ORIGINAL RESEARCH

Estimated Pulse Wave Velocity is Associated with Intracranial Arterial Stenosis: A Secondary Analysis Based on A Korean Population

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Abstract: The estimated pulse wave velocity (ePWV) was recently proposed to indicate artery stiffness. Although arterial stiffness contributes to intracranial arterial stenosis (ICAS), the correlation between ePWV and ICAS remains unclear. This secondary analysis included 1,011 neurologically healthy Korean participants from a cross-sectional database to explore the association between ePWV and prevalent ICAS. Brain magnetic resonance angiography (MRA) was performed for all patients at their presentation to access the ICAS. The ePWV was derived as: $ePWV = 9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times mean\ blood\ pressure\ (MBP) + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$. The prevalence of ICAS was 9.99% (n=101). In multivariable logistic regression analyses, per 1m/s increment of ePWV causes 1.36 times the risk of ICAS prevalence after fully adjusting potential confounders. When dividing ePWV into tertiles, the ICAS risk increased by 1.98 times when ePWV increased from the first tertile to the third tertile. Moreover, the relationship between ePWV and ICAS was linear and robust, as suggested by smooth curve fitting and stratification analysis. In conclusion, the ePWV was positively and independently associated with prevalent ICAS in the Korean population.

Keywords: Estimated pulse wave velocity; Arterial stiffness; Intracranial arterial stenosis.

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INTRODUCTION

Intracranial arterial stenosis (ICAS) is a significant etiology of stroke and a high-risk factor for recurrent stroke worldwide [1-3]. Strokes resulting from ICAS account for up to 50% of all ischemic strokes in East Asia [1-3]. With the progress of ICAS, the risk of stroke onset and recurrence increases despite proper medical treatment [4, 5]. Compared with those without ICAS, stroke patients with ICAS show a higher risk of having a younger age, more severe symptoms, longer hospitalization duration, and a higher recurrence rate [2, 3]. In addition, evidence has shown that increased ICAS is closely correlated with a raised risk of dementia and Alzheimer's disease, and the correlation is independent of stroke [6]. Moreover, with the deterioration of ICAS, the cognitive impairment is more likely to exacerbate [7, 8]. Under these circumstances, finding an easily accessible indicator to improve and simplify ICAS identification may help alleviate the disease burden.

Arterial stiffness contributes to the presence of ICAS. Arterial stiffness is an essential determinant of increased blood pressure in old

populations and has been reported to be correlated with multiple cardio-cerebral vascular events [9-11]. Pathological studies have shown that arterial stiffness causes increased pulse pressure, which could be transmitted into cerebral arteries and lead to vascular remodeling inwardly and lumen narrowing [12]. Clinical research has also reported that arterial stiffness is closely correlated to atherosclerotic diseases, including ICAS [13-15]. Measurement of pulse wave velocity (PWV) is mainly used to access arterial stiffness [16], with the measured carotid-femoral PWV (cfPWV) as a gold standard evaluation [17]. Elevated measured PWV may increase the risk of intracranial atherosclerosis and predict a poor post-stroke functional outcome in stroke patients [18, 19]. However, the cfPWV may be unavailable in clinical practice since the evaluation of cfPWV relies on specialized equipment and expertise [20].

Consequently, a recent study proposed a potential proxy of cfPWV named estimated pulse wave velocity (ePWV) to indicate arterial stiffness [20, 21]. Furthermore, several studies suggested that ePWV was associated with the prevalence of atherosclerotic diseases, such as hypertension, cardiovascular disease (CVD), and stroke [21-24]. However, the potential correlation between ePWV and ICAS remains unclarified. Therefore, we aimed to explore the correlation between ePWV and prevalent ICAS based on a Korean Population.

METHODS

Data source

This present work was a hospital-based cross-section secondary analysis. The data were shared by Lee *et al.* and published in an open-access scientific journal [25]. We used the data in our present study and cited the original author and source following the copyright statement of the original research. More detailed information is displayed on the website "https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0143355." The data were also used in our previous research [26] and Yao *et al.*'s research [27]. The source research for our present analyses has obtained approval from the CHA Bundang Medical Center (IRB No. BD-2010083) and complied with the ethical standards of the Declaration of Helsinki. Informed consent was provided by all the participants prior to their inclusion in the research. The ethics committee of Shanghai Tenth People's Hospital approved our work (IRB No.23K30).

Data were recorded including demographic, clinical data, and brain magnetic resonance angiography (MRA), which was performed for clinical purposes. Participants were sampled from patients who attended the neurology outpatient clinic or healthcare center from March 2008 to December 2014 at CHA Bundang Medical Center according to the inclusion and exclusion criteria. Our previously published study has elaborated the inclusion and exclusion criteria [26]. In short, the study included neurologically healthy patients aged 45 years or over who had taken brain magnetic resonance imaging (MRI) and MRA. We excluded those with inadequate medical information (n=93), absent laboratory test results (n=154), absent cerebral MRI/MRA results (n=84), with a history or newly founded abnormal in the neurological system (n=67), and history of severe liver diseases (n=32). Finally, we included 1,011 participants in analyses (Fig. 1).

Data collection and measurements

Brain MRA with a 1.5T MR system was performed for all the participants during their medical attendance. Images were reviewed by a neurologist and a radiologist, who were blinded to other patient information. ICAS was determined if more than 50% stenosis or complete occlusion was presented in intracranial large arteries, including anterior, middle, and posterior cerebral arteries, distal vertebral and internal carotid arteries, and basilar arteries [25, 28]. The laboratory data were obtained by standard laboratory experiments.

Diabetes was determined if fasting plasma glucose (FPG) ≥126 mg/dL or on anti-diabetes medication or insulin [25]. Hypertension was defined as repeated measurements of systolic blood pressure (SBP) ≥140 mmHg, or/and diastolic blood pressure (DBP) ≥90 mmHg, or if the patient was on anti-hypertension therapy [25]. If the patient has smoked within a year before attendance, smoking would be determined. Hypercholesterolemia was diagnosed if total cholesterol was 240 mg/dL or higher or if the patient was taking lipid-lowering medicines [25]. If the patient has a history of asymptomatic angiographically confirmed coronary artery occlusion, symptomatic coronary artery disease, or surgery on the coronary artery, then coronary artery occlusive disease (CAOD) was considered. We calculated the eGFR using the Modification of Diet in Renal

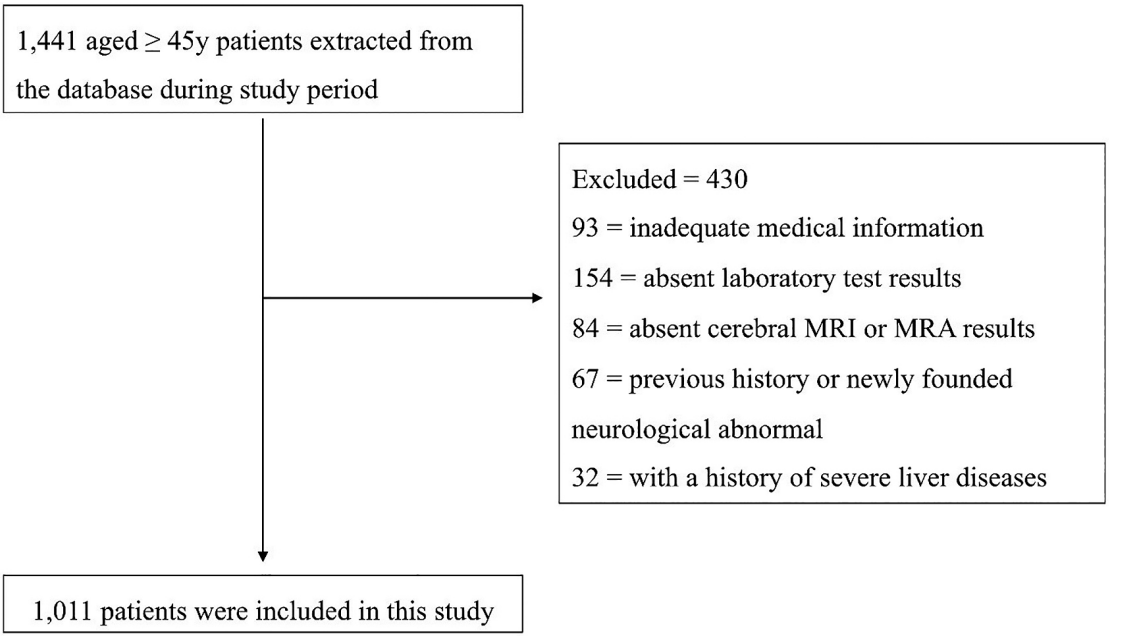

Figure 1. Flow chart of the enrollment of participants.

Disease Study equation [29]. The MBP was calculated as DBP + 1/3 (SBP – DBP). The ePWV was derived as: ePWV = 9.587 − 0.402 × age + 4.560 × 10^{-3} × age^2 − 2.621 × 10^{-5} × age^2 × MBP + 3.176 × 10^{-3} × age × MBP – 1.832 ×10^{-2} × MBP [20].

Statistical analysis

Continuous variables were exhibited as mean ± standard deviation (SD) for normal distribution and median (25%-75%) for skewed distribution. Categorical variables were displayed as counts (%). We conducted the Student's t-test (or Mann-Whitney test) for inter-group comparison of continuous variables. For inter-group comparison of categorical variables, the Chi-square (χ^2) test (or Fisher's exact test) was performed.

To explore the correlation between ePWV and ICAS, multivariate logistic regression analysis was performed. Furthermore, smooth curve fitting and stratification analyses were introduced to explore the linearity and consistency of the correlation. The covariables were sampled following three criteria: First, variables associated with ICAS significantly in the univariate regression models. Second, variables confirmed to be ICAS risk factors. Third, variables associated with ICAS significantly in previous research. Since the ePWV was generated from the equation based on blood pressure, the ePWV and blood pressure variables are highly correlated with each other, and consequently multicollinearity may arise [30]. To avoid the potential bias caused by multicollinearity [30, 31], we did not adjust blood pressure variables in the logistic regression models in our present study. We also referred to previously published studies about ePWV and cardiovascular events, and the blood pressure was also unadjusted in their analyses [21, 22, 24, 32-36].

Data analyses were performed using statistical software packages R (http://www.R-project.org, The R Foundation), SPSS 26.0 software (IBM Corp), and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) for data analyses. A two-tailed P value < 0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the characteristics of 1,011 participants enrolled in our study. The prevalence of ICAS was 9.99% (n=101). Compared with subjects without ICAS, subjects with ICAS showed higher levels of age, SBP, MBP, FPG, and triglyceride (all P values <0.05). The ICAS patients were more likely to present with hypertension, diabetes, and CAOD (P values <0.05). Furthermore, the ICAS group showed a significantly lower eGFR level (P value <0.001). Ultimately, we observed a significantly greater ePWV level in the ICAS group compared with the counterparts (P value <0.001).

Characteristics	Total	Without ICAS (N=910)	With ICAS (N=101)	P value
Age, years	64.16 ± 9.13	63.72 ± 9.06	68.13 ± 8.76	<0.001
Sex (male, %)	359 (35.51)	322 (35.38)	37 (36.63)	0.803
Smoking (%)	205 (20.28)	188 (20.66)	17 (16.83)	0.364
SBP (mmHg)	131.70 ± 18.32	130.88 ± 17.81	139.06 ± 21.09	<0.001
DBP (mmHg)	80.04 ± 11.52	79.89 ± 11.45	81.35 ± 12.15	0.229
MBP (mmHg)	97.3 ± 12.5	96.89 ± 12.37	100.58 ± 13.53	0.005
FPG (mg/dL)	108.00 (95.00-146.50)	108.00 (95.00-142.75)	128.00 (99.00-173.00)	0.001
Total cholesterol (mg/dL)	193.85 ± 39.82	193.91 ± 39.11	193.26 ± 45.93	0.876
Triglyceride (mg/dL)	127.00 (88.00-180.50)	125.00 (87.00-175.00)	146.00 (96.00-216.00)	<0.001
Hypertension (%)	579 (57.27)	508 (55.82)	71 (70.30)	0.005
DM (%)	224 (22.16)	187 (20.55)	37 (36.63)	<0.001
Hyperlipidemia (%)	332 (32.8)	296 (32.53)	36 (35.64)	0.527
CAOD (%)	52 (5.14)	42 (4.62)	10 (9.90)	0.023
Statin medication (%)	227 (22.45)	197 (21.65)	30 (29.70)	0.066
eGFR (mL/min/1.73 m2)	74.10 ± 16.81	74.75 ± 16.57	68.33 ± 17.98	<0.001
ePWV (m/s)	10.3 ± 1.8	10.17 ± 1.81	11.19 ± 1.71	<0.001

Abbreviations: ICAS: intracranial arterial stenosis; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; FPG: fasting plasma glucose; DM: diabetes mellitus; CAOD: coronary artery occlusive disease; eGFR: estimated glomerular filtration rate; ePWV: Estimated Pulse Wave Velocity.

Table 1. Characteristics of participants.

	OR (95% CI)					
	Crude	P value	Model I	P value	Model II	P value
ePWV (m/s)	1.35 (1.21, 1.51)	<0.001	1.32 (1.07, 1.63)	0.011	1.36 (1.09, 1.69)	0.006
ePWV (tertiles)	—	—	—	—	—	—
1st tertile (<9.39 m/s)	Reference	—	Reference	—	Reference	—
2nd tertile (9.39-11.03 m/s)	2.98 (1.55, 5.73)	0.001	2.50 (1.20, 5.20)	0.014	2.42 (1.16, 5.08)	0.019
3rd tertile (≥11.03m/s)	4.55 (2.43, 8.52)	<0.001	3.18 (1.28, 7.91)	0.013	2.98 (1.19, 7.44)	0.019
P for trend	—	<0.001	—	0.021	—	0.032

Crude: unadjusted; Model 1: adjusted for age, sex; Model 2: adjusted for age, sex, diabetes mellitus, coronary artery occlusive disease, hyperlipidemia, statin medication, smoking, fasting plasma glucose, and eGFR.
Abbreviations: ICAS: intracranial arterial stenosis; OR: odds ratio; CI: confidence interval; ePWV: Estimated Pulse Wave Velocity.

Table 2. Multivariable logistic regression analysis of ePWV for the presence of ICAS.

Table 2 displays the results of multivariate logistic regression analyses. The risk of ICAS increased by 35% per 1 m/s increment of ePWV in the unadjusted model (P <0.001), which was stable to 36% in the fully adjusted model (P value = 0.006). After dividing ePWV into tertiles, we observed a 1.98 times increased risk for the 3rd tertile against the 1st tertile in model 2. Furthermore, the risk of prevalent ICAS was rising across the tertiles, and the trend was significant (P for trend = 0.032). Findings from the smooth curve fitting confirmed the linear relationship observed in Table 2 (Fig. 2).

To investigate the consistency of the association in specific subpopulations, participants were divided into subgroups using several identified risk factors of ICAS, and stratification analyses were conducted. The inter-group interactions were insignificant (all P > 0.05, Fig. 3), which supported the consistency and robustness of the correlation between ePWV and ICAS in subgroups.

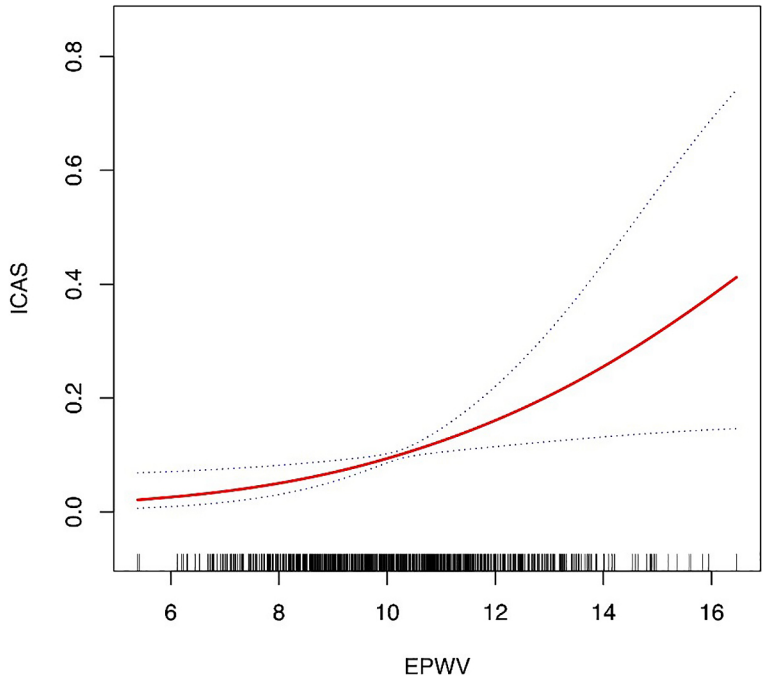

Figure 2. Smoothing curve fitting of the relationship between ePWV and the presence of ICAS. The solid line represents the estimated risk of ICAS, and the dotted lines represent a pointwise 95% CI. Smooth curve fitting was performed using a generalized additive model to determine the correlation between ePWV and the risk of ICAS after adjusting for age, sex, diabetes, CAOD, hyperlipidemia, statin medication, smoking, fasting glucose, and eGFR. Abbreviations: CAOD: coronary artery occlusive disease; ePWV: Estimated Pulse Wave Velocity; ICAS: intracranial arterial stenosis.

DISCUSSION

The current study revealed that people with elevated ePWV are more likely to present with ICAS independent of cardiovascular risk factors. Further smooth curve fitting and subgroup analysis supported that the ePWV was linearly and robustly associated with the presence of ICAS.

The ePWV was proposed as a cost-effective and easily accessible indicator of the severity of arterial stiffness [20]. A previous study has confirmed that ePWV was useful in evaluating arterial stiffness and has a similar prognosis predictive value as measured cfPWV [20]. Since arterial stiffness was a significant risk contributor to atherosclerosis, subsequent studies have also unfolded the association between ePWV and multiple atherosclerotic diseases, such as prevalent CVD, adverse CVD outcomes, heart failure, and hypertension [24, 33, 35, 37]. However, the correlation between ePWV and ICAS is still unclear. Because atherosclerosis is a primary cause of ICAS, we hypothesized that ePWV might also correlate with the presence of ICAS.

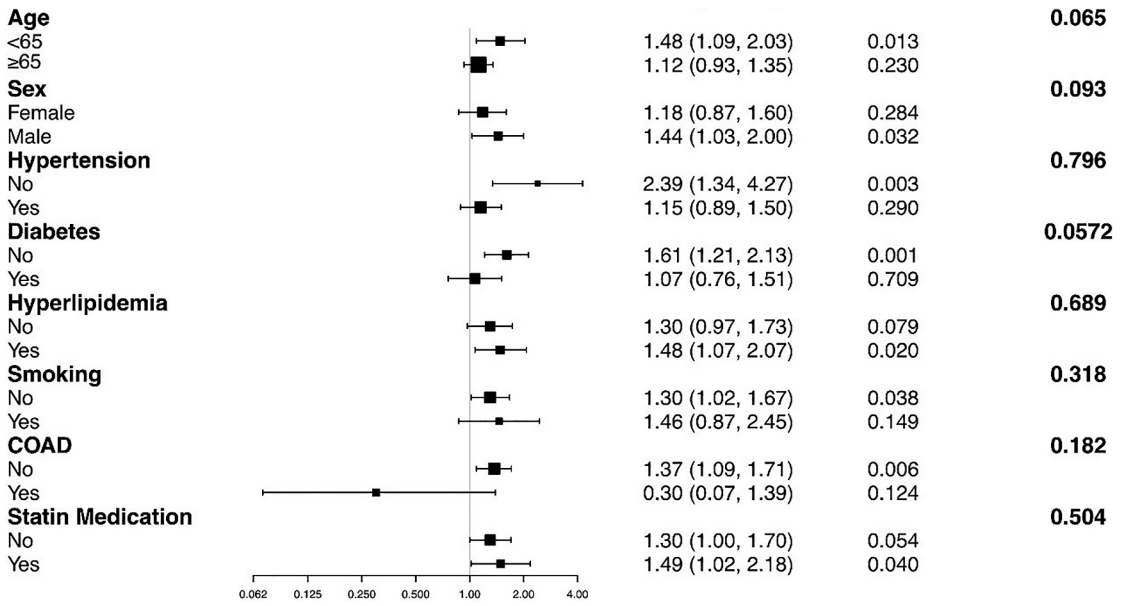

Figure 3. Subgroup analysis for the effect of ePWV on the ICAS. The dots express the estimates of the OR of ICAS for ePWV and the lines demonstrated the corresponding 95% CI. The multivariate logistic models adjusted for age, sex, diabetes, CAOD, hyperlipidemia, statin medication, smoking, fasting glucose, and eGFR, except for the stratified variable. None of the stratified variables significantly modified the impact of ePWV on the risk of ICAS (all P for interaction >0.05).

Abbreviations: OR: odds ratio; CAOD: coronary artery occlusive disease; ePWV: Estimated Pulse Wave Velocity; ICAS: intracranial arterial stenosis; CI: confidence interval.

Our hypothesis was confirmed in the present study. Results of the multivariate logistic regression models suggested that the ePWV was positively associated with prevalent ICAS, independent of demographic and clinical variables. The smooth curve fitting result showed elevated ePWV level was linearly correlated with increased risk of ICAS. Moreover, the association was consistent in specific subgroups without significant interactions with the stratifying risk factors. Therefore, our main results may be reasonably applied to these subpopulations.

Based on the knowledge that ePWV is a proxy of arterial stiffness and ICAS is primarily caused by atherosclerosis, several possible mechanisms may explain the observed association between ePWV and ICAS. Firstly, arterial stiffness could be a risk contributor to atherosclerosis. Increased arterial stiffness reduces compliance and pulsatile pressure, resulting in vessel wall damage, remodeling, and atherosclerosis [38]. Secondly, arterial stiffness and atherosclerosis may interact as both cause and effect in a self-perpetuating and reinforcing manner. Apart from being the consequence of arterial stiffness, atherosclerosis can also aggravate arterial stiffness in advanced stages [39, 40]. Therefore, a synergistic association may exist between arterial stiffness and atherosclerosis. In addition, both arterial stiffness and atherosclerotic stenosis advance with aging and accelerate with the presence of risk factors, including hypertension, diabetes, hyperlipidemia, and chronic inflammation status [41-45]. Therefore, sharing common risk factors and similar pathophysiology etiology between arterial stiffness and ICAS could be another possible explanation.

Consistent with the present results, several previous research also supported the effectiveness of arterial stiffness markers in assessing the risk of ICAS. Our previous Chinese-population-based cohort study supported the correlation between arterial stiffness and ICAS [15]. In our previous research [15], we evaluated arterial stiffness using measured Brachial-ankle pulse wave velocity (baPWV). The results indicated that increased baPWV was independently correlated with a higher prevalence of ICAS [15]. Moreover, an inverse association was observed between baPWV and the internal carotid artery diameter [15]. In Zhang *et al.*'s work [46], multiple arterial stiffness measures, including

cfPWV, ambulatory arterial stiffness index (AASI), and 24-h pulse pressure (PP), were conducted to detect the relationship between arterial stiffness and ICAS in the untreated hypertension population. Their findings showed that cfPWV and 24-h PP could help evaluate the risk of ICAS in a hypertensive population [46]. Contrarily, office PP and AASI showed no significant correlation with ICAS [46]. However, measurement of these indicators, including cfPWV, baPWV, and 24-hour PP, relies on specific devices and expertise and is thus inconvenient to obtain, especially in primary health care hospitals. On the contrary, ePWV is determined using age and MBP and can be obtained easily. Therefore, it may be convenient and valuable for ePWV to apply to clinical, especially in primary healthcare conditions.

Our study still has some limitations. First, the data of our present analyses were derived from a cross-sectional study. The findings of our investigation can only implicate a correlation between ePWV and the prevalent ICAS. Longitudinal prospective research was needed to identify the causality between ePWV and the development of ICAS. Second, the subjects in our analyses were sampled from a hospital-based Korean population. As a result, whether our findings can be extrapolated to the general population from other countries or regions remains to be determined. Third, some variables were inaccessible in our current work due to the limitation of data sources for secondary analysis. Unrecorded variables may introduce residual confounding and bring bias to analyses. This problem seems difficult to avoid, as it also exists in other observational studies. Therefore, large population-based study studies recording more variables will be helpful to address this disadvantage.

CONCLUSION

In conclusion, our present work revealed a positive and linear relationship between ePWV and prevalent ICAS, independent of cardiovascular risk factors. Moreover, our findings showed that the correlation was robust in some common subpopulations.

Abbreviations

AASI: ambulatory arterial stiffness index; baPWV: Brachial-ankle pulse wave velocity; CAOD: coronary artery occlusive disease; cfPWV: carotid-femoral pulse wave velocity; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ePWV: estimated pulse wave velocity; FPG: fasting plasma glucose; ICAS: intracranial arterial stenosis; IRB: Institutional Review Board; MBP: mean blood pressure; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PP: pulse pressure; SBP: systolic blood pressure; SD: standard deviation; OR: odds ratio; CI: confidence interval.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

The source study was reviewed and approved by the IRB of CHA Bundang Medical Center (IRB No. BD-2010-083). All persons gave their informed consent before their inclusion in the study. The ethics committee of Shanghai Tenth People's Hospital approved our current study (IRB No.23K30).

Author contributions

YZ performed data analysis and wrote manuscript drafting. WT, XS, and JN revised the manuscript. All authors have reviewed the manuscript and agreed to publication.

Consent for publication

All the authors gave their consent for publication.

Availability of data and materials

The original data can be obtained on the website "https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0143355".

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