

Reversed L-shaped Association Between Baseline Brachial-ankle Pulse Wave Velocity and Short-Term Risk of First Stroke in Patients With Hypertension: A Population-based Cohort Study

Lihua Hu

Peking University First Hospital

Chonglei Bi

People's Hospital of Rongcheng, Shangdon

Lishun Liu

China Agricultural University

Yun Song

China Agricultural University

Yue Zhang

China Pharmaceutical University

Binyan Wang

Anhui Medical University

Chongqian Fang

People's Hospital of Rongcheng

Hai Ma

Family Planning Association of Uganda: Reproductive Health Uganda

Xiao Huang

Nanchang University Second Affiliated Hospital

Yan Zhang

Peking University First Hospital

Huihui Bao

Nanchang University Second Affiliated Hospital

Ping Li

Nanchang University Second Affiliated Hospital

Xiping Xu

China Agricultural University

Xiaobin Wang

Johns Hopkins University - Homewood Campus: Johns Hopkins University

Xiaoshu Cheng

Nanchang University Second Affiliated Hospital

Yong Huo

Peking University First Hospital

Jianping Li (✉ lijianping03455@pkufh.com)

Peking University First Hospital

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Abstract

Background: Brachial–ankle pulse wave velocity (baPWV) is available as a noninvasive measure of arterial stiffness. However, little information is available on the association between baPWV and the short-term risk of stroke in patients with hypertension. Therefore, our current study aimed to assess the association between baseline baPWV and short-term risk of first stroke. We were particularly interested in identifying those individuals at high risk of developing stroke among patients with hypertension.

Methods: From January 1, 2017, to December 31, 2017, a total of 9787 individuals without preexisting stroke from the China Hypertension Registry Study were included in this analysis. Follow-up continued until December 31, 2018. The primary outcome was first stroke. The crude and adjusted risks of first stroke were estimated by hazard ratios (HRs) and 95% CIs using Cox proportional hazards models, without or with adjusting for pertinent covariates, respectively.

Results: During a median follow-up of 20.8 months, there were 138 total first strokes including 123 first ischemic strokes and 15 first hemorrhagic strokes. Smooth curve showed that the relationship between baPWV and risk of first stroke and first ischemic stroke was curvilinear and reversed L-shaped. High baPWV levels (≥ 21.31 m/s) was associated with increased risk of first stroke (HR = 1.52; 95% CI: 1.05-2.21) and first ischemic stroke (HR = 1.53; 95% CI: 1.03-2.26) compared to low baPWV levels (< 21.31 m/s). E-value analysis suggested robustness to unmeasured confounding. Our findings may propose the applicability of baPWV measurement for prediction of stroke development, especially in subjects with a low cardiovascular (CVD) risk.

Conclusions: High baPWV levels (≥ 21.31 m/s) were associated with increased the short-term risk of first stroke among Chinese hypertensive adults, compared to low baPWV levels, supporting a reversed L-shaped association. Our findings warrant additional investigation.

Introduction

Stroke is the leading cause of death in China and the second leading cause of death in the world^[1, 2]. Primary prevention is regarded as the best option to reduce the population burden of stroke^[3]. Specifically, hypertension is a well-recognized major modifiable risk factor for stroke^[4]. Despite great efforts to identify traditional risk factors and interventions focusing on modifying unhealthy lifestyles, rising stroke incidence and mortality are still observed in China. Therefore, there is an urgent need to identify novel modifiable risk factors to inform the primary prevention of stroke and to identify those individuals at highest risk of developing stroke among patients with hypertension.

Arteriosclerosis is a recognized predictor of cardiovascular diseases and stroke^[5-7]. Carotid-femoral pulse wave velocity (cfPWV) is the gold standard for measuring large arterial stiffness. As it is time consuming to measure, involves manipulation of the femoral artery area, and has bad reproducibility with requiring a highly skilled technician, the brachial-ankle pulse wave velocity (baPWV) is launched. BaPWV

is available as a noninvasive measure of central and peripheral arterial stiffness^[8]. Moreover, baPWV has been reported to be closely correlated with the directly measured cfPWV^[9]. The measurement of baPWV has been proposed for the early detection of vascular damage in hypertensive patients^[10].

Indeed growing evidence has established the associations of baPWV with uncontrolled blood pressure (BP), cardiovascular mortality and morbidity among the general population^[11–14]. Although few studies have found a relationship between increased baPWV and incidence of stroke^[12, 15, 16], the reference values for baPWV are still unknown in healthy populations and patients at increased cardiovascular risk. Additionally, whether baPWV maintains a predictive value in hypertensive patients requires further investigation, for evidence on the association is limited.

Therefore, our current study aimed to assess the association between baseline baPWV and short-term risk of first stroke using data from China Hypertension Registry Study (CHRS). We were particularly interested in identifying those individuals at high risk of developing stroke among patients with hypertension.

Methods

Study design and population

Our present study is a subset of the CHRS which was an ongoing community-based non-intervention, prospective, observational, multicenter, real-world registry study and was mainly conducted in Rongcheng county, Shandong province, Lianyungang, Jiangsu province, China and Wuyuan county, Jiangxi province. The CHRS study recruited consecutive consenting individuals with hypertension (untreated or treated with antihypertensive drugs) or with suspected hypertension. It was designed to assess the related factors of hypertension affecting its prognosis, and finally to construct the risk prediction model of cardio-cerebral and renal vascular diseases. Exclusion criteria were: psychological or nervous system impairment and inability to provide informed consent or unwillingness/inability to adhere to study protocol. All participants were asked to perform the epidemiological questionnaire and physical examination. The study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China. All participants signed an approved written consent after it was explained to them.

The current study utilized data from the Rongcheng CHRS. From January 2017 to December 2017, 111297 patients with hypertension or with suspected hypertension in Shandong Rongcheng were screened, and we collected their baseline general information. 10935 participants were randomly selected for baPWV assessment. Next, we selected participants according to the exclusion criteria listed below: ankle brachial index (ABI) < 0.90 (n = 638), having history of stroke (n = 385), and having history of atrial fibrillation (n = 125).

BaPWV measurement

In this study, the exposure variable was baseline baPWV. BaPWV was automatically measured by PWV/ABI instruments (form PWV/ABI, BP-203RPE; Omron-Colin, Japan)^[17]. The validation of this automatic device and its reproducibility have been previously published^[18]. Occlusion and monitoring cuffs matched with oscillometric sensors were wrapped around subjects' arms and the ankles, and pulse volume wave forms of the bilateral brachial and posterior tibial arteries were recorded simultaneously to determine the time interval between the initial increase in brachial and tibial waveforms (the transit time, Tba). The transmission distance from the brachium to ankle was calculated according to body height. The path length from the suprasternal notch to the brachium (Lb) was obtained using the following equation: $Lb = 0.2159 \times \text{height of the patient (cm)} - 2.0734$. The path length from the suprasternal notch to the ankle (La) was obtained using the following equation: $La = 0.8129 \times \text{height of the patient (cm)} + 12.328$. And the baPWV value was calculated as the ratio of transmission distance from the brachium to ankle divided by the transit time: $baPWV = (La - Lb)/Tba$. The maximum of the right and left-side baPWV values was used for final analysis^[18].

Outcomes

The primary outcome of this study was a first nonfatal or fatal stroke. Secondary outcomes included first ischemic stroke (fatal and nonfatal) and first hemorrhagic stroke (fatal and nonfatal). Data were linked to stroke data through December 31st, 2018. The short-term stroke occurred within 2 years of follow-up. Information on incidence of stroke for all participants was obtained via the Center for Disease Control and Prevention of Rongcheng and checked against the national health insurance system with electronic linkage to all hospitalizations, or ascertained through active follow-up. Diseases were coded according to the International Classification of Diseases, Tenth Revision. Secondary outcomes included first ischemic stroke (I63) and first hemorrhagic stroke (I60–I61). The primary outcome (first nonfatal or fatal stroke) included first ischemic stroke (I63), first hemorrhagic stroke (I60–I61), and no type stroke (I64).

Local authorities from medical institutions are required to report all new cases of stroke to the local Center for Disease Control and Prevention. A report card which includes information on demographics, diagnostic basis, and date of stroke is required to be submitted on the 28th of each month. Quality control, including finding and deleting repeated cases, error checking, and determining any missed cases, is completed by trained officials. Furthermore, the local Center for Disease Control and Prevention is also responsible for deleting repeated cases and finding logistical errors and missed cases. In addition, 5% of all uploaded cases are randomly chosen for further confirmation by phone or door-to-door interviews.

Covariates

At this baseline assessment, participants reported on their lifestyle, medical conditions and demographic information; medical history, health status, and medication intake were queried by trained health professionals. The anthropometric examinations included weight, height, waist circumference and hip circumference. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m^2). Variables thought to be confounders based on existing literature

and clinical judgment were included. Therefore, the following variables were used to construct the fully adjusted model. Continuous variables included age (years), BMI (kg/m^2), systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg). Categorical variables consisted of sex, smoking (current smoker, former smoker or never smoker), drinking (current drinker, former drinker or never drinker), education status (less than high school, high school/equivalent, or greater than high school), labor intensity (light, moderate or heavy), sleep quality (poor, moderate or good), self-reported history of diseases [hypertension, diabetes, hyperlipidemia and coronary heart disease (CHD)], medication use (antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs). Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 or self-reported history of hypertension or use of medications to treat hypertension^[20].

Statistical analysis and Sensitivity analysis

Data are presented as mean \pm SD for continuous variables and as frequency (%) for categorical variables. The population characteristics by baPWV quartiles were compared using analysis of Variance (ANOVA) tests (continuous variables), or χ^2 tests (categorical variables), accordingly. Crude cumulative incidence across baPWV quartiles was estimated using Kaplan-Meier curves. Restricted cubic spline, and Cox proportional hazards models were performed to evaluate the association between baseline baPWV and first stroke and its subtypes. Potential confounders included in the Cox proportional hazards models were all adjusted for the same covariates: age, sex, BMI, education status, smoking status, drinking status, labor intensity, sleep quality, hypertension, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs. BaPWV was evaluated using models for categorical variables according to quartiles. The lowest quartile (Q1) of baPWV was considered as a reference group. The crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated by the Cox proportional hazards regression model.

The robustness of these findings was assessed in multiple sensitivity analyses. First, we explored the potential for unmeasured confounding between baPWV and first stroke by calculating E-values^[21]. The E-value quantifies the required magnitude of an unmeasured confounder that could negate the observed association between baPWV and first stroke. Second, in further exploratory analyses, potential effect modifications of the association between baPWV and first stroke were assessed for the variables: age (< 65 vs. 65 years), sex, BMI (< 25 vs. 25 kg/m^2), SBP (< 140 vs. 140 mm Hg), DBP (< 90 vs. 90 mm Hg), smoking status, sleep quality, self-reported diabetes, self-reported hyperlipidemia and self-reported CHD.

All analyses were performed using the statistical package R (<http://www.R-project.org>, The R Foundation) and a 2-sided type I error probability of 0.05.

Results

Baseline characteristics of study participants

As shown in Fig. 1, a total of 9787 participants were included in this analysis. The baseline characteristics for all participants and by baPWV quartiles are listed in Table 1. The mean age was 66.7 ± 7.9 years, and 34.4% of subjects were men ($n = 3363$). 97.3% (9521/9787) were hypertensive patients. The mean baPWV level at baseline was 19.1 ± 4.5 m/s. A higher baPWV value was associated with female sex, older age, higher blood pressures, higher presence of hypertension, diabetes mellitus, CHD and higher use of glucose-lowering drugs. BMI, current smoking, education level, labor intensity, history of hyperlipidemia and use of lipoprotein-lowering drugs were negatively associated with baPWV.

Table 1
Baseline characteristics of participants according to baseline baPWV quartiles

Characteristics*	Total	BaPWV, m/s				P value
		Q1 (< 16.00)	Q2 (16.00- 18.33)	Q3 (18.33- 21.31)	Q4 (≥ 21.31)	
N	9787	2436	2455	2445	2451	
Sex, n (%)						< 0.001
Male	3363 (34.4)	918 (37.7)	857 (34.9)	816 (33.4)	772 (31.5)	
Female	6424 (65.6)	1518 (62.3)	1598 (65.1)	1629 (66.6)	1679 (68.5)	
Age, y	66.7 \pm 7.9	62.3 \pm 7.7	65.3 \pm 7.3	67.9 \pm 6.8	71.3 \pm 7.0	< 0.001
BMI, kg/m ² [¶]	27.1 \pm 3.7	27.6 \pm 3.8	27.3 \pm 3.7	27.0 \pm 3.6	26.5 \pm 3.6	< 0.001
SBP, mm Hg	155.8 \pm 19.5	148.4 \pm 17.7	153.6 \pm 17.9	157.9 \pm 18.7	163.3 \pm 20.6	< 0.001
DBP, mm Hg	88.0 \pm 10.8	87.7 \pm 10.4	87.8 \pm 10.7	87.7 \pm 10.7	88.8 \pm 11.4	< 0.001
BaPWV, m/s	19.1 \pm 4.5	14.5 \pm 1.2	17.2 \pm 0.7	19.7 \pm 0.8	25.2 \pm 4.1	< 0.001
Smoking status, n (%)						< 0.001
Never	7815 (79.9)	1898 (77.9)	1946 (79.3)	1965 (80.4)	2006 (81.8)	

Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile).

Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.

*Data are presented as number (%) or mean \pm SD.

[¶]BMI was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m²).

[†]Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 or self-reported history of hypertension or use of medications to treat hypertension.

Characteristics*	Total	BaPWV, m/s				P value
		Q1 (< 16.00)	Q2 ($16.00-18.33$)	Q3 ($18.33-21.31$)	Q4 (≥ 21.31)	
Former	687 (7.0)	162 (6.7)	189 (7.7)	161 (6.6)	175 (7.1)	
Current	1284 (13.1)	376 (15.4)	320 (13.0)	318 (13.0)	270 (11.0)	
Drinking status, n (%)						0.685
Never	7863 (80.3)	1935 (79.4)	1991 (81.1)	1964 (80.3)	1973 (80.5)	
Former	260 (2.7)	73 (3.0)	65 (2.6)	57 (2.3)	65 (2.7)	
Current	1664 (17.0)	428 (17.6)	399 (16.3)	424 (17.3)	413 (16.9)	
Education, n (%)						< 0.001
<High school	8776 (89.7)	2072 (85.1)	2162 (88.1)	2236 (91.5)	2306 (94.1)	
High school	927 (9.5)	336 (13.8)	269 (11.0)	185 (7.6)	137 (5.6)	
>High school	84 (0.9)	28 (1.1)	24 (1.0)	24 (1.0)	8 (0.3)	
Labor intensity, n (%)						< 0.001
Light	6551 (66.9)	1553 (63.8)	1630 (66.4)	1648 (67.4)	1720 (70.2)	
Moderate	2426 (24.8)	651 (26.7)	629 (25.6)	586 (24.0)	560 (22.8)	

Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile).

Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.

*Data are presented as number (%) or mean \pm SD.

[¶]BMI was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m^2).

[†]Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 or self-reported history of hypertension or use of medications to treat hypertension.

Characteristics*	Total	BaPWV, m/s				P value
		Q1 (< 16.00)	Q2 ($16.00-18.33$)	Q3 ($18.33-21.31$)	Q4 (≥ 21.31)	
Heavy	810 (8.3)	232 (9.5)	196 (8.0)	211 (8.6)	171 (7.0)	
Sleep quality, n (%)						0.519
Poor	4973 (50.8)	1253 (51.4)	1241 (50.5)	1213 (49.6)	1266 (51.7)	
Moderate	3066 (31.3)	761 (31.2)	762 (31.0)	803 (32.8)	740 (30.2)	
Good	1748 (17.9)	422 (17.3)	452 (18.4)	429 (17.5)	445 (18.2)	
Hypertension, n (%) [†]	9521 (97.3)	2310 (94.8)	2394 (97.5)	2396 (98.0)	2421 (98.8)	< 0.001
Self-reported diabetes, n (%)	1792 (18.3)	318 (13.1)	412 (16.8)	508 (20.8)	554 (22.6)	< 0.001
Self-reported hyperlipidemia, n (%)	1732 (17.7)	426 (17.5)	465 (18.9)	467 (19.1)	374 (15.3)	0.001
Self-reported CHD, n (%)	1546 (15.8)	342 (14.0)	381 (15.5)	396 (16.2)	427 (17.4)	0.012
Medication use, n (%)						
Antihypertensive drugs	7772 (79.4)	1901 (78.0)	1933 (78.7)	1977 (80.9)	1961 (80.0)	0.067
Glucose-lowering drugs	1144 (11.7)	186 (7.6)	258 (10.5)	327 (13.4)	373 (15.2)	< 0.001
Lipoprotein-lowering drugs	156 (1.6)	51 (2.1)	52 (2.1)	24 (1.0)	29 (1.2)	< 0.001
Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile).						
Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.						
*Data are presented as number (%) or mean \pm SD.						
[¶] BMI was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m^2).						
[†] Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 or self-reported history of hypertension or use of medications to treat hypertension.						

Characteristics*	Total	BaPWV, m/s				P value
		Q1 (< 16.00)	Q2 ($16.00-18.33$)	Q3 ($18.33-21.31$)	Q4 (≥ 21.31)	
Antiplatelet drugs	362 (3.7)	82 (3.4)	84 (3.4)	86 (3.5)	110 (4.5)	0.122
Q1: quartile 1 (lowest quartile); Q2: quartile 2; Q3: quartile 3; Q4: quartile 4 (highest quartile).						
Abbreviations: BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.						
*Data are presented as number (%) or mean \pm SD.						
†BMI was calculated as the body weight in kilograms divided by the square of the height in meters (kg/m^2).						
‡Hypertension was defined by ≥ 1 of the following criteria: systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 or self-reported history of hypertension or use of medications to treat hypertension.						

Survival analysis according to baPWV status

During a median follow-up of 20.8 months, there were 138 total first strokes including 123 first ischemic strokes and 15 first hemorrhagic strokes. The Kaplan-Meier curves of the cumulative event rate of first stroke and first ischemic strokes in the baPWV quartiles are shown in Fig. 2. Unadjusted first stroke curves of Q1, Q2 and Q3 were virtually superimposable (Fig. 2A). Subjects in baPWV Q4 displayed significantly greater first stroke than those in Q1, Q2 and Q3 ($P = 0.011$ by log-rank test). Similarly, unadjusted first ischemic stroke curves of Q1, Q2 and Q3 were virtually superimposable (Fig. 2B). Subjects in baPWV Q4 displayed significantly greater first ischemic stroke than those in Q1, Q2 and Q3 ($P = 0.014$ by log-rank test).

Association between baPWV and risk of first stroke (total and subtypes)

We also tried to use GAM model and penalized spline method to find the nonlinear relationship between baPWV and short-term risk of first stroke (Fig. 3). Adjusted smooth curve showed that the relationship between baPWV and short-term risk of first stroke and first ischemic stroke was curvilinear and reversed L-shaped. On the left of inflection point, the estimated dose-response curve was consistent with a horizontal line. The risk of first stroke and first ischemic stroke increased with the increase of baPWV on the right of inflection point.

In Table 2, Cox regression analysis was used to estimate the effect of baPWV on short-term risk of first stroke and its subtypes. When baseline baPWV values were assessed as quartiles, in crude model (model 1), the HRs (95% CI) for participants in the Q2 (16.00 to < 18.33 m/s), Q3 (18.33 to < 21.31 m/s) and Q4 (\geq 21.31 m/s) were 1.18 (95% CI: 0.71–1.97), 1.03 (95% CI: 0.61–1.75) and 1.89 (95% CI: 1.19–3.02), respectively compared with those in Q1 (Table 2). Compared with baPWV in Q1-Q3 (< 21.31 m/s), baPWV in Q4 (\geq 21.31 m/s) was associated with a 77% higher risk of first stroke (OR = 1.77; 95% CI, 1.25–2.50). In the multivariate model with adjustment for age, sex, BMI, education status, smoking status, drinking status, labor intensity, sleep quality, hypertension, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs (model 3), subjects with baPWV \geq 21.31 m/s had a 52% increased short-term risk of first stroke (HR = 1.52; 95% CI: 1.05–2.21) compared with those with baPWV < 21.31 m/s.

Table 2
Associations of baseline baPWV with first stroke and its subtypes

BaPWV, m/s	Event (%)	Model 1*		Model 2†		Model 3‡	
		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
First stroke							
Quartiles							
Q1 (< 16.00)	27 (1.11)	Ref.		Ref.		Ref.	
Q2 (16.00-18.33)	32 (1.30)	1.18 (0.71, 1.97)	0.531	1.08 (0.65, 1.82)	0.760	1.05 (0.63, 1.77)	0.850
Q3 (18.33-21.31)	28 (1.15)	1.03 (0.61, 1.75)	0.901	0.89 (0.52, 1.53)	0.679	0.87 (0.50, 1.50)	0.605
Q4 (≥ 21.31)	51 (2.08)	1.89 (1.19, 3.02)	0.007	1.48 (0.89, 2.46)	0.132	1.46 (0.87, 2.45)	0.147
Categories							
Q1-Q3 (< 21.31)	87 (1.19)	Ref.		Ref.		Ref.	
Q4 (≥ 21.31)	51 (2.08)	1.77 (1.25, 2.50)	0.001	1.50 (1.04, 2.18)	0.031	1.52 (1.05, 2.21)	0.027
First ischemic stroke							
Quartiles							
Q1 (< 16.00)	23 (0.94)	Ref.		Ref.		Ref.	
Q2 (16.00-18.33)	28 (1.14)	1.21 (0.70, 2.10)	0.499	1.11 (0.63, 1.93)	0.725	1.06 (0.61, 1.86)	0.826
Q3 (18.33-21.31)	26 (1.06)	1.13 (0.64, 1.97)	0.677	0.96 (0.54, 1.71)	0.890	0.93 (0.52, 1.66)	0.810
Q4 (≥ 21.31)	46 (1.88)	2.00 (1.21, 3.30)	0.007	1.53 (0.89, 2.64)	0.125	1.52 (0.87, 2.63)	0.139
Categories							
*Model 1: unadjusted.							
†Model 2: adjusted for age and sex.							
‡Model 3: model 2 + BMI, education status, smoking status, drinking status, labor intensity, sleep quality, hypertension, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs.							

BaPWV, m/s	Event (%)	Model 1*		Model 2†		Model 3‡	
		HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Q1-Q3 (< 21.31)	77 (1.05)	Ref.		Ref.		Ref.	
Q4 (≥ 21.31)	46 (1.88)	1.80 (1.25, 2.59)	0.002	1.50 (1.02, 2.22)	0.041	1.53 (1.03, 2.26)	0.035
First hemorrhagic stroke							
Quartiles							
Q1 (< 16.00)	4 (0.16)	Ref.		Ref.		Ref.	
Q2 (16.00-18.33)	4 (0.16)	1.00 (0.25, 3.98)	0.994	0.97 (0.24, 3.94)	0.965	1.00 (0.24, 4.12)	0.998
Q3 (18.33-21.31)	2 (0.08)	0.50 (0.09, 2.74)	0.425	0.48 (0.08, 2.74)	0.408	0.49 (0.08, 2.84)	0.426
Q4 (≥ 21.31)	5 (0.20)	1.27 (0.34, 4.73)	0.721	1.18 (0.27, 5.13)	0.824	1.26 (0.28, 5.72)	0.764
Categories							
Q1-Q3 (< 21.31)	10 (0.14)	Ref.		Ref.		Ref.	
Q4 (≥ 21.31)	5 (0.20)	1.53 (0.52, 4.47)	0.440	1.52 (0.48, 4.85)	0.475	1.61 (0.50, 5.21)	0.430
*Model 1: unadjusted.							
†Model 2: adjusted for age and sex.							
‡Model 3: model 2 + BMI, education status, smoking status, drinking status, labor intensity, sleep quality, hypertension, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs.							

Similarly, a significantly higher short-term risk of first ischemic stroke (HR = 1.53; 95% CI: 1.03–2.26) was found in participants in Q4 (≥ 21.31 m/s) compared with participants in Q1-Q3 (< 21.31 m/s).

Participants in high baPWV (≥ 21.31 m/s) had a 61% higher short-term risk of first hemorrhagic stroke (HR = 1.61, 95% CI: 0.50–5.21), but there did not reach statistical significance.

Sensitivity Analysis

We generated an E-value to assess the sensitivity to unmeasured confounding. Higher baPWV (≥ 21.31 m/s) are associated with an increase in first stroke by univariate analysis (HR, 1.77, 95% CI: 1.25–

2.50) and multivariable analysis (HR, 1.52, 95% CI: 1.05–2.21). The E-value was 2.94, meaning that residual confounding could explain the observed association if there exists an unmeasured covariate having a relative risk association ≥ 2.94 with both first stroke and baPWV. Therefore, it is unlikely that an unmeasured or unknown confounder would have a substantially greater effect on first stroke (relative risk exceeding 2.94) than these known risk factors. Consistently, the primary findings were robust, unless an unmeasured confounder existed with a higher relative risk of first ischemic stroke, with an HR higher than 3.00.

In addition, stratified analyses were performed to assess the association of baseline baPWV (≥ 21.31 m/s vs. Q1-3, < 21.31 m/s) with first stroke and first ischemic stroke in various subgroups (Figure S1 and Figure S2). Regardless of subgroup, compared with low baPWV (< 21.31 m/s), high baPWV (≥ 21.31 m/s) was positively associated with the short-term risk of first stroke and first ischemic stroke. As shown in Fig. 4, compared with low baPWV (< 21.31 m/s), high baPWV (≥ 21.31 m/s) was associated with a 3.30-fold (95% CI: 1.13–9.62) increase in the short-term risk of first stroke in the subgroup with SBP < 140 mm Hg, whereas the association was weaker in the subgroup with SBP ≥ 140 mm Hg (HR = 1.29, 95%CI: 0.86–1.93). The magnitude of the association between the baPWV and the incidence of stroke tended to be greater in DBP < 90 mm Hg group (HR = 1.78; 95% CI: 1.06–2.98) as compared with that in the subgroup with DBP ≥ 90 mm Hg (HR = 1.09, 95%CI: 0.62–1.91). Similarly, the association of high baPWV with the short-term risk of first ischemic stroke was significant in hypertensive patients with SBP < 140 mm Hg (HR = 4.14, 95%CI: 1.35–12.68) and DBP < 90 mm Hg (HR = 1.86, 95%CI: 1.07–3.23) (Figure S1). There was no association between baPWV and the short-term risk of first ischemic stroke among patients with inadequate hypertension control (Figure S1). These findings suggest that the magnitude of the association between the baPWV and the incidence of first stroke tended to be greater in the subgroup with controlled BP as compared with that in the subgroup with uncontrolled BP.

Discussion

We found that high baPWV levels (≥ 21.31 m/s) were associated with increased the short-term risk of first stroke among Chinese hypertensive adults, compared to low baPWV levels, supporting a reversed L-shaped association between baPWV and risk of first stroke. Sensitivity analyses showed consistent results. These results suggest that a baPWV of 21.31 m/s as the threshold for high risk in hypertensive patients. Furthermore, our study extends the results of previously published related studies by demonstrating that the association between baPWV and first stroke risk could be modified by SBP and DBP levels. Our findings warrant additional investigation.

Several previous studies have reported the association between baPWV and CVD and cerebrovascular diseases. A meta-analysis including 14673 Japanese participants without preexisting CVD established baPWV as an independent predictor of the risk of development of CVD^[22]. Yong Bum Kim et al^[16] used data from 1282 Korea participants and found that baPWV with both acute and chronic cerebral small vessel disease. Ting Li et al^[23] indicated that increased baPWV were objective indicators of increased risk of ischemic stroke in patients with type 2 diabetes. These studies showed a linear association between

baPWV and CVD. Of note, to our knowledge, only one study investigated the baPWV-stroke association in hypertension patients. Yun Song et al^[12] conducted a prospective cohort study of 3310 Chinese hypertensive adults and found that high baPWV (≥ 20.85 m/s) was significantly associated with an increased risk of first stroke.

Our study provides some new insights into this field. First, we found that high baPWV levels (≥ 21.31 m/s) were associated with increased first stroke risk among Chinese hypertensive patients, supporting a threshold effect of baPWV on stroke. Toshiaki Ohkuma et al^[24] proposed that the optimal cutoff value of baPWV for CVD in patients with hypertension was 18.3 m/s. Moreover, the threshold of baPWV varies by population and health conditions^[25–28]. Our study findings have important clinical implications. To date, none of the stroke prevention guidelines have considered PWV as a predictor in risk assessment. Our findings raised that individuals with baPWV ≥ 20 m/s were at high risk of developing stroke among patients with hypertension. Several possible mechanisms for could explain the association between baPWV and incidence of first stroke. BaPWV, is not only considered as a marker of atherosclerosis, but also has a pathophysiologic role, which could promote the development of hypertension, macro/microvascular damage, and brain structural injury^[29, 30]. Moreover, baPWV may be associated with stroke risk factors which in turn are important predictors of stroke^[31]. Additionally, high baPWV is associated with the development of stroke through endothelial dysfunction, extracellular matrix disorder, elevated endothelial permeability, mechanical force on the inner wall of blood vessels, and vascular aging^[19, 32]. Possibly, arterial stiffness may also increase in patients with endothelial dysfunction, oxidative stress, and inflammatory conditions, which could increase the risk of stroke^[15, 33]. However, more studies are needed to confirm our findings and further elucidate the specific biological mechanisms.

Second, the magnitude of the effect of high baPWV on the risk of development of stroke was greater in hypertensive patients with well controlled BP. There was no association between baPWV and risk of stroke among patients with inadequate hypertension control. Consistent with our results, Toshiaki Ohkuma et al^[22] also found that the association between baPWV and the risk of development of CVD was stronger in the participants without diabetes mellitus or hypertension than in those with either/both of these diseases. However, one previous study reported that participants with high baPWV and inadequate hypertension control had the highest risk of stroke compared with other groups. Differences in ethnics and methodological variations in baPWV measurements may possibly explain this discrepancy. Several considerations may explain the presence of this hypertension control paradox. While inadequate hypertension control is a major risk factor for stroke, subjects with the risk factor are also supposed to have higher baPWV levels in both the case group and the control group. Consequently, residual confoundings were inevitable when we analyzed association of high baPWV and risk of stroke in subjects with the factor. One hypothesis that has been proposed to explain this paradox is that by virtue of inadequate hypertension control, patients are offered earlier and more aggressive treatments to manage stroke risk factors. This may be related to the earlier, more intensive and closely monitored use of antiplatelet and anti-dyslipidaemic medications. Therefore, the findings may propose the applicability

of baPWV measurement for prediction of stroke development, especially in subjects with a low atherosclerotic disease risk.

Potential limitations of our study should also be noted. First, the potential for residual confounding exists, as with all observational studies. Specifically, blood glucose and lipids could not be measured. We used the E-value sensitivity analysis to quantify the potential implications of unmeasured confounders and found that an unmeasured confounder was unlikely to explain the entirety of baPWV effect. Second, our study was underpowered to investigate the association between baPWV and risk of first hemorrhagic stroke. Third, the participants were all hypertensive from China; thus, the generalizability to general population or other ethnic groups should be further verified. Fourth, the measurements of baPWV were only conducted at baseline. More frequent measurements of baPWV would provide more useful information. Fifth, follow-up time in the present study was short. However, the significant association between baPWV and risk of stroke was still observed, indicating high baPWV could increase the short-term risk of stroke. Despite these limitations, the strengths of the present study were the inclusion of a large number of participants, which allowed for sufficient statistical power to detect differences, the adjustments for confounders, and the subgroup analyses. Moreover, the threshold effect of baPWV on first stroke risk was observed. Furthermore, our results suggest that measurement of the baPWV may provide additional predictive information for future development of stroke in hypertensive patients with controlled BP.

Conclusion

In summary, high baPWV levels (≥ 21.31 m/s) were associated with increased the short-term risk of first stroke among Chinese hypertensive adults, compared to low baPWV levels, supporting a reversed L-shaped association between baPWV and risk of first stroke. Our findings may further propose the applicability of baPWV measurement for prediction of stroke development, especially in subjects with a low atherosclerotic disease risk.

Abbreviations

CVD, cardiovascular; cfPWV, carotid-femoral pulse wave velocity; BP: blood pressure; CHRS, China Hypertension Registry Study; ABI, ankle brachial index; CHD, coronary heart disease; ANOVA, analysis of Variance; BaPWV, brachial-ankle pulse wave velocity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the declaration of helsinki and was approved by the Institute of Biomedicine, Anhui Medical University, Hefei, China. Informed written consent was obtained from all patients before their enrollment in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare they have no actual or potential competing financial interests.

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Authors' contributions

Conceptualization and methodology: XPX, YH, JPL. Software: LHH, LSL. Validation: YS, YZ. Formal analysis: LHH, YZ. Investigation: LHH, CLB, LSL, BYW, CQF, HM, XH, YZ. Data curation: LSL, YS, YZ. Writing (original draft preparation): LHH. Writing (review and editing): CLB, LSL, YS, BYW, CQF, HM, XH, YZ, XPX, XBW, YH, JPL. Supervision: XPX, YH, JPL. Project administration: CLB, LSL, YS, BYW, HM. Funding acquisition: XPX, XH. All authors read and approved the final manuscript.

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Figures

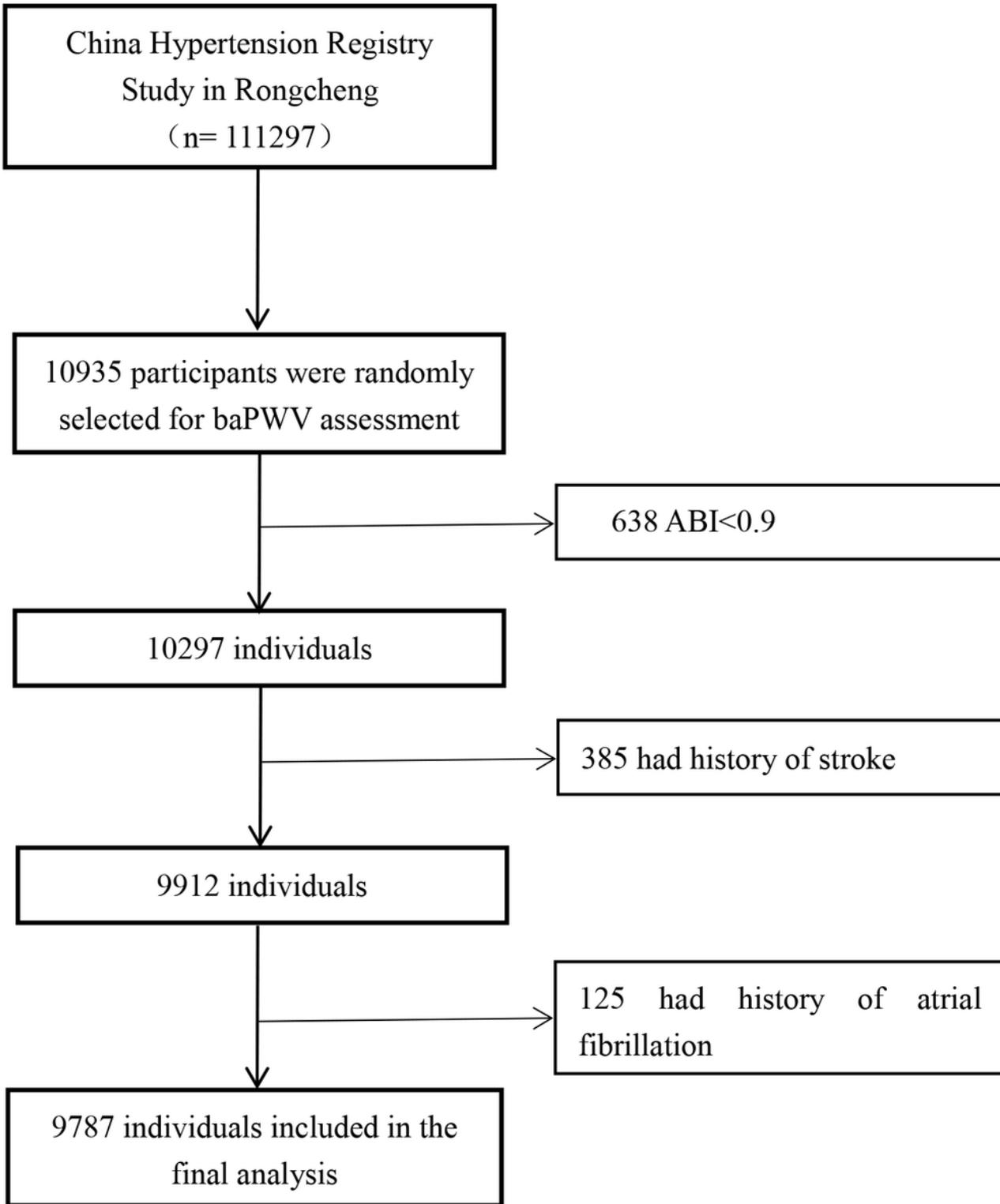
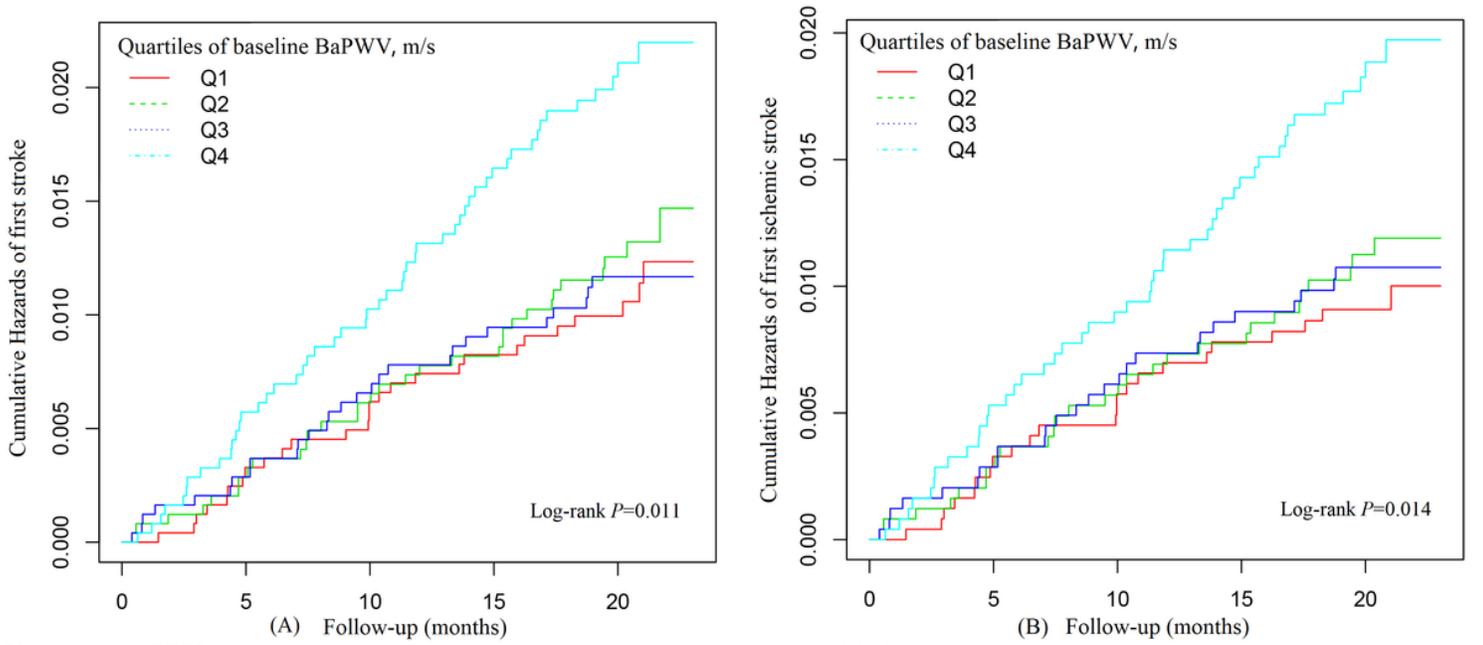


Figure 1

Flow chart of study populations.



No. at risk by baPWV quartiles (m/s)						No. at risk by baPWV quartiles (m/s)					
Q1 (<16.00)	Q2 (16.00-18.33)	Q3 (18.33-21.31)	Q4 (≥ 21.31)			Q1 (<16.00)	Q2 (16.00-18.33)	Q3 (18.33-21.31)	Q4 (≥ 21.31)		
2436	2455	2445	2451	2428	2437	2436	2455	2445	2451	2428	2437
2421	2448	2438	2437	2421	2426	2421	2448	2438	2437	2421	2426
2412	2431	2415	2409	2412	2409	2412	2431	2415	2409	2412	2409
1671	1689	1701	1644	1671	1644	1671	1689	1701	1644	1671	1644

Figure 2

Kaplan–Meier survival curves for unadjusted first stroke (A) and first ischemic stroke (B) according to quartiles of baseline brachial-ankle pulse wave velocity (BaPWV).

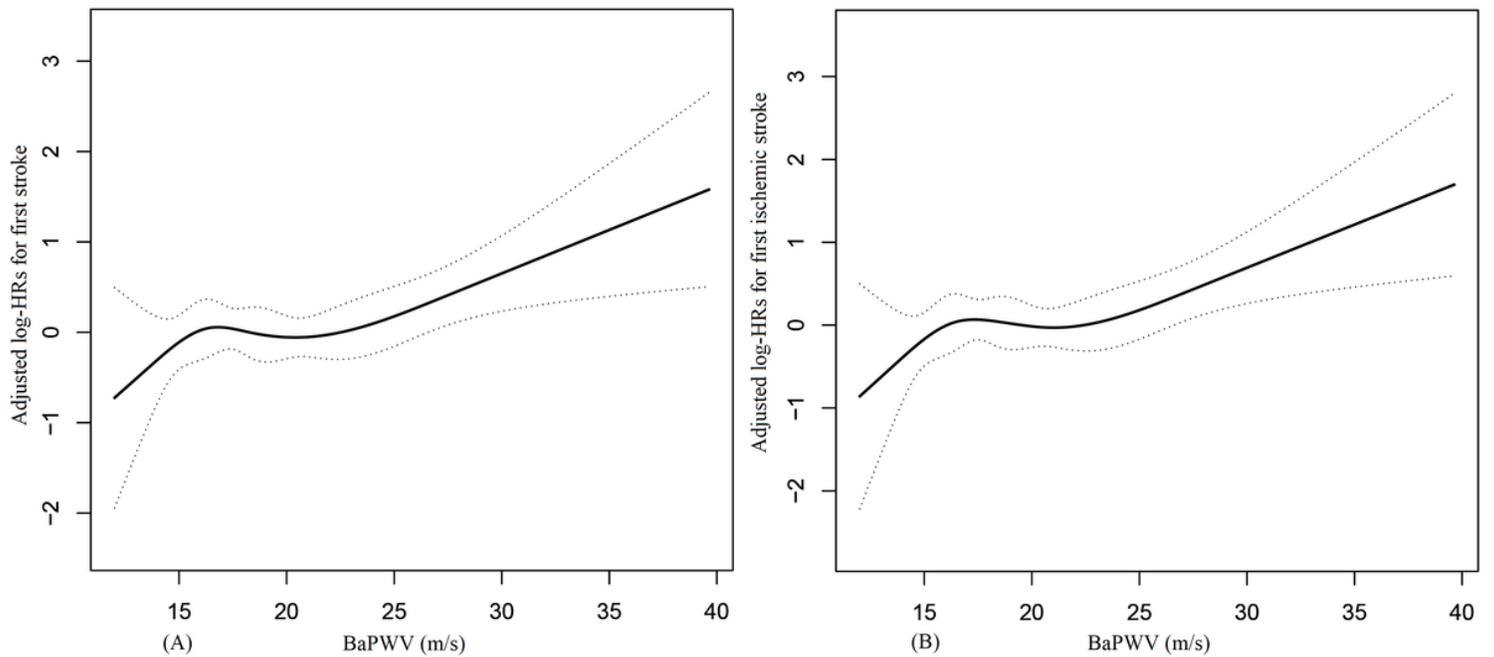


Figure 3

The association between baseline baPWV and incident risk of first stroke (A) and first ischemic stroke (B). Adjusted for age, sex, BMI, education status, smoking status, drinking status, labor intensity, sleep quality, hypertension, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs.

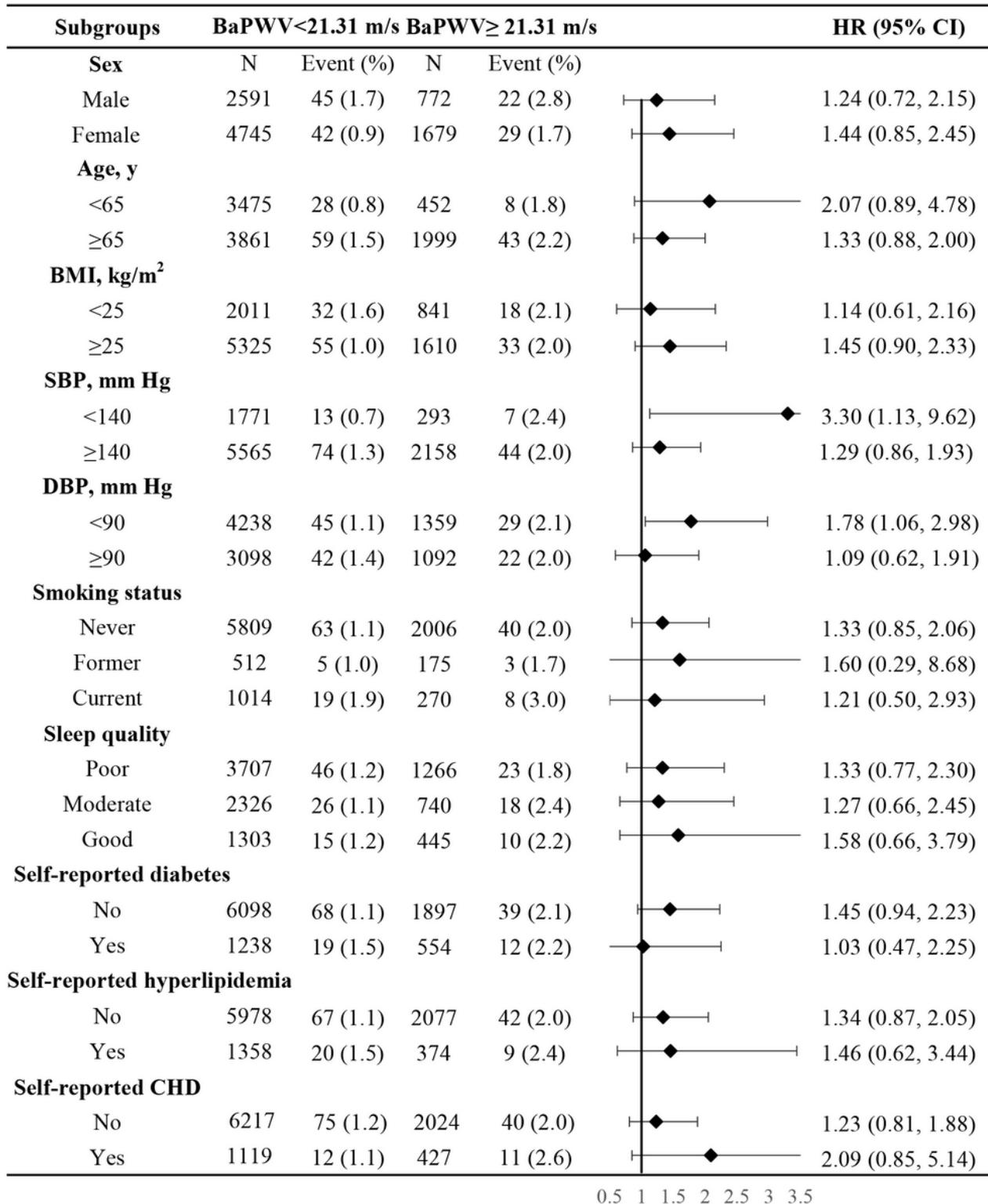


Figure 4

The association between baseline baPWV (Q4 vs. Q1-Q3) and incident risk of first stroke in various subgroups. Adjusted for age, sex, BMI, SBP, DBP, education status, smoking status, drinking status, labor intensity, sleep quality, self-reported of diabetes, self-reported hyperlipidemia, self-reported CHD, antihypertensive drugs, glucose-lowering drugs, lipoprotein-lowering drugs and antiplatelet drugs, except for the stratifying variable.

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