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Research Paper

Estimated pulse wave velocity and cardiovascular events in Chinese

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ABSTRACT

The estimated pulse-wave velocity (ePWV) as measure for arterial wall stiffness is associated with an increased risk of cardiovascular disease (CVDs) and all-cause death in Western populations. We investigated the association between ePWV and the incidence of CVDs (myocardial infarction, cerebral infarction, cerebral hemorrhage) and all-cause death in Chinese. The community-based longitudinal Kailuan Study included 98,348 participants undergoing biennial clinical examinations. During a mean follow-up of 10.32 ± 2.14 years, 6967 CVD events (myocardial infarction, n = 1610; cerebral infarction, n = 4634; cerebral hemorrhage, n = 1071) and 9780 all-cause deaths occurred. Stratified by age, sex and presence of cardiovascular risk factors, the incidence of CVDs and all-cause death were higher ($P < 0.01$) in individuals with ePWV values ≥ 10 m/s than in those with ePWV values < 10 m/s. After adjusting for age, age squared and other conventional cardiovascular risk factors, an ePWV value of ≥10 m/s or each ePWV increase by 1 m/s increased ($P < 0.01$) the risk for CVDs by 32% (Hazard ratio (HR):1.32; 95% confidence interval (CI):1.23–1.42) and 22% (HR:1.22; 95%CI:1.18–1.27), respectively, and increased the risk for all-cause death significantly ($P < 0.01$) by 28% (HR:1.28; 95%CI:1.20–1.37) and 10% (HR:1.10; 95%CI:1.07–1.13), respectively. The mean brachial-ankle PWV, measured in 43,208 individuals, was 15.30 ± 3.51 cm/s, with a mean difference of 6.45 m/s (95% limits of agreement:1.24–11.7) to the ePWV. Independently of cardiovascular risk factors, ePWV was associated with CVDs and all-cause mortality in Chinese.

1. Introduction

Arterial hypertension is caused by a panoply of factors including stiffness of the aorta or arteriosclerosis, and vice versa, hypertension is a major risk factor for aortic stiffness [1–3]. In addition, aortic stiffness by itself and in association with other risk factors such as hypertension is one of the major causes for cardiovascular diseases (CVD) and all-cause death [1,4,5]. It is usually assessed by measuring the carotid-femoral pulse wave velocity (cfPWV) or the brachial-ankle pulse wave velocity (baPWV) [1,5–7]. With hypertension being the most important modifiable risk factor for the development of CVDs, predictive risk scores for CVDs, such as the Framingham Risk Score and the Systematic Coronary Risk Evaluation (SCORE), have included hypertension to calculate the risk for eventual CVD and all-cause death [8–10]. Since the predictive value of these algorithms has remained relatively low, the parameter of PWV has been added to the algorithms to improve the individual CVD risk estimation [11]. The measurement of the PWV, either as the cfPWV or as the baPWV, is performed in a standardized manner using commercially available devices [12–14]. Since the measurement of PWV is not routinely performed in clinical practice, the aortic stiffness has been estimated by using equations including age and the mean blood pressure (BP) as parameters [7,15]. Also artificial intelligence has been applied to estimate the PWV by analyzing an un-calibrated part of the carotid pressure waveform [15]. The calculations of the cfPWV correlated well with *in-vivo* measurements of the PWV in patients with cardiovascular risk factors (linear correlation coefficient $r^2 = 0.45$). As compared to traditional risk scores, they predicted better the development of CVDs, in particular in patients with untreated hypertension [7].

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Most of the studies mentioned above were performed in Western populations. Since lifestyle parameters markedly influence the risk of CVDs and since all-cause death markedly differs between Western countries and mainland China, we performed this study to re-investigate the association between the estimated PWV (ePWV) and clinical outcomes in a Chinese cohort, and to compare the ePWV with the measured baPWV. To avoid the potential bias by a referral of study participants, we chose a community-based recruitment of the study participants.

2. Methods

The Kailuan study (registration number: ChiCTR-TNC-1100148) is a prospective community-based cohort study that was performed in the community of Kailuan in the industrial city of Tangshan [16,17]. The Ethics Committees of the Kailuan General Hospital confirmed that the study followed the guidelines of the Helsinki Declaration and approved it. All participants signed a written informed consent. Data, analytic methods, and study materials will be made available to other researchers upon request. The participants in the Kailuan study were employees and retirees of the Kailuan Group Company that is a coal mining industry in Tangshan. At baseline of the study between June 2006 and October 2007, we examined the study population of 101,510 individuals (81,110 men) with an age ranging between 18 years and 98 years. We performed re-examinations in two-year intervals up to the end of the follow-up on December 31, 2017 or up to the time at which a CVD event including myocardial infarction and stroke or death occurred, whichever came first. In this study, we included those participants with a complete set of baseline data after an exclusion of those with missing data of age, waist circumference, blood pressure, and fasting serum concentrations of triglycerides, high-density lipoprotein and glucose.

All study participants underwent an interview with a standardized questionnaire including questions on demographic, socioeconomic and clinical parameters. We measured anthropometric parameters such as body height and weight. For the measurement of BP, we obtained three readings at 5-min intervals after the participants had rested in a chair for at least 5 min. We used the average of three measurements for further data analysis. We obtained blood samples under fasting conditions and analyzed them biochemically. Hypertension was defined as a systolic blood pressure of $\geq$140 mmHg and/or a diastolic blood pressure of $\geq$90 mmHg, or a history of hypertension, or taking antihypertensive drugs.

The main outcome parameters were incident CVD events including myocardial infarction, cerebral infarction and cerebral hemorrhage, and all-cause death. All study participants were linked to the Municipal Social Insurance Institution and the Hospital Discharge Register which allowed the detection of an incident CVD. To identify additional study participants with CVD events, we reviewed the discharge lists from the 11 Kailuan hospitals during the study period from 2006 to 2017, and we asked the study participants at each re-examination about a previous CVD event. For all suspected CVD events, three experienced masked physicians reviewed the medical records and adjudicated. Incident myocardial infarction was diagnosed according to the criteria of the World Health Organization on the basis of clinical symptoms, changes in the serum concentrations of cardiac enzymes and/or biomarkers, and electrocardiogram results [18,19]. Stroke was diagnosed according to the World Health Organization criteria, based on symptoms, clinical signs, images obtained by computed tomography or magnetic resonance imaging, and other diagnostic reports [20]. Information about death was collected from vital statistics offices, with the death certificates reviewed by the study clinicians (S.W., Y.W.) [16,17].

We measured the baPWV using the BP-203RPEIII network arteriosclerosis detection device (Omron Health Medical Co. Ltd., Dalian China). The room temperature was kept between 22 °C and 25 °C. The participants reclined on a flat bed. The BP cuffs were applied to the upper arms and ankles of the lower limbs. The upper arm cuff airbag marker was aligned to the brachial artery, and the bottom of the cuff was 2–3 cm distant from the elbow socket. The lower extremity cuff airbag sign was located on the medial side of the lower extremity, the lower cuff margin was 1–2 cm distant from the medial malleolus. After a rest for at least 5 min in the supine position, the measurements were performed. The measurements were repeated and the second value was used as the final result.

As described by Greve and colleagues in detail, we used for the calculation of the ePWV in individuals with cardiovascular risk factors the equation of ePWV = 9.58748315543126–0.402467539733184*age $+4.56020798207263*10^{-3}*age^2 - 2.6207705511664*10^{-5}*age^2*MBP$ $+3.1762450559276*10^{-3}*age*MBP-1.83215068503821*10^{-2}*MBP$ (MBP: mean blood pressure) [7]. For individuals without cardiovascular risk factors, we calculated the ePWV as: ePWV = 4.62–0.13*age $+0.0018*age^2$ + 0.0006*age*MBP +0.0284*MBP. Individuals without cardiovascular risk factors were defined as non-smokers without any components of a metabolic syndrome and without a history of myocardial infarction or stroke.

Statistical analysis was performed using the SAS software (Version 9.2, SAS Institute, Cary, NC). The primary outcomes were cardiovascular events (a composite endpoint of myocardial infarction, cerebral infarction and cerebral hemorrhage) and all-cause death. Continuous variables with a normal distribution were expressed as the mean and standard deviation and compared using the independent-sample *t*-test. Due to the skewed distribution of the serum concentrations of the C-reactive protein and triglycerides, we performed a logarithmic transformation of these values and expressed them as median and quartiles. Categorical variables were described as percentages with 95% confidence intervals (CI), and they compared using the Chi-square test. The cumulative incidence rates of outcome events were calculated by the life table method in each subgroup stratified by age, sex, whether or not accompanied by cardiovascular risk factors. They were compared using the log-rank test. Cox proportional hazard models were used to estimate the hazard ratios (HR) and 95% CIs of the outcome events. In the primary analysis, we examined the association of ePWV with each type of outcome event after adjustment for the following cardiovascular risk factors in the model: sex (male/female), smoking status (never and past, current, $\geq$1 cigarettes/day), drinking status (never and past, current, $\geq$1 time/day), education level (elementary school, high school or above), exercise (none, occasionally or frequently, $\geq$1 times/week), income level (<1000 yuan/month, $\geq$1000 yuan/month), history of myocardial infarction (yes/no), history of stroke (yes/no), chronic kidney disease (yes (i.e., an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or proteinuria)/no), hypertension (yes/no), pulse pressure, body mass index, and fasting serum concentrations of total cholesterol, glucose, uric acid and C-reactive protein. In a second step, we examined whether ePWV added significant prognostic information to a model including conventional cardiovascular risk factors as mentioned above. Model discrimination was assessed with the use of Harrell's C-statistic, Categorical net reclassification index (NRI) and integrated discrimination improvement (IRI). For that calculation, the prediction probability of the model based on the conventional cardiovascular risk factors and the other model based on the conventional cardiovascular risk factors plus ePWV was calculated using a logistic regression model. According to the prediction probability, the study participants were divided into low-risk (<5%), medium-risk (5%–10%) and high-risk ($\geq$10%) groups. The effectiveness of reclassification was tested using the net reclassification index [NRI¼(((up-reclassified patients with events/total number of patients with events)-(down-reclassified patients with events/total number of patients with events))-((upreclassified patients without events/total number of patients without events)-(down-reclassified patients without events/total number of patients without events)))] and the integrated discrimination improvement [IDI (Pnew,events-Pold,events)-(Pnew,non-events- Pold,non-events), with *P* as the mean of the predicted probabilities]. A univariate regression analysis was used to assess the relation between ePWV and baPWV. Bland-Altman plotting was performed for the assessment of the consistency between ePWV and baPWV. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Table 1
Baseline characteristics.

Variables	Participants with conventional cardiovascular risk factors		t/χ^2	*P*
	No n = 12985	Yes n = 85363		
Age, years	45.16 ± 12.56	52.79 ± 12.25	−64.76	<0.001
Men	6947 (53.5%)	71,657 (83.9%)	6510.16	<0.001
ePWV, m/s	7.64 ± 1.35	9.33 ± 2.00	−123.81	<0.001
BMI, kg/m^2	22.72 ± 2.73	25.40 ± 3.46	−100.54	<0.001
WC, cm	77.59 ± 6.71	88.50 ± 9.65	−161.60	<0.001
SBP, mmHg	111.50 ± 9.81	134.03 ± 20.72	−202.02	<0.001
DBP, mmHg	73.63 ± 6.90	85.02 ± 11.64	−157.19	<0.001
MAP, mmHg	88.78 ± 7.45	104.62 ± 14.27	−194.21	<0.001
TG, mmol/L	0.90 (0.67–1.18)	1.37 (0.96–2.09)	−128.48	<0.001
TC, mmol/L	4.76 ± 0.93	4.98 ± 1.17	−23.31	<0.001
LDL, mmol/L	2.24 ± 0.80	2.36 ± 0.93	−15.83	<0.001
HDL, mmol/L	1.60 ± 0.34	1.54 ± 0.41	18.72	<0.001
Fbg, mmol/L	4.89 ± 0.55	5.57 ± 1.78	−87.98	<0.001
CRP, mg/L	0.51 (0.20–1.44)	0.89 (0.32–2.33)	−29.16	<0.001
SUA, mmol/L	255.61 ± 69.94	295.38 ± 84.88	−58.54	<0.001
eGFR, mL/min/1.73m^2	85.59 ± 27.95	81.55 ± 25.18	15.53	<0.001
High school or above	4301 (33.9%)	14,858 (17.9%)	1758.11	<0.001
Exerciser	11,794 (93.2%)	75,197 (90.9%)	72.68	<0.001
Income level≥ 1000 RMB/month	1126 (8.9%)	5273 (6.4%)	111.99	<0.001
Current drinker	2663 (20.9%)	33,437 (40.0%)	1711.89	<0.001
CKD	1928 (14.9%)	19,000 (22.3%)	369.43	<0.001
China-PAR score			6871.81	<0.001
< 5% (low risk)	11,584 (89.2%)	43,133 (50.5%)		
5%–10% (intermediate risk)	940 (7.2%)	21421 (25.1%)		
≥10% (high risk)	461 (3.6%)	20809 (24.4%)		
History of MI	0	1254 (1.5%)	193.22	<0.001
History of stroke,	0	2492 (2.9%)	388.93	<0.001
Hypertension	0	43,664 (51.2%)	11945.41	<0.001
Current smoker	0	33,295 (39.0%)	7656.84	<0.001
Components of MS				
Abdominal obesity	0	41,941 (49.1%)	11123.56	<0.001
Dyslipidemia	0	35,787 (41.9%)	8557.75	<0.001
High BP	0	56,012 (65.6%)	19792.88	<0.001
IFG or diabetes	0	17,025 (19.9%)	3131.93	<0.001

ePWV: estimated pulse wave velocity; BMI: body mass index; WC: waist circumstance; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; TG: triglyceride; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; Fbg: fasting blood glucose; CRP: C-reactive protein; SUA: serum uric acid; MI: myocardial infarction; IFG: impaired fasting glucose; eGFR: estimated glomerular filtration rate; MS: metabolic syndrome; CKD: chronic kidney disease.

3. Results

Out of the total of 101,510 individuals, the current study included 98,348 participants with a complete set of baseline data after excluding individuals with missing data of age, waist circumference, blood pressure, and fasting serum concentrations of triglycerides, high-density lipoprotein and glucose (Table 1). The study participants as compared to the excluded individuals had a lower age (51.78 ± 12.56 years versus 56.52 ± 14.96 years; $P < 0.001$), lower pulse pressure (47.54 ± 14.13 mmHg versus 49.72 ± 15.19 mmHg; $P < 0.001$) and higher diastolic BP (83.52 ± 11.78 mmHg versus 82.07 ± 12.06 mmHg; $P < 0.001$). They did not differ significantly in systolic BP (131.1 ± 21.06 mmHg versus 131.8 ± 21.92 mmHg; $P = 0.12$), mean BP (102.5 ± 14.58 mmHg versus 102.0 ± 14.97 mmHg; $P = 0.08$) and the rate of controlled BP (2.61% (95%CI: 2.51%, 2.71%) versus 2.78% (95% CI: 2.24%, 3.42%); $P = 0.54$). During a mean follow-up of 10.3 ± 2.1 years (interquartile range, 0–13.9), we observed 6967 CVD events (myocardial infarction, n = 1610; cerebral infarction, n = 4634; cerebral hemorrhage, n = 1071) and 9780 all-cause deaths.

The mean ePWV was 9.11 ± 2.01 m/s. It increased significantly with older age, and it was higher in men than in women (Tables 2 and 3). Stratified by age, sex and presence of cardiovascular risk factors or the China-PAR score, the incidence of CVDs and all-cause death were higher ($P < 0.01$) in those with ePWV values of ≥10 m/s than in those with ePWV values of <10 m/s (Table 4) (Fig. 1) [21]. After adjusting for age, age squared and other conventional cardiovascular risk factors, an ePWV value of ≥10 m/s or each increase in the ePWV by 1 m/s increased the risk for CVDs significantly ($P < 0.01$) by 32% (Hazard ratio (HR):1.32; 95% confidence interval (CI):1.23–1.42) and 22% (HR:1.22; 95% CI:1.18–1.27), respectively, and increased the risk for all-cause death significantly ($P < 0.01$) by 28% (HR:1.28; 95%CI:1.20–1.37) and 10% (HR:1.10; 95%CI:1.07–1.13), respectively (Table 4).

Adding the parameter of ePWV to a model with adjustment for the cardiovascular risk factors and with adjustment for age and age squared did not change significantly the area under the receiver operator curve (Table 5). In a similar manner, adding the ePWV parameter to the model (with adjustment for age and age squared) did not increase the NRI value and the IDI value significantly (Table 5). For that analysis, we calculated the NRI value and the IDI value both for participants with one or more cardiovascular risk factors and for participants without any cardiovascular risk factor. When the incident CVD was taken as the outcome event, the NRI value and IDI value for the model with the ePWV added were 0.96% and 0.23%, respectively for participants with a cardiovascular risk factor, and −1.81% and 0.22%, respectively, for participants without any cardiovascular risk factor. When all-cause death was taken as the outcome event, the NRI value and the IDI value for the model with the ePWV added were 0.37% and 0.06%, respectively for the participants with a cardiovascular risk factor, and 0.02% and 0%, respectively for the participants without any cardiovascular risk factor (Tables 6 and 7). Adding the parameter of ePWV to a model with adjustment for the cardiovascular risk factors but without additional adjustment for age and age squared significantly increased the area under the receiver operator curve and increased the NRI value and the IDI value. When the incident CVD was taken as the outcome event, the NRI value and IDI value for the

Table 2
The distribution of estimated pulse-wave velocity stratified by age and sex in the study participants with conventional cardiovascular risk factors.

Age, years	Sex	N	ePWV, m/s	
			Median (10-90pc)	Mean ± 2 Standard Deviations
<30	Total	3932	6.67 (6.03–7.30)	6.65 ± 1.04
	Men	3543	6.68 (6.06–7.33)	6.67 ± 1.02
	Women	389	6.43 (5.81–7.00)	6.44 ± 0.98
30–39	Total	7719	7.11 (6.24–8.20)	7.18 ± 1.60
	Men	6680	7.14 (6.30–8.26)	7.23 ± 1.60
	Women	1039	6.85 (5.92–7.82)	6.86 ± 1.52
40–49	Total	21532	8.02 (6.93–9.53)	8.15 ± 2.12
	Men	17349	8.06 (6.99–9.58)	8.20 ± 2.12
	Women	4183	7.83 (6.68–9.33)	7.94 ± 2.10
50–59	Total	30877	9.25 (8.00–10.94)	9.37 ± 2.36
	Men	25447	9.26 (8.02–10.97)	9.39 ± 2.38
	Women	5430	9.18 (7.89–10.79)	9.27 ± 2.30
60–69	Total	13724	10.98 (9.59–12.58)	11.04 ± 2.38
	Men	11828	10.99 (10.23–11.82)	11.05 ± 2.40
	Women	1896	10.90 (9.52–12.41)	10.95 ± 2.22
≥70	Total	7579	12.89 (11.38–14.72)	12.98 ± 2.66
	Men	6810	12.93 (11.40–14.78)	13.02 ± 2.68
	Women	769	12.58 (11.19–14.22)	12.65 ± 2.42
Total	Total	85363	9.05 (6.94–12.13)	9.33 ± 4.00
	Men	71657	9.10 (6.97–12.24)	9.39 ± 4.06
	Women	13706	8.83 (6.80–11.54)	9.02 ± 3.66

ePWV: estimated pulse wave velocity; SD: standard deviation.

Table 3
The distribution of estimated pulse-wave velocity stratified by age and sex in the study participants without conventional cardiovascular risk factors.

Age, years	Sex	N	Estimated pulse-wave velocity (m/s)	
			Median (10-90pc)	Mean ± 2 standard deviations
<30	Total	1874	6.29 (5.76–6.73)	6.29 ± 0.70
	Men	909	6.44 (5.89–6.76)	6.39 ± 0.66
	Women	965	6.21 (5.66–6.66)	6.19 ± 0.70
30–39	Total	2597	6.64 (6.05–7.14)	6.62 ± 0.80
	Men	957	6.81 (6.26–7.21)	6.76 ± 0.74
	Women	1640	6.55 (5.98–7.07)	6.54 ± 0.80
40–49	Total	3890	7.42 (6.71–8.00)	7.37 ± 0.98
	Men	1669	7.50 (6.85–8.06)	7.47 ± 0.94
	Women	2221	7.33 (6.63–7.93)	7.30 ± 1.00
50–59	Total	3245	8.39 (7.64–9.08)	8.37 ± 1.10
	Men	2210	8.46 (7.72–9.15)	8.44 ± 1.08
	Women	1035	8.25 (7.51–8.94)	8.22 ± 1.10
60–69	Total	952	9.84 (8.95–10.68)	9.83 ± 1.32
	Men	814	9.86 (9.01–10.70)	9.85 ± 1.30
	Women	138	9.71 (8.67–10.63)	9.68 ± 1.48
≥70	Total	427	11.55 (10.57–13.35)	11.77 ± 2.26
	Men	388	11.58 (10.58–13.44)	11.80 ± 2.26
	Women	39	11.38 (10.06–12.77)	11.44 ± 2.24
Total	Total	12985	7.40 (6.24–9.30)	7.64 ± 2.70
	Men	6947	7.86 (6.45–10.05)	8.06 ± 2.96
	Women	6038	6.99 (6.08–8.35)	7.16 ± 1.94

model with the ePWV added were 8.61% and 0.71%, respectively for participants with a cardiovascular risk factor, and 12.13% and 1.02%, respectively, for participants without any cardiovascular risk factor. When all-cause death was taken as the outcome event, the NRI value and the IDI value for the model with the ePWV added were 23.17% and 7.09%, respectively for the participants with a cardiovascular risk factor, and 20.14% and 11.06%, respectively for the participants without any cardiovascular risk factor.

Out of the total of 98,348 individuals with complete baseline data and follow-up examinations for up to 10 years, 54,212 participants underwent measurement of the baPWV test since 2010. After an exclusion of those individuals with extremely outlying values of the baPWV (n = 70), with an ankle-brachial index (ABI) of <0.9 (n = 2087), with missing values of the waist circumference measurement, age, determination of

Table 4
Hazard ratios and 95% confidence intervals of cardiovascular events and all-cause mortality.

Outcome	Estimated pulse-wave velocity (m/s)		
	<10 m/s	≥10 m/s	Each 1 m/s increase
CVD			
Case/n	2891/69,227	4076/29,121	
Cumulative Incidence	5.30%	18.68%**	
Model 1	1	3.82 (3.64–4.00)**	1.40 (1.39–1.42)**
Model 2	1	2.12 (1.99–2.25)**	1.28 (1.26–1.30)**
Model 3	1	1.32 (1.23–1.42)**	1.22 (1.18–1.27)**
All-cause mortality			
Case/N	2940/69,227	6840/29,121	
Cumulative Incidence	5.74%	26.40%**	
Model 1	1	6.07 (5.81–6.34)**	1.57 (1.56–1.59)**
Model 2	1	4.20 (3.98–4.44)**	1.56 (1.54–1.57)**
Model 3	1	1.28 (1.20–1.37)**	1.10 (1.07–1.13)**

CVD: a composite endpoint of myocardial infarction, cerebral infarction and cerebral hemorrhage.
Model 1: unadjusted.
Model 2: adjusted for sex (male/female), smoking status (never and past, current, ≥1 cigarettes/day), drinking status (never and past, current, ≥1 time/day), education level (elementary school, high school or above), exercise (none, occasionally or frequently, ≥1 times/week), income level (<1000 yuan/month, ≥1000 yuan/month), history of MI (yes/no), history of stroke(yes/no), chronic kidney disease (yes/no), hypertension (yes/no), pulse pressure, body mass index, and fasting serum concentrations of total cholesterol, glucose, uric acid and C-reactive protein.
Model 3: adjusted for age, age squared and all the factors in model 2.
**$P < 0.001$.

blood pressure and measurements of the serum concentrations of triglyceride, high-density lipoprotein and glucose (n = 8847), a total of 43,208 individuals were eventually included in the analysis of a consistency between the baPWV measurements and the calculated ePWV values. The individuals included into this analysis as compared to those excluded had a lower age (49.54 ± 12.90 years versus 50.16 ± 13.49 years; $P < 0.001$), lower systolic BP (132.2 ± 19.21 mmHg versus 133.1 ± 19.82 mmHg; $P = 0.003$), lower pulse pressure (50.10 ± 14.31 mmHg versus 51.66 ± 14.75 mmHg; $P < 0.001$), higher diastolic BP (82.14 ± 10.99 mmHg versus 81.45 ± 11.50 mmHg; $P < 0.001$) and higher baPWV (15.30 ± 3.51 m/s versus 14.91 ± 3.55 m/s, $P < 0.001$). They did not differ significantly in the rate of controlled BP (1.95% (95%CI: 1.82%, 2.09%) versus 2.00% (95%CI: 1.68%, 2.37%); $P = 0.78$)) and mean BP (102.2 ± 13.07 mmHg versus 102.1 ± 13.58 mmHg; $P = 0.76$). The age of the study participants was at baseline 49.54 ± 12.90 years, and the average systolic BP/diastolic BP was 132.2 ± 19.21/82.14 ± 10.99 mmHg.

The mean baPWV was 15.30 ± 3.51 cm/s. As derived from the Bland-Altman plots, the mean difference between the measured baPWV and the ePWV was 6.45 m/s (95% LoA (limits of agreement): 1.24–11.66) (Supplementary Table 1; Supplementary Figs. 1 and 2). The comparison with the ePWV revealed that the baPWV showed lower hazard ratios of cardiovascular events and all-cause mortality for each 1 m/s increase in the estimated in the velocity (Supplementary Table 2).

4. Discussion

In our study population of Chinese adults, the incidence of CVDs and all-cause death was higher ($P < 0.01$) in those with ePWV values of ≥10 m/s than in those with ePWV values of <10 m/s, with stratification by age, sex and presence of cardiovascular risk factors. After adjusting for the age, age squared and other conventional cardiovascular risk factors, an ePWV value of ≥10 m/s or each increase in the ePWV by 1 m/s

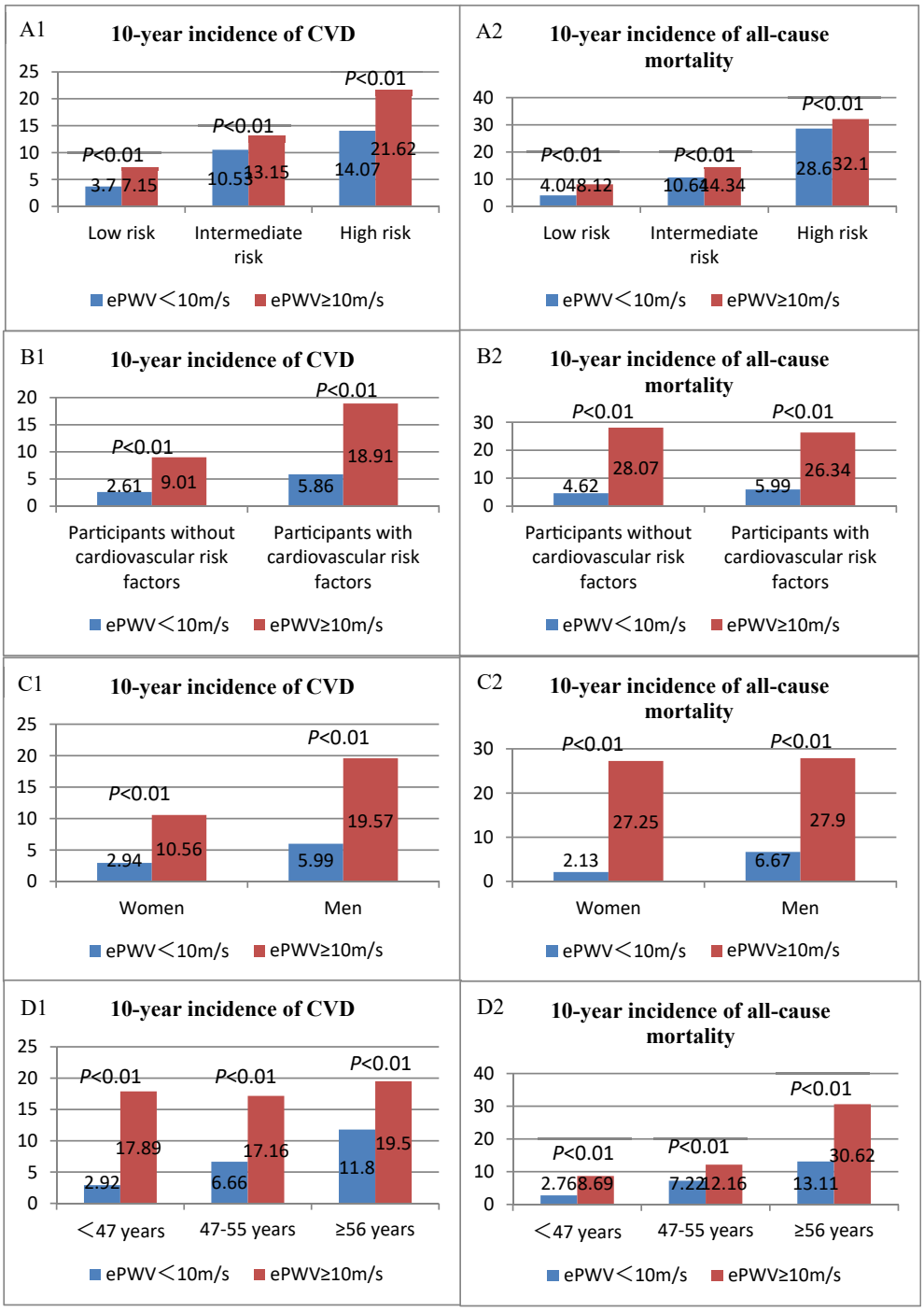

Fig. 1. The cumulative incidence rate of cardiovascular events and all-cause mortality in different subgroups (A: China-PAR score subgroup; B:participants with and without risk factors; C: sex subgroup; D: age subgroup).

increased the risk for CVDs significantly ($P < 0.01$) by 32% and 22%, respectively, and increased the risk for all-cause death by 28% and 10%, respectively. The baPWV showed a mean difference to the ePWV of 6.44 m/s.

The results of our study on Chinese agree with the observations made in previous investigations on non-Chinese ethnicities and demonstrating the association between the ePWV and CVD events. In the study by Greve and colleagues, the ePWV and the measured cfPWV added independently to the Systematic COronary Risk Evaluation (SCORE) for the prediction of the combined outcome of nonfatal myocardial infarction, cardiovascular death, ischemic heart disease and stroke (HR: 1.38; 95% CI: 1.09–1.76; and HR: 1.18; 95%CI: 1.01–1.38), and they added to the Framingham risk score (HR: 1.33; 95%CI: 1.06–1.66; and HR: 1.16; 95% CI: 0.99–1.37) [7]. The authors concluded that the ePWV predicted major cardiovascular events independently of the SCORE, the Framingham risk score and the cfPWV, so that these traditional risk scores might have underestimated the association of age and BP on arterial stiffness and CVD. Vlachopoulos and colleagues reported that in the population of the SPRINT study the ePWV predicted the primary composite cardiovascular outcome (myocardial infarction, other acute coronary

Table 5
Area under the ROC (receiver operator characteristic) curve in models with and without estimated pulse-wave velocity (ePWV) for each event type.

Participants		CVD		All-cause mortality	
	ePWV added	No	Yes	No	Yes
Overall	Model 1	0.720 (0.714–0.726)	0.743** (0.737–0.749)	0.755 (0.750–0.760)	0.819** (0.814–0.823)
	Model 2	0.746 (0.740–0.751)	0.749** (0.743–0.754)	0.824 (0.820–0.828)	0.825** (0.820–0.829)
Participants without risk factors	Model 1	0.727 (0.699–0.755)	0.767** (0.741–0.793)	0.787 (0.766–0.808)	0.850** (0.831–0.869)
	Model 2	0.777 (0.753–0.800)	0.777 (0.754–0.801)	0.859 (0.842–0.876)	0.859 (0.842–0.876)
Participants with risk factors	Model 1	0.701 (0.695–0.708)	0.725** (0.719–0.731)	0.743 (0.737–0.748)	0.808** (0.803–0.812)
	Model 2	0.727 (0.722–0.733)	0.731** (0.725–0.737)	0.813 (0.809–0.818)	0.814** (0.809–0.819)

CVD: a composite endpoint of myocardial infarction, cerebral infarction and cerebral hemorrhage.
Model 1 including sex (male/female), smoking status(never and past, current, ≥1 cigarettes/day), drinking status (never and past, current, ≥1 time/day), education level (elementary school, high school or above), exercise (none, occasionally or frequently, ≥1 times/week), income level (<1000 yuan/month, ≥1000 yuan/month), history of MI (yes/no), history of stroke(yes/no), chronic kidney disease (yes/no), hypertension (yes/no), pulse pressure, body mass index, total cholesterol, fasting blood glucose, uric acid and CRP.
Model 2 including age, age squared and all the factors in model 1.
**$P < 0.001$.

syndromes, stroke, heart failure, or death from cardiovascular causes) with a HR of 1.30 (95%CI: 1.17–1.43; $P < 0.001$) and all-cause death with a HR of 1.65 (95%CI: 1.46–1.86; $P < 0.001$) independent of the Framingham Risk Score [10]. The parameter of the ePWV slightly improved the C-statistic model for the primary outcome from 0.676 (95% CI: 0.65–0.70) to 0.683 (95% CI: 0.66–0.71; $P = 0.049$) and improved the C statistic model for all-cause death from 0.67 (95%CI: 0.64–0.69) to 0.69 (95%CI: 0.66–0.72; $P = 0.03$). The net reclassification index indicated an improvement in the risk discrimination for survival compared with the Framingham Risk Score (categorical net reclassification index = 0.111; $P < 0.001$). The authors concluded that the ePWV predicted the outcomes independently of the Framingham Risk Score, and assumed that parameters of aortic stiffness were useful for the prediction of CVD. In our study, adding the parameter of ePWV to the model with adjustment for cardiovascular risk factors and with additional adjustment for age and age squared did not, however without additional adjustment for age and age squared, did significantly increase the predictive value of the model. One may consider that the formula for the calculation of the ePWV already included the parameters of age and age squared, so that a double adjustment for both parameters might have overweighed the influence of age on the model. Without doubt however, from a pathophysiological perspective, age has to be included in any predictive model for CVD outcomes, also since they occur at increasing age also independently from the presence of other CVD risk factors.

Table 6
Changes in the conventional cardiovascular risk prediction model by incorporating estimated pulse-wave velocity (ePWV).

Participants	Outcome	Old Model	New Model			
			<5%	5%–10%	≥10%	Reclassified
Overall	CVD	<5%	933	66	0	7%
		5%–10%	88	1880	226	14%
		≥10%	0	216	3558	6%
	No CVD	<5%	42412	1240	0	3%
		5%–10%	1865	24499	1493	12%
		≥10%	0	1717	18155	9%
	NRI (95%CI): 0.76% (0.05%–1.46%), $P = 0.036$					
	IDI (95%CI): 0.22% (0.17%–0.27%), $P < 0.001$					
Participants without risk factors	CVD	<5%	174	1	0	1%
		5%–10%	7	65	2	12%
		≥10%	0	1	12	8%
	No CVD	<5%	11451	29	0	0%
		5%–10%	33	1091	6	3%
		≥10%	0	15	98	13%
	NRI (95%CI): 1.81% (−4.28%-0.67%), $P = 0.153$					
	IDI (95%CI): 0% (−0.02%-0.02%), $P = 0.815$					
Participants with risk factors	CVD	<5%	734	67	0	8%
		5%–10%	86	1797	226	15%
		≥10%	0	217	3578	6%
	No CVD	<5%	30638	1128	0	4%
		5%–10%	1745	23475	1574	12%
		≥10%	0	1833	18265	9%
	NRI (95%CI): 0.96% (0.22%–1.70%), $P = 0.011$					
	IDI (95%CI): 0.23% (0.18%–0.28%), $P < 0.001$					

NRI: net reclassification index (categorical); IDI: integrated discrimination improvement; CVD: a composite endpoint of myocardial infarction, cerebral infarction and cerebral hemorrhage. Old model including age, age squared, sex (male/female), smoking status(never and past, current, ≥1 cigarettes/day), drinking status (never and past, current, ≥1 time/day), education level (elementary school, high school or above), exercise (none, occasionally or frequently, ≥1 times/week), income level (<1000 yuan/month, ≥1000 yuan/month), history of MI (yes/no), history of stroke(yes/no), chronic kidney disease (yes/no), hypertension (yes/no), pulse pressure, body mass index, total cholesterol, fasting blood glucose, uric acid and CRP. New model including factors in the old model plus ePWV.

In agreement with the previous studies performed mostly on Western populations, our study on Chinese confirms the value of the ePWV as marker of aortic stiffness for the prediction of future cardiovascular events and all-cause death and extends the knowledge about the association between ePWV and risk of CVD and all-cause death to the population from mainland China. It shows that despite marked differences between the Western countries and China in lifestyle and diet, including the living conditions for Chinese before the economic rise of the country, the value of the ePWV parameter for assessing the risk of future CVD and death is valid for all these ethnicities.

The observations made in our study may have clinical implications. In this study as in previous investigations on populations of different ethnicities, the ePWV showed a predictive ability that was equal or higher than that of traditional risk scores such as the Framingham Risk Score. It suggests that ePWV and the traditional risk scores, although they include the parameters of age and BP, may not address the same risk constellation. The traditional risk scores as well as the ePWV may not fully take into account the cardiovascular risks so that adding the parameter of the ePWV to the scores improves the risk prediction of CVD and all-cause mortality. The finding that the ePWV, when not additionally adjusted for age and age squared, was associated with all-cause deaths including those of non-cardiovascular etiology agrees with previous studies on other ethnicities with associations between the cfPWV and non-cardiovascular death [22–24]. It agrees with the notion that vascular aging also is a biomarker for aging in general so that some

Table 7
Changes in the all-cause death risk prediction model by incorporating estimated pulse-wave velocity (ePWV).

Participants	Outcome	Old Model	New Model			
			<5%	5%–10%	≥10%	Reclassified
Overall	Death	<5%	1085	43	0	4%
		5%–10%	38	1334	80	8%
		≥10%	0	65	7135	1%
	No Death	<5%	45654	629	0	1%
		5%–10%	910	19548	678	8%
		≥10%	0	638	20511	3%
	NRI (95%CI): 0.48% (0.15%–0.80%), $P = 0.004$					
	IDI (95%CI): 0.06% (0.03%–0.09%), $P < 0.001$					
Participants without cardiovascular risk factors	Death	<5%	155	0	0	0%
		5%–10%	1	64	1	3%
		≥10%	0	0	275	0%
	No Death	<5%	10454	7	0	0%
		5%–10%	5	1211	2	1%
		≥10%	0	6	804	1%
	NRI (95%CI): 0.02% (−0.55%-0.58%), $P = 0.956$					
	IDI (95%CI): 0% (−0.01%-0.01%), $P = 0.989$					
Participants with cardiovascular risk factors	Death	<5%	920	39	0	4%
		5%–10%	42	1265	77	9%
		≥10%	0	67	6874	1%
	No Death	<5%	35151	585	0	2%
		5%–10%	838	18371	667	8%
		≥10%	0	639	19828	3%
	NRI (95%CI): 0.37% (0.03%–0.72%), $P = 0.035$					
	IDI (95%CI): 0.06% (0.03%–0.10%), $P < 0.001$					

NRI: net reclassification index (categorical); IDI: integrated discrimination improvement. Old model including age, age squared, sex (male/female), smoking status(never and past, current, ≥1 cigarettes/day), drinking status (never and past, current, ≥1 time/day), education level (elementary school, high school or above), exercise (none, occasionally or frequently, ≥1 times/week), income level (<1000 yuan/month, ≥1000 yuan/month), history of MI (yes/no), history of stroke(yes/no), chronic kidney disease (yes/no), hypertension (yes/no), pulse pressure, body mass index, total cholesterol, fasting blood glucose, uric acid and CRP. New model including factors in the old model plus ePWV.

pathophysiological pathways may contribute to aortic stiffness as well as non-cardiovascular conditions [25,26].

As also shown for Western populations, the ePWV and the baPWV differed in our study population by 6.44 m/s on an average (Supplementary Figs. 1 and 2).

The limitations of our study should be discussed. First, it has to be taken into account that the ePWV referred to the cfPWV and not to the baPWV which we measured in our study. Previous investigations showed however that the baPWV was strongly correlated with the cfPWV, and the American Heart Association recommended the baPWV as "class I, level of evidence B″, as one of the common measures for arterial stiffness in clinical settings [27,28]. Second, men were over-represented in our study population so that our study population was not fully representative for the population of China. Strengths of the study include the large, community-based cohort with a high retention, the standardized data collection protocols, and the inclusion of potential confounders such as BMI, household income, health behaviors and serum concentrations of glucose and blood lipids into the multivariable analysis.

In conclusion, in this adult Chinese community, the ePWV was associated with the risk of CVDs and all-cause mortality, independently of cardiovascular risk factors. It indicates that the calculation of the ePWV and its inclusion in prognostic scores for CVD and all-cause death is useful also for Chinese.

Disclosure/Conflict of Interest

None.

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Appendix ASupplementary data

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