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Original Article

Association between the Estimated Pulse Wave Velocity and Stroke: A Population Based Cross-Sectional Study

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Abstract:

Aims: Pulse wave velocity (PWV) is a well-established measure of arterial stiffness which has been linked to cardiovascular disease. In recognition of the challenges associated with measuring PWV, researchers have developed an alternative method by equations rely on age and mean arterial pressure (ePWV). However, whether this parameter is indeed associated with stroke, has not been fully verified.

Methods: The current study was a branch of the ChinaHEART cohort in middle China that involved a total of 6860 community-dwelling adults. We examine the association between ePWV and stroke in a cross-sectional survey.

Results: According to restricted cubic spline analysis, the odds of stroke was increased in individuals with a higher level of ePWV; ROC analysis indicated that ePWV had good discriminatory power for stroke (AUC=0.746 in the adjusted model); according to logistic regression, the OR of each 1 m/s increase of ePWV was 1.26 (1.14-1.39, P<0.001), and the high ePWV group (≥10 m/s) had 2.22 (1.54-3.21, P<0.001) times risk of incident stroke.

Conclusions: This study demonstrates that ePWV is independently linked to stroke. These findings support the use of vascular aging markers in the fight against stroke.

Key words: ePWV, stroke, population study, cross-sectional study.

1. Introduction

Stroke is a major cause of death and disability worldwide. According to the Global Burden of Disease Study 2019, stroke is the second leading cause of death and the third leading cause of death and disability combined worldwide.(GBD 2019 Stroke Collaborators, 2021) Studies have shown that identifying high-risk individuals and implementing effective intervention and management can significantly reduce the incidence of adverse cerebrovascular events and disease burden.(D'Agostino et al., 2008) Framingham risk score and other scoring tools are commonly used to assess the risk of cardiovascular disease.(Damen et al., 2016) Recent studies have shown that in predicting the risk of adverse cardiovascular events, the assessment of arterial stiffness can provide independent predictive value beyond the Framingham risk score.(Bérard et al., 2013; Ohkuma et al., 2017)

Pulse wave velocity (PWV) is a well-established measure of arterial stiffness, which has been linked to cardiovascular disease, renal outcomes, and mortality in the literature. Currently, there are various non-invasive methods to measure PWV, including carotid-femoral PWV (cfPWV) and

brachial-ankle PWV, with cfPWV being considered the gold standard.(Townsend et al., 2015) Despite the standardization, simplicity, and noninvasive nature of cfPWV measurement, its use in large cohort studies has been limited by various factors. These include the requirement for specialized equipment and technical proficiency, which may not be available in resource-constrained environments or research studies that do not involve in-person data collection with suitably trained and equipped personnel.(Vlachopoulos et al., 2015; Williams et al., 2018) Consequently, researchers have endeavored to develop and validate an alternative method for measuring PWV, in recognition of the challenges associated with measuring cfPWV.(Greve et al., 2016) Previous studies have demonstrated that arterial stiffness can be derived from validated equations (ePWV), which rely on age and mean arterial pressure.(Reference Values for Arterial Stiffness' Collaboration, 2010) As aortic pulse wave velocity can be estimated mathematically, the need for specialized equipment is eliminated, thereby increasing its clinical applicability. However, the utility of this parameter, especially whether this parameter is indeed associated with stroke, has not been fully verified.(Jae et al., 2021, 2022; Zhou et al., 2023)

In this article, we examine the association between ePWV and stroke in a cross-sectional survey. We estimate overall models that control statistically for gender, BMI, disease history, blood glucose and lipid levels. Multivariable analyses consider potential confounders, including socioeconomic status; health behaviors (e.g., physical activity and smoking); comorbid disease conditions and associated medication use; and blood biomarkers that are correlated with CVD.

Methods

Participants

This cross-sectional study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.(von Elm et al., 2008) The study data were applied from the ChinaHEART (Health Evaluation And risk Reduction through nationwide Teamwork) Cohort, a nationwide, government-funded, and population-based CVD screening study.(Wang et al., 2023) The details of the design and methods of the ChinaHEART cohort have been described elsewhere.(Lu et al., 2016) The current study was a branch of the ChinaHEART cohort in middle China that involved a total of 6860 community-dwelling adults enrolled by two township hospitals in Luohe city during March 2021 - February 2022. Those who were aged 35 to 75 years residing in the nearby area of the two township hospitals were eligible for this study and were recruited by research assistants. The study protocol was approved by the institutional ethic board of Fuwai Hospital and was further approved by the local ethic board of Luohe Central Hospital. All participants signed informed consent. All the performances were in accordance with the Declaration of Helsinki.

Data Collection and Variables

Information on demographics (age and sex), socioeconomic status, smoking and drinking status, comorbid condition, medical history, and current medication used was collected during face-to-face interviews by trained staff. Height and body weight were measured using standard protocols, and body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured two times on the right upper arm after 5 min of rest in a seated position using an electronic blood pressure monitor. Fasting plasma glucose and lipid profiles were measured using fingertip blood samples. ePWV was calculated from age and mean blood pressure (MBP):
$ePWV=9.587-0.402\times age+4.560\times10^{-3}\times age^2-2.621\times10^{-5}\times age^2\times MBP+3.176\times10^{-3}\times age\times MBP-1.832\times10^{-2}\times MBP$. MBP was calculated as DBP +0.4 (SBP−DBP).(Greve et al., 2016)

Statistics

Based on whether the participants had a history of stroke, we divided the participants into case and control groups; and the control group was further divided into four subgroups based on the quartiles of ePWV levels. We used the Kolmogorov-Smirnov normality test to test the normality of continuous variables. If the data meet the normal distribution, the study uses mean ± standard deviation (SD) to describe the corresponding data distribution; if the data does not conform to the normal distribution, the median (interquartile range) is used to describe the corresponding data distribution. For comparisons between different

groups, t-test or analysis of variance is used if data meet normal distribution; if data do not conform to normal distribution, rank sum test is used. Chi-square tests were used to compare the differences of the percentages of categorical variables between different groups. We conducted logistic regression analyses to examine the association between ePWV and stroke. In the logistic regression, we employed crude model without adjustment, and the adjusted model controlled for multiple variants including gender, marriage, BMI, waist, fasting glucose, TG, TC, LDL, HDL, smoking, alcoholic, diabetes, hypertension, and coronary artery disease. Potential nonlinear associations between the levels of ePWV and the risk of stroke were examined with restricted cubic splines analyses adjusted for multiple variables, with five knots located at the 5th, 27.5th, 50th, 72.5th and 95th percentiles. To determine the discriminatory power of ePWV for stroke, we adopted the receiver operating characteristic (ROC) curve analysis, the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) index.

Results

A total of 6,860 subjects were enrolled in this study, including 192 stroke patients and 6,668 non-stroke controls. Demographic Characteristics and Clinical Parameters were listed in Table 1. There were no significant differences in married status, current smoking, drinking, CHD history, BMI, DBP, and HR between the stroke and non-stroke groups, while differences with respect to the following parameters were all statistically significant ($p < 0.05$): gender, age, hypertension, diabetes, TC, LDL, TG, HDL, Glu, Waist and SBP. The ePWV level of the stroke group was higher than the non-stroke group. The distribution of all the studied parameters was illustrated in Figure 1 (continuous variables) and Figure 2 (categorial variables).

Table 1 Basic clinical characteristics of the study population

	Non-stroke	Stroke	P
Number	6668	192	
Female (%)	4179 (62.7)	95 (49.5)	<0.001
Age (mean (SD))	57.60 (10.23)	63.01 (8.21)	<0.001
Age group (%)			<0.001
35-39	382 (5.7)	1 (0.5)	
40-49	1111 (16.7)	12 (6.2)	
50-59	2175 (32.6)	53 (27.6)	
60-69	2076 (31.1)	78 (40.6)	
70-75	924 (13.9)	48 (25.0)	
Married (%)	5914 (88.7)	174 (90.6)	0.472
Current smoke (%)	1334 (20.0)	37 (19.3)	0.873
Drinking (%)	372 (5.6)	8 (4.2)	0.494
HTN (%)	1483 (22.2)	96 (50.0)	<0.001
DM (%)	404 (6.1)	24 (12.5)	<0.001
CHD (%)	104 (1.6)	6 (3.1)	0.158
BMI (mean (SD))	25.30 (3.35)	25.75 (3.49)	0.063
TC (mean (SD))	4.88 (1.09)	4.62 (1.35)	0.001
HDL (mean (SD))	1.47 (0.34)	1.41 (0.33)	0.022
TG (mean (SD))	1.74 (0.88)	1.58 (0.85)	0.015
LDL (mean (SD))	2.67 (0.92)	2.52 (1.12)	0.044
Glu (mean (SD))	5.83 (1.48)	6.19 (1.88)	0.001
Waist (mean (SD))	86.24 (9.53)	89.21 (10.13)	<0.001
SBP (mean (SD))	137.71 (16.66)	145.00 (17.23)	<0.001
DBP (mean (SD))	83.70 (10.80)	84.51 (11.88)	0.307
HR (mean (SD))	76.54 (10.27)	77.67 (10.99)	0.132
ePWV (mean (SD))	9.94 (1.75)	10.93 (1.44)	<0.001

Data are presented as mean (SD) for normally distributed variables, median (IQR) for non-normally distributed variables, and number (percentage) for categorical variables. HTN, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

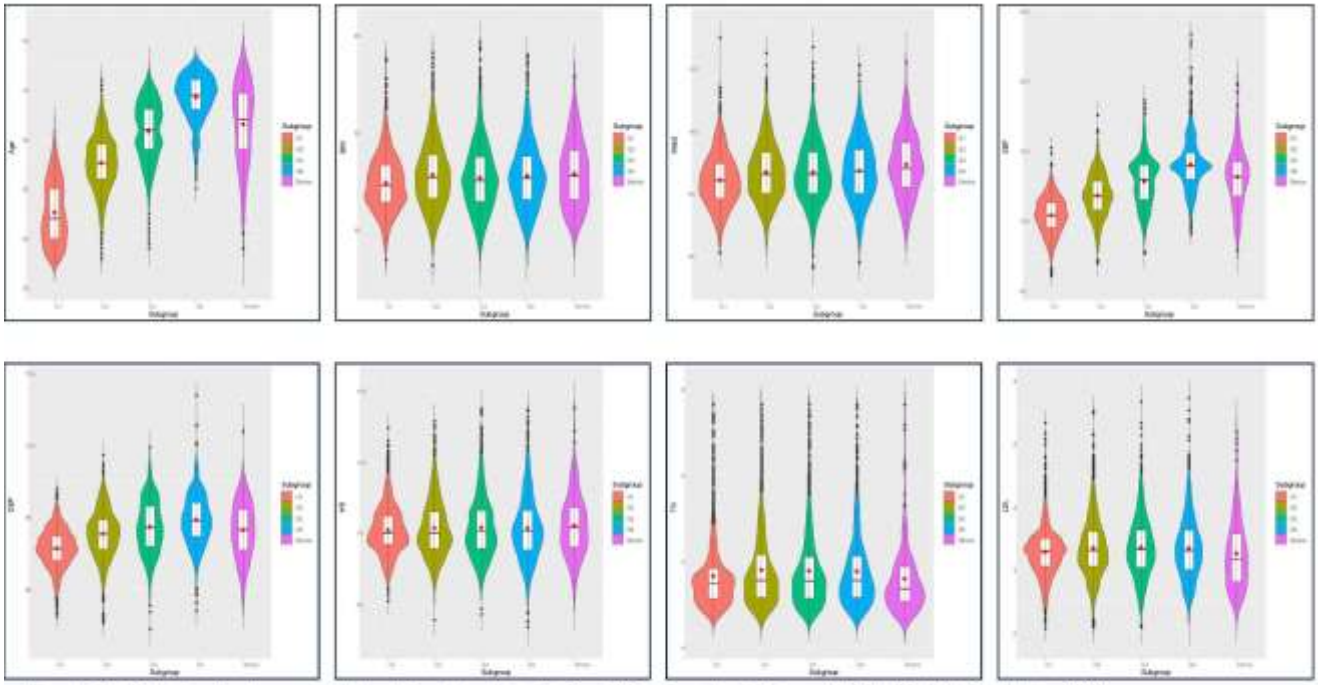


Figure 1. The distribution of continuous variables by violin and box plots. Significant difference was detected for age, TC, LDL, TG, HDL, Glu, Waist and SBP.

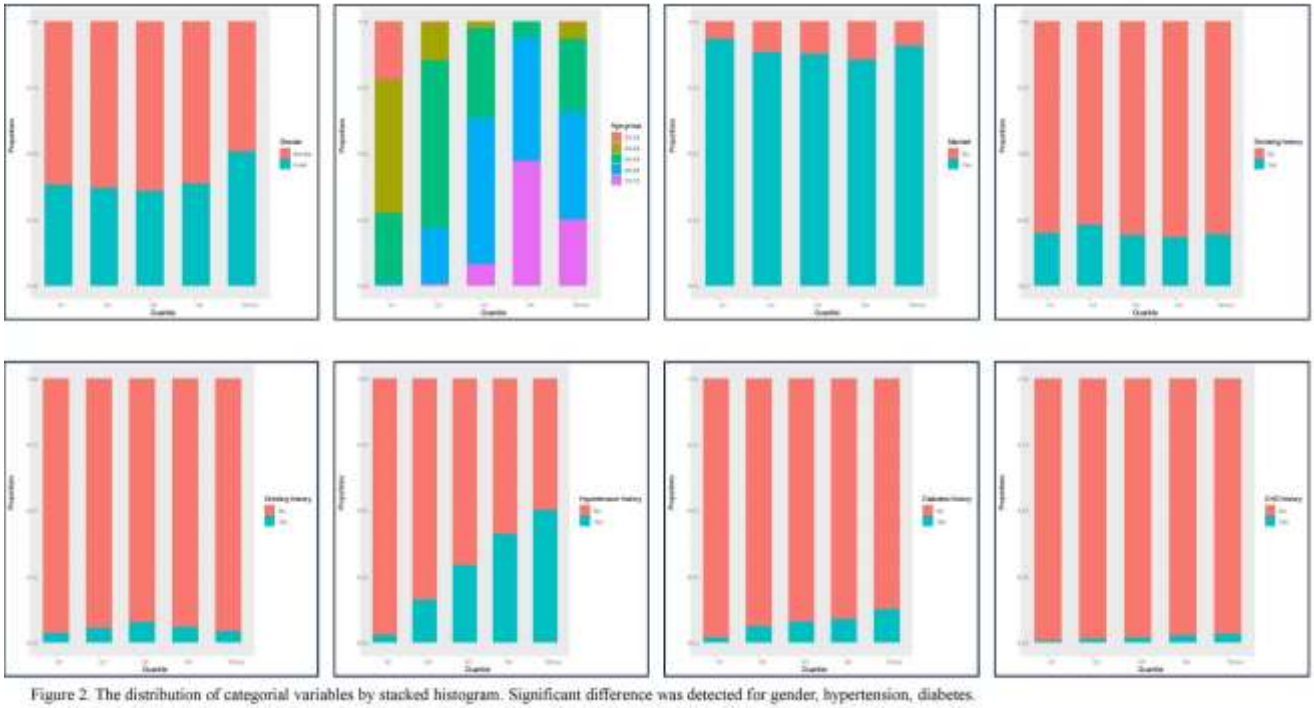


Figure 2. The distribution of categorial variables by stacked histogram. Significant difference was detected for gender, hypertension, diabetes.

In Figure 3, we used restricted cubic spline to assess the relationship between ePWV and stroke. It indicated the odds of stroke increased in individuals with a higher level of ePWV. The discriminatory power of ePWV was evaluated by the ROC analysis (Figure 4). In the crude model, the discriminatory power of ePWV for stroke displayed an AUC of 0.663 (0.629-0.698), with a cut-off value of 10.005 (sensitivity 0.77, specificity 0.50). For convenience, we defined

high ePWV as ≥10m/s, and this cut-off value was used in subsequent logistic regression analyses. When the ROC analysis incorporates all covariates, the AUC increased to 0.746 (0.712-0.781). ROC analyses by gender found that in the crude model, the AUC of ePWV for male was 0.640 (0.587-0.693), for female was 0.687 (0.644-0.731); in the fully adjusted model, the AUC for male was 0.755 (0.702-0.808), for female was 0.740 (0.693-0.786). The results of reclassification analysis showed that NRI (0.291, 95% CI: 0.143–0.439, P<0.001) and IDI (0.004, 95% CI: 0.004–0.006, P=0.008) was significant after adding ePWV into traditional risk factors.

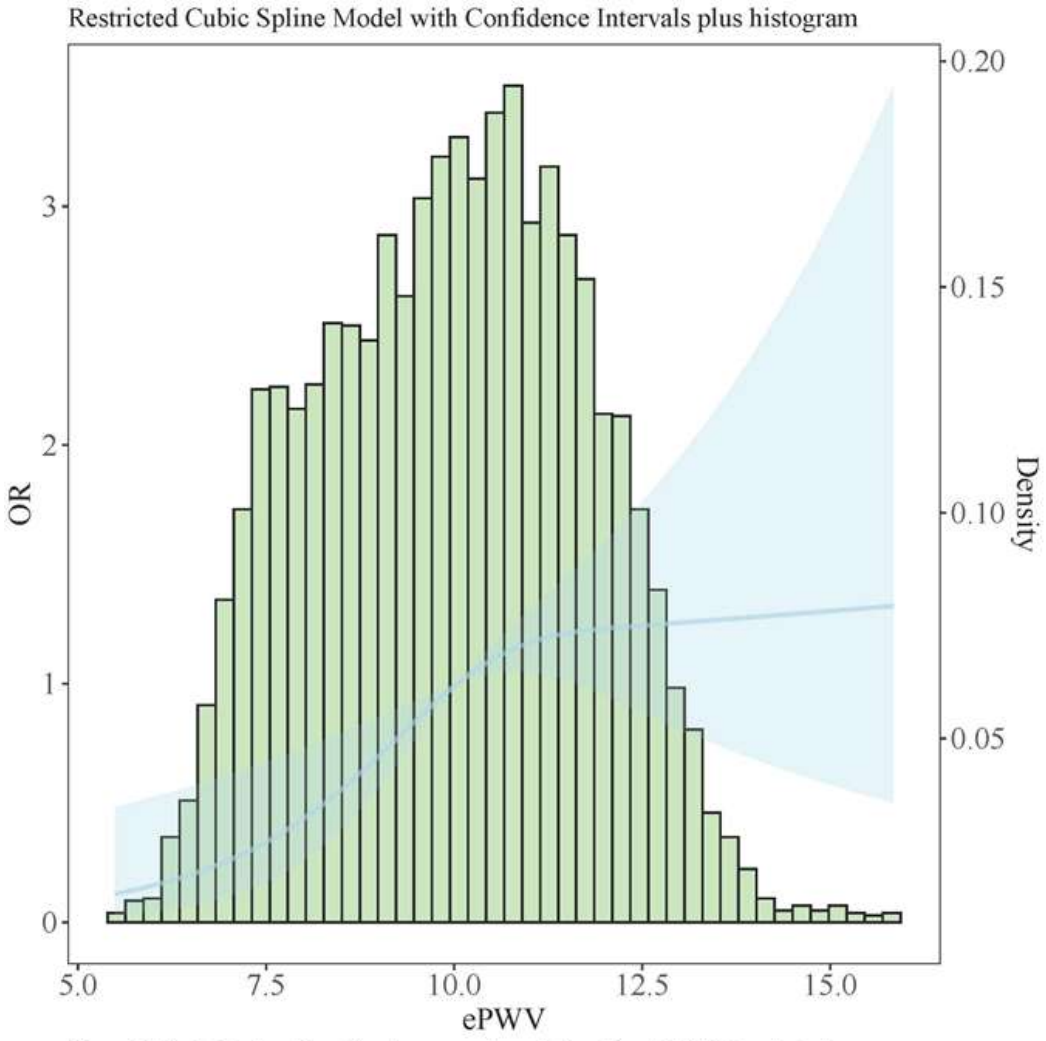
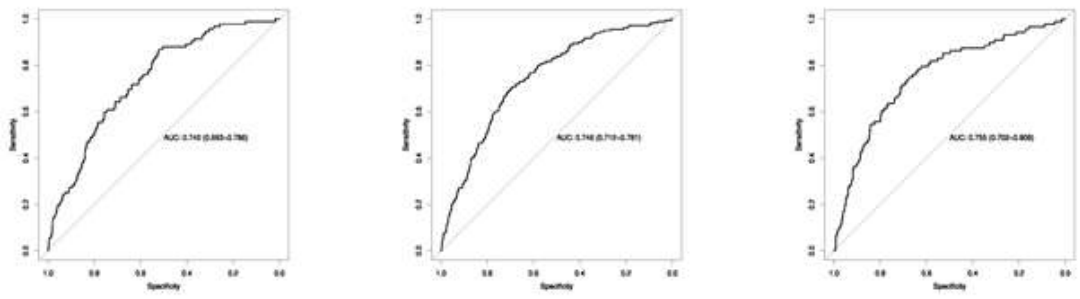


Figure 3. Restricted cubic spline to assess the relationship of ePWV and stroke.



A. All participants B. Male C. Female

Figure 4. ROC curve to illustrate the discriminatory power of ePWV for stroke.

Table 2. Association between ePWV and stroke by logistic regression

	Crude		Adjusted*	
	Odds Ratio (95% CI)	p-alue	Odds Ratio	P-value
All				
Each 1 m/s increment	1.40 (1.29-1.53)	<0.001	1.26 (1.14-1.39)	<0.001
Low ePWV (<10 m/s) vs. High ePWV (≥10 m/s)	3.25 (2.32-4.55)	<0.01	2.22 (1.54-3.21)	<0.001
Male				
Each 1 m/s increment	1.33 (1.18-1.50)	<0.001	1.17 (1.02-1.34)	0.023
Low ePWV (<10 m/s) vs. High ePWV (≥10 m/s)	2.60 (1.66-4.09)	<0.001	1.79 (1.08-2.94)	0.025
Female				
Each 1 m/s increment	1.48 (1.31-1.68)	<0.001	1.34 (1.16-1.55)	<0.001
Low ePWV (<10 m/s) vs. High ePWV (≥10 m/s)	4.22 (2.52-7.08)	<0.001	2.84 (1.63-4.94)	<0.001

***Adjusted for gender, marriage, bmi, waist, fasting glucose, TG, TC, LDL, HDL, smoking, alcoholic, diabetes, hypertension and coronary artery disease.**

The results of association analysis by logistic regression were listed in Table 2. In the crude model, each 1 m/s increase of ePWV increased the risk of prevalent stroke by 40.0%; compared with low ePWV, those with high ePWV (≥10m/s) had 3.25 times risk of prevalent stroke. With the adjustment of covariates, the OR of each 1 m/s increase of ePWV reduced to 1.26, and the high ePWV group had 2.22 times risk of prevalent stroke. The stratified analyses by gender revealed the same trend towards a positive association between ePWV and stroke.

Discussion

In the present study, we found that ePWV was positively correlated with stroke. After adjusting for related risk factors, the association was observed to be significant. Stratified analysis based on gender and age group found that this association was consistent across all subgroups. ROC analyses indicated that ePWV has good discriminatory power for stroke.

The results of the present study align with previous research indicating an association between arterial stiffness and cardiovascular disease (CVD), albeit with variations in study design, populations, and endpoints used.(Chen et al., 2016; Mattace-Raso et al., 2006; Ohkuma et al., 2017; Sequí-Domínguez et al., 2020; Vlachopoulos et al., 2019; Zhou et al., 2023) The findings suggest that ePWV could serve as a target factor in intervention studies to establish causality and assess the magnitude of stroke risk reduction. Furthermore, this non-invasive technique, easily derived from routine examinations, holds potential for future prognostic research in identifying individuals at higher risk of stroke.

Given the rapid aging of the population and the established link between arterial stiffness and stroke, the burden of aging-related stroke is expected to rise. Lifestyle modifications, such as aerobic exercise,(Park et al., 2020) weight loss,(Tanabe et al., 2021) and dietary sodium restriction,(D'Elia et al., 2018) have shown promise in reversing or mitigating arterial aging. Considering that arterial aging is a recognized risk factor for stroke, adopting healthy vascular aging strategies can effectively delay or reduce age-related increases in arterial stiffness and stroke incidence. Implementing these strategies would significantly contribute to stroke prevention.

The main strength of this study is that we have a good study design and a strict standard research process management system. There are relevant standards for the collection of all clinical data, including the assessment of medical history and

risk factors and the measurement of blood pressure and blood lipids, which ensures the accuracy and completeness of our study data. Furthermore, we used multivariate logistic regression and corrected for traditional CVD risk factors, ensuring robust and reliable results. However, this study also has some limitations. First, our study is a local branch of the national study, where all the participants were residents, and thus the findings were universal and underrepresented. However, the estimation of the study parameters depends only on blood pressure and age, which seems to ignore the effects of regional differences and lifestyle. Secondly, this study was designed as a retrospective observational study, which cannot assess the predictive value of arteriosclerosis for the occurrence of stroke or whether the intervention for arteriosclerosis could reduce the incidence of subsequent stroke events. These issues require our ongoing follow-up of the study population to conclude.

In conclusion, this study demonstrates that the estimation of PWV based on age and blood pressure is independently linked to stroke in a representative sample of middle-aged and older adults in China. These findings support the use of vascular aging markers in the fight against stroke.

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Author Contributions

Conceptualization: YS; Methodology: HW and QX; Formal analysis and investigation: SH, JW and HW; Writing-original draft preparation: SH, JW and HW; Writing: SH and HW; Funding acquisition: HW and QX; Supervision: YS. All authors contributed to subsequent revisions and approved the final version. All authors read and approved the final manuscript.

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Competing Interests: The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was conducted with approval from the Ethics Committee of Fuwai Hospital (2014–574) as the Central Ethic. The local Ethics Committee of Luohe Central Hospital gave consent to the Central Ethic. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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