current study since VAg is a driver of age-related chronic disease (eg, vascular cognitive impairment and Alzheimer's disease) and mortality,[3] not merely the CVD events. In specific, arterial stiffening transmits the flow pulsation deep into the microvasculature of the brain leading to the impairment of local regulation of microvascular perfusion (eg, by impairing endothelium), which has deleterious effects on the delivery of oxygen, nutrients and the clearance of reactive oxygen species or amyloid-β,[4,33] and thus negatively affects the brain's cognitive function.[34] Increasing evidence suggests that antioxidants (eg, curcumin, ginkgo biloba) can improve or stabilize cognitive functions, memory, and Alzheimer's disease by targeting key pathway involved in oxidative stress and inflammation, and by improving vascular endothelial dysfunction.[35,36]

Strengths and Limitations

As mentioned above, strengths of the present study include the contemporary and multicentric data, external validation, the relatively large sample size and CA range, and a longer follow-up period, thereby strengthening the credibility of conclusions and improve the generalization to other population. In addition, integrated the assessments of both structural and functional changes of the arteries may reflect the overall VAg profile better than only one parameter alone for a given individual.

However, some limitations of the current study should be mentioned. First, the data for VA calculation and definition of VAg phenotypes was retrospectively collected from a multicentric cross-sectional cohort, which was less standardized than data collected from the prospective cohort. However, the measurements of risk factors were all performed at major regional central hospitals qualified for the health examinations. Second, we did not consider the effect of medication into the model of VA calculation since there was a large amount of missing data on medication history. Evidence suggests that several cardiovascular medications including the anti-hypertensive agent, antihyperlipidaemic agent and anti-diabetes agent promote the health of arteries by anti-inflammatory, anti-oxidative and anti-proliferative pathways.[11] However, aortic stiffness was considered to reflect not only the current damage of arteries but also its regression or progression which resulted from therapeutic actions.[14] Nevertheless, more detailed indicators of sociodemographic, medical and lifestyle needed to be further collected using standardized and unified methods in prospective cohort to refine the VA calculation model. Third, the proportion of SUPERNOVA individuals was far higher in the validation set (15.5%) than in the training set (10%) in our study, since the cutoffs to define VAg phenotypes were obtained from the training set. And the distribution of CA in the training set differed from that in the validation set ($P < 0.001$, Table S2). The proportion of individuals aged ≥70 years was 4.8% in the training set, while the proportion of individuals aged ≥70 years was 17.8% in the validation set (data not shown). Therefore, future longitudinal multicenter studies are needed to confirm the best cutoff values for VAg phenotypes before implementing the cutoffs in clinical practice. Finally, we use baPWV rather than carotid-femoral pulse wave velocity (cfPWV, the gold standard measurement of arterial stiffness) to assess the functional property of arteries. However, it has been demonstrated that baPWV correlated with cfPWV well[37] and baPWV has been recommended by the Hypertension Guideline in Japan and Europe for hypertension management.[20,38]

Conclusion

In conclusion, this is the first study to evaluate the clinical implications of VAg phenotypes using multicentric data and undergone external validation in China. Our results emphasized that the classification of VAg phenotypes may be a potential tool to identify individuals who are highly susceptible to conventional cardiovascular risk factors at a younger

age, or individuals who are resilience to conventional cardiovascular risk factors at an elderly age, and individuals who are affected by the nonconventional risk factors, particularly in women. However, the data for VA calculation and definition of VAg phenotypes were collected retrospectively from the periodic health screening medical records in three hospitals. Therefore, future large longitudinal multicenter studies with more detailed sociodemographic, medical and lifestyle indicators collected using standardized and unified methods are needed to validate and refine the calculation model of VA and to confirm the best cutoffs for VAg phenotypes. Moreover, more external validation in other populations should be conducted to strengthen the generalizability of our findings.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Laurent S. Defining vascular aging and cardiovascular risk. *J Hypertens*. 2012;30:S3–8. doi:10.1097/HJH.0b013e328353e501
2. Gonzalez LDM, Romero-Orjuela SP, Rabeya FJ, Del Castillo V, Echeverri D. Age and vascular aging: an unexplored frontier. *Front Cardiovasc Med*. 2023;10:1278795. doi:10.3389/fcvm.2023.1278795
3. Ungvari Z, Tarantini S, Sorond F, Merkely B, Csiszar A. Mechanisms of vascular aging, a geroscience perspective: JACC focus seminar. *J Am Coll Cardiol*. 2020;75(8):931–941. doi:10.1016/j.jacc.2019.11.061
4. Ungvari Z, Tarantini S, Donato AJ, Galvan V, Csiszar A. Mechanisms of vascular aging. *Circ Res*. 2018;123(7):849–867. doi:10.1161/CIRCRESAHA.118.311378
5. Chen R, Xu P, Song P, Wang M, He J. China has faster pace than Japan in population aging in next 25 years. *Biosci Trends*. 2019;13(4):287–291. doi:10.5582/bst.2019.01213
6. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andres V. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol*. 2020;75(8):919–930. doi:10.1016/j.jacc.2019.11.062
7. Groenewegen KA, den Ruijter HM, Pasterkamp G, Polak JF, Bots ML, Peters SA. Vascular age to determine cardiovascular disease risk: a systematic review of its concepts, definitions, and clinical applications. *Eur J Prev Cardiol*. 2016;23(3):264–274. doi:10.1177/2047487314566999
8. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743–753. doi:10.1161/CIRCULATIONAHA.107.699579
9. Cuende JI, Cuende N, Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. *Eur Heart J*. 2010;31(19):2351–2358. doi:10.1093/eurheartj/ehq205
10. Perk J, De Backer G, Gohlke H, et al. [European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts)]. Linee guida europee sulla prevenzione delle malattie cardiovascolari nella pratica clinica (versione 2012). Quinta Task Force congiunta della Societa Europea di cardiologia e di altre societa sulla prevenzione delle malattie cardiovascolari nella pratica clinica (costituita da rappresentanti di nove societa e da esperti invitati). *G Ital Cardiol*. 2013;14(5):328–392. doi:10.1714/1264.13964
11. Climie RE, Alastruey J, Mayer CC, et al. Vascular ageing: moving from bench towards bedside. *Eur J Prev Cardiol*. 2023;30(11):1101–1117. doi:10.1093/eurjpc/zwad028
12. Bruno RM, Nilsson PM, Engstrom G, et al. Early and supernormal vascular aging: clinical characteristics and association with incident cardiovascular events. *Hypertension*. 2020;76(5):1616–1624. doi:10.1161/HYPERTENSIONAHA.120.14971
13. Mitnitski A, Howlett SE, Rockwood K. Heterogeneity of human aging and its assessment. *J Gerontol a Biol Sci Med Sci*. 2017;72(7):877–884. doi:10.1093/gerona/glw089
14. Laurent S, Boutouyrie P, Cunha PG, Lacolley P, Nilsson PM. Concept of Extremes in Vascular Aging. *Hypertension*. 2019;74(2):218–228. doi:10.1161/HYPERTENSIONAHA.119.12655
15. Cao Q, Li M, Wang T, et al. Association of early and supernormal vascular aging categories with cardiovascular disease in the Chinese population. *Front Cardiovasc Med*. 2022;9:895792. doi:10.3389/fcvm.2022.895792
16. Zuo Y, Chen S, Tian X, Wang P, Wu S, Wang A. Association of vascular aging with cardiovascular disease in middle-aged Chinese people: a prospective cohort study. *JACC Asia*. 2023;3(6):895–904. doi:10.1016/j.jacasi.2023.07.014
17. Sigl M, Winter L, Schumacher G, et al. Comparison of functional and morphological estimates of vascular age. *In Vivo*. 2023;37(5):2178–2187. doi:10.21873/invivo.13317
18. Lisan Q, van Sloten T, Boutouyrie P, et al. Sleep apnea is associated with accelerated vascular aging: results from 2 European community-based cohort studies. *J Am Heart Assoc*. 2021;10(15):e021318. doi:10.1161/JAHA.120.021318

19. Poredos P, Jezovnik MK. Preclinical carotid atherosclerosis as an indicator of polyvascular disease: a narrative review. *Ann Transl Med*. 2021;9 (14):1204. doi:10.21037/atm-20-5570
20. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res*. 2019;42(9):1235–1481. doi:10.1038/s41440-019-0284-9
21. Wu S, Huang Z, Yang X, et al. Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. *Circ Cardiovasc Qual Outcomes*. 2012;5(4):487–493. doi:10.1161/CIRCOUTCOMES.111.963694
22. Liu LS; Writing Group of Chinese Guidelines for the Management of H. 2010 Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2011;39(7):579–615.
23. American Diabetes A.. 2. classification and diagnosis of diabetes: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1): S13–S28. doi:10.2337/dc19-S002
24. Guideline, J. Joint committee issued Chinese guideline for the management of dyslipidemia in a. [2016 Chinese guideline for the management of dyslipidemia in adults]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2016;44(10):833–853. doi:10.3760/cma.j.issn.0253-3758.2016.10.005
25. Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European stroke conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis*. 2012;34(4):290–296. doi:10.1159/000343145
26. Sander D, Kukla C, Klingelhofer J, Winbeck K, Conrad B. Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: a 3-year follow-up study. *Circulation*. 2000;102(13):1536–1541. doi:10.1161/01.cir.102.13.1536
27. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res*. 2002;25(3):359–364. doi:10.1291/hypres.25.359
28. Nilsson Wadstrom B, Fatehali AH, Engstrom G, Nilsson PM. A vascular aging index as independent predictor of cardiovascular events and total mortality in an elderly urban population. *Angiology*. 2019;70(10):929–937. doi:10.1177/0003319719857270
29. Weber T, Mayer CC. "Man is as old as his arteries" taken literally: in search of the best metric. *Hypertension*. 2020;76(5):1425–1427. doi:10.1161/ hypertensionaha.120.16128
30. Park KE, Pepine CJ. Assessing cardiovascular risk in women: looking beyond traditional risk factors. Trends in cardiovascular medicine. *Feb*. 2015;25(2):152–153. doi:10.1016/j.tcm.2014.10.024
31. Hu SS. Writing committee of the report on cardiovascular H, diseases in C. cardiovascular risk factors in China. *J Geriatr Cardiol*. 2024;21 (2):153–199. doi:10.26599/1671-5411.2024.02.008
32. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol*. 2019;16(4):203–212. doi:10.1038/s41569-018-0119-4
33. Cortes-Canteli M, Iadecola C. Alzheimer's disease and vascular aging: JACC focus seminar. *J Am Coll Cardiol*. 2020;75(8):942–951. doi:10.1016/ j.jacc.2019.10.062
34. Nazzi C, Avenanti A, Battaglia S. The involvement of antioxidants in cognitive decline and neurodegeneration: mens sana in corpore sano. *Antioxidants*. 2024;13(6). doi:10.3390/antiox13060701
35. Nunes YC, Mendes NM, Pereira de Lima E, et al. Curcumin: a golden approach to healthy aging: a systematic review of the evidence. *Nutrients*. 2024;16(16). doi:10.3390/nu16162721
36. Pagotto GLO, Santos L, Osman N, et al. Ginkgo biloba: a leaf of hope in the fight against alzheimer's dementia: clinical trial systematic review. *Antioxidants*. 2024;13(6):651. doi:10.3390/antiox13060651
37. Tanaka H, Munakata M, Kawano Y, et al. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. *J Hypertens*. 2009;27(10):2022–2027. doi:10.1097/HJH.0b013e32832e94e7
38. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European society of hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41(12):1874–2071. doi:10.1097/HJH.0000000000003480