Longitudinal Study of Brachial-Ankle Pulse Wave Velocity and Change in Estimated Glomerular Filtration Rate among Chinese Adults

Junjuan Li^a Liufu Cui^b Xinyuan Zhang^c Jinhong Hou^a Aitian Wang^d
Yuntao Wu^e Jinjie Huang^a Jing Zhou^a Yihan Ma^f Jingli Gao^d
Shouling Wu^e

^aDepartment of Nephrology, Kailuan General Hospital, Tangshan, China; ^bDepartment of Rheumatology and Immunology, Kailuan General Hospital, Tangshan, China; ^cDepartment of Nutritional Sciences, Pennsylvania State University, State College, PA, USA; ^dDepartment of Intensive medicine, Kailuan General Hospital, Tangshan, China; ^eDepartment of Cardiology, Kailuan General Hospital, Tangshan, China; ^fGraduate School, North China University of Science and Technology, Tangshan, China

Keywords

Brachial-ankle pulse wave velocity · Estimated glomerular filtration rate · Change rate · Longitudinal study

Abstract

Background and Objectives: Studies on the association between arterial stiffness and kidney function have generated inconsistent results. Whether arterial stiffness is linked to decline in renal function warrants further study. This study aimed to investigate the association between brachial-ankle pulse wave velocity (baPWV) and longitudinal change in estimated glomerular filtration rate (eGFR) among Chinese adults. **Methods:** In this longitudinal study, 8,264 participants in a community-based cohort had baPWV measured in 2010–2011 and were followed in subsequent surveys through to 2016. During each survey visit, fasting blood samples were collected for serum creatinine and eGFR was calculated. Participants were divided into 5 groups (Q1–Q5) by baPWV quintile. The association between baPWV and longitudinal changes in eGFR was assessed using generalized estimating equa-

tion models. **Results:** A total of 8,045 participants were included in the final analysis. The average age was 54 ± 12 years (age range 24–97 years), and mean eGFR was 93.0 ± 18.6 mL/min/1.73 m². There was an inverse linear association between baseline baPWV and eGFR change rate ($p < 0.001$). Compared with Q1 (lowest) group, the mean differences and 95% CI in eGFR decrease rate among Q2–Q5 groups were -0.23 ($-0.62, 0.16$), -0.67 ($-1.06, -0.28$), -1.11 ($-1.50, -0.72$), and -1.30 ($-1.69, -0.92$) mL/min/1.73 m² per year, respectively, after adjustment for age, gender, and other potential confounders (p trend < 0.0001). For each 100 cm/s increase in baPWV at baseline, the fully adjusted mean difference in eGFR decrease rate was -0.14 mL/min/1.73 m² per year (95% CI $-0.18, -0.10$; $p < 0.0001$). Compared with participants with baPWV $< 1,400$ cm/s, the fully adjusted mean difference in eGFR decrease rate was -0.92 mL/min/1.73 m² per year (95% CI $-1.18, -0.66$) for those with baPWV $\geq 1,400$ cm/s ($p < 0.0001$). **Conclusions:** Participants with a higher baPWV at baseline had a greater decrease in eGFR over time. Future

Junjuan Li and Liufu Cui contributed equally to this work.

studies could examine the relationship between baPWV and decline in renal function in higher risk cohorts, and its potential role in targeting reno-protective interventions to those who may benefit from them most.

© 2021 The Author(s)

Published by S. Karger AG, Basel

Introduction

The prevalence of CKD is estimated to be 8–16% worldwide [1] and approximately 11% in China [2]. Even early-stage CKD is associated with an increased risk of cardiovascular disease [3–5], and arterial stiffness is considered a mediator of this cardiorenal interaction [6]. The kidney is a high-flow but low-resistance organ and changes in arterial stiffness may affect its function via multiple pathogenic ways (e.g., hemodynamic stress, microvascular ischemia, and endothelial dysfunction) [7].

Previous studies of the association between arterial stiffness and kidney function are inconsistent. Some studies have found a significant inverse association [8–10], suggesting arterial stiffness contributes to the development of renal damage [11], whereas other studies have not [12, 13]. For instance, in the Framingham Heart Study, higher pulse wave velocity (PWV) was associated with onset of new albuminuria but not decline in renal function [14]. In another cohort, pulse pressure but not brachial-ankle pulse wave velocity (baPWV) was a predictor of decline in renal function [15]. Of note, few studies have examined the potential dose-response association of arterial stiffness and decline in renal function.

PWV is an index of arterial stiffness, which can be measured noninvasively [16]. Although aortic (carotid-femoral) PWV is currently the gold standard for measuring arterial stiffness [17], baPWV correlates well with central aortic PWV [18] (correlation coefficient = 0.73) [19] and has been widely accepted for measuring arterial stiffness in clinical practice [20]. In the current study, we aimed to investigate the association between baPWV and longitudinal change in estimated glomerular filtration rate (eGFR) in a large, community-based Chinese population from the Kailuan study (Registration No. ChiCTR-TNC-11001489).

Materials and Methods

Participants

The Kailuan Study is an ongoing, multicenter, population-based cohort study of 101,510 participants (81,110 men and 20,400 women, 18–98 years old) in the Kailuan community located in Tangshan, a northern industrial city in China. Participants consist

of current and retired workers in the service of the Kailuan (Group) Co., Ltd., who reside in the Kailuan community. In the Kailuan Study, all participants underwent baseline questionnaire assessments of lifestyle and health status, and clinical and laboratory examinations in 2006–2007; follow-up assessments were conducted every 2 years. All assessments were conducted in the 11 hospitals responsible for healthcare in this community.

Arterial stiffness was assessed during 2010–2016 using baPWV. There were 22,681 participants who were randomly enrolled in several cohorts nested within the Kailuan study to examine the relationship between arterial stiffness and a variety of chronic conditions (these cohorts were (a) stroke cohort, (b) older persons cohort (age ≥ 60 years), (c) hypertensive disorders of pregnancy cohort, and (d) peripheral vascular disease cohort) as detailed elsewhere [21]. We included 8,264 participants who had baPWV examination during 2010–2011 (referred to as “baseline” in the current study), and 2 subsequent surveys through 2016. We excluded participants with ESKD at baseline and during follow-up ($n = 47$), with missing information on serum creatinine ($n = 90$), or extreme values of baPWV (greater than 99% quantile or less than 1% quantile, $n = 82$) at baseline. Finally, a total of 8,045 participants (5,580 men and 2,465 women) were included (Fig. 1).

Assessment of eGFR

Overnight fasting (8–12 h) venous blood samples were collected using vacuum tubes containing EDTA before 9:00 a.m. during each health examination. Serum creatinine was assessed using sarcosine oxidase assay method (Creatinine kit, BioSino Bio-technology and Science Inc, Beijing, China), as described previously [22]. The eGFR was then computed, using serum creatinine, sex, and age, according to the CKD Epidemiology Collaboration equation [23].

Measurement of baPWV

In this study, baPWV was measured using a BP-203RPEIII networked arteriosclerosis detection device (Omron Healthcare (China) Co., Ltd.) by nurses trained with a standard protocol provided by the manufacturer. The majority of measurements (7,987/8,045, 99.2%) were taken in the coordinating center (Kailuan General Hospital), and measuring equipment was tested regularly. Participants refrained from smoking or drinking beverages for 24 h before the examination. Each participant was measured twice in supine position after resting in air-conditioned room (22–25°C) for at least 5 min. The upper arms and ankles were wrapped in blood pressure (BP) cuffs. The lower edge of the arm cuff was placed 2–3 cm above the transverse striation of the cubital fossa, while the lower edge of the ankle cuff was placed 1–2 cm above the superior aspect of the medial malleolus. Electrodes of the electrocardiogram were placed on both wrists, and a microphone to detect heart sounds was placed on the left edge of the sternum. The maximum of the left- or right-side baPWV was used in analysis. BaPWV $\geq 1,400$ cm/s was considered as arterial stiffness [24].

Measurement of BP

A standardized protocol for measurements of an auscultatory BP was executed by a trained physician using a mercury sphygmomanometer with appropriate cuff sizes. The midpoint of the right upper arm was ascertained by measuring the length from the tip of the shoulder to the tip of the elbow and dividing this length by 2. The cuff was wrapped around the straightened arm at the midpoint identified and the cuff was checked to ensure that it was nei-

Fig. 1. Flowchart of the study population. The definition of extreme values of baPWV was values greater than 99% quantile or less than 1% quantile at baseline. baPWV, brachial-ankle pulse wave velocity.

ther too tight nor too loose. Three readings in sitting position were measured after participants had 15 min of quiet rest in a chair. The average of 3 measurements was used for data analysis. In a validation study conducted among 116 participants of the Kailuan study, the systolic blood pressure (SBP) measured by arteriosclerosis detection device was highly associated with that assessed by mercury sphygmomanometer (correlation coefficient = 0.94; $p < 0.001$). We computed mean arterial BP (MAP) as $1/3 \text{ SBP} + 2/3 \text{ diastolic blood pressure (DBP)}$.

Assessment of Covariates

Information on covariates was collected via questionnaires during both baseline and follow-up health examination and included education level (primary school, middle school, or college), income level (<1,000 RMB/month, 1,000–3,000 RMB/month, or $\geq 3,000$ RMB/month), occupation (white collar, blue collar, or coal miner), physical activity (never or rarely, <4 times/week, or ≥ 4 times/week), smoking status (never, past smoker, or current smoker), alcohol consumption (never, past drinker, or current drinker), use of medications (e.g., hypoglycemic agents and antihypertensive), and history of cancer, myocardial infarction (MI), and stroke. Weight and height were measured by trained field workers during the interview; BMI was calculated as weight (kg)/height (m^2).

The fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured using an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of the Kailuan General Hospital. Diabetes was defined as a FBG concentration $\geq 7 \text{ mmol/L}$ or active treatment with insulin or any oral

hypoglycemic agent. Impaired fasting glucose was defined as a FBG concentration between 5.6 and 6.9 mmol/L.

Statistical Analysis

We used generalized estimating equation (GEE) models to estimate the longitudinal association between baseline baPWV and the change in eGFR. Baseline baPWV was divided into quintiles (Q1, <1,272 cm/s group, reference; Q2, 1,272–1,407 cm/s group; Q3, 1,408–1,552 cm/s group; Q4, 1,553–1,785 cm/s group; and Q5, 1,786–2,899 cm/s group). Three multivariate models were fitted as follows: model 1 was a univariate analysis; model 2 was adjusted for age and sex; model 3 was further adjusted for educational level, income level, physical activity, smoking status, drinking status, history of MI, history of stroke, history of cancer, MAP, BMI, FBG, TG, TC, LDL, HDL, and hs-CRP. Trends in mean differences of eGFR change across groups of baPWV were assessed in GEE models by taking the baPWV group number as a continuous variable.

To test the robustness of the main findings, several sensitivity analyses were conducted by excluding participants with history of MI or stroke or cancer, medication, hypertension, or obesity (BMI $\geq 28 \text{ kg/m}^2$). Because the 4 lipid variables were likely to be correlated, an additional sensitivity analysis was conducted using only TC. We also tested interactions between baPWV and age, sex, smoking status, drinking status, physical activity, MAP, BMI, FBG, TG, TC, LDL, HDL, and hs-CRP in relation to change of eGFR by adding multiplicative terms in the GEE models.

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc, Cary, NC). Categorical data were presented as percentage, and continuous data were presented as mean $\pm$ standard deviation. $p < 0.05$ was regarded as significant for 2-sided tests.

Table 1. The characteristics, health behaviors, and clinical diagnoses in the different levels of baPWV in 2010

baPWV in 2010, cm/s	Q1 <1,272	Q2 1,272–1,407	Q3 1,408–1,552	Q4 1,553–1,785	Q5 1,786–2,899
N	1,525	1,547	1,566	1,615	1,792
Means of baPWV in 2010, cm/s	1,172±76.61	1,342±39.71	1,477±41.81	1,657±66.95	2,088±253.49
Man, %	753 (49.38)	1,074 (69.42)	1,172 (74.84)	1,219 (75.48)	1,362 (76.00)
Age, year	46.60±7.13	49.52±7.74	51.57±9.02	55.80±9.01	63.97±13.32
Educational level					
Primary	58 (3.80)	72 (4.65)	108 (6.90)	142 (8.79)	288 (16.07)
Middle	716 (46.95)	789 (51.00)	859 (54.85)	891 (55.17)	918 (51.23)
College	751 (49.28)	686 (44.34)	599 (38.25)	582 (36.04)	586 (32.70)
Income level					
<1,000/month	1,295 (84.92)	1,318 (85.20)	1,356 (86.59)	1,408 (87.18)	1,503 (83.87)
1,000–3,000/month	110 (7.21)	97 (6.27)	86 (5.49)	77 (4.77)	169 (9.43)
>3,000/month	120 (7.87)	132 (8.53)	124 (7.92)	130 (8.05)	120 (6.70)
Physical activity (every time more than 20 min)					
Never	686 (44.98)	678 (43.83)	659 (42.08)	641 (39.69)	732 (40.85)
<4 times/week	612 (40.13)	565 (36.52)	588 (37.55)	591 (36.59)	545 (30.41)
4+ times/week	227 (14.89)	304 (19.65)	319 (20.37)	383 (23.72)	515 (28.74)
Smoking status					
Never	1,076 (70.56)	928 (59.99)	842 (53.77)	887 (54.92)	1,048 (58.48)
Past smoker	50 (3.28)	60 (3.88)	101 (6.45)	87 (5.39)	140 (7.81)
Current smoker	399 (26.16)	559 (36.13)	623 (39.78)	641 (39.69)	604 (33.71)
Drinking status					
Never	1,089 (71.41)	928 (59.99)	854 (54.53)	941 (58.27)	1,105 (61.66)
Past drinker	8 (0.52)	10 (0.65)	22 (1.40)	28 (1.73)	31 (1.73)
Current drinker	428 (28.07)	609 (39.37)	690 (44.06)	646 (40.00)	656 (36.61)
MI history					
Yes	14 (0.92)	16 (1.03)	21 (1.34)	36 (2.23)	46 (2.57)
Stroke history					
Yes	13 (0.85)	17 (1.10)	21 (1.34)	43 (2.66)	105 (5.86)
Cancer history					
Yes	14 (0.92)	7 (0.45)	16 (1.02)	14 (0.87)	16 (0.89)
eGFR in 2010, mL/min/1.73 m ² per year	98.29±17.92	94.94±18.36	94.18±17.33	92.03±19.66	86.81±19.76
C-reactive protein, mg/L					
<1	967 (63.41)	916 (59.21)	845 (53.96)	789 (48.85)	809 (45.15)
1–3	382 (25.05)	457 (29.54)	473 (30.20)	515 (31.89)	568 (31.70)
≥3	176 (11.54)	174 (11.25)	248 (15.84)	311 (19.26)	415 (23.16)
SBP, mm Hg	116.02±13.89	124.70±14.36	130.28±15.38	137.47±17.75	146.10±19.29
DBP, mm Hg	77.60±9.55	82.92±9.78	85.40±10.64	87.13±11.56	87.05±12.49
MAP, mm Hg	87.18±9.97	93.14±10.87	97.98±12.21	102.60±13.25	109.06±15.71
FBG, mmol/L	5.17±0.82	5.42±1.09	5.60±1.43	5.81±1.67	6.07±1.92
BMI, kg/m ²	24.51±3.20	25.11±3.25	25.50±3.44	25.51±3.33	25.12±3.40
TG, mmol/L	1.17±0.82	1.31±0.95	1.43±1.06	1.55±1.0	1.47±1.07
TC, mmol/L	4.79±0.89	5.01±1.77	5.08±0.97	5.14±1.06	5.30±2.21
LDL-C, mmol/L	2.42±0.67	2.66±0.77	2.69±0.72	2.76±0.90	2.70±0.83
HDL-C, mmol/L	1.64±0.43	1.61±0.52	1.58±0.44	1.57±0.60	1.60±0.48

Continuous variables were reported as means ± SD. Categorical variables were reported as N (%). baPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; AMP, mean arterial blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein.

Table 2. Mean differences and 95% CI in eGFR change (mL/min/1.73 m² per year) from 2010 to 2016 in different levels of baseline baPWV

baPWV in 2010, cm/s	Q1 <1,272	Q2 1,272–1,407	Q3 1,408–1,552	Q4 1,553–1,785	Q5 1,786–2,899	Each 100 cm/s increased in baPWV	<1,400	≥1,400
Model 1	0 (ref)	-0.17 (-0.57, 0.22)	-0.64 (-1.04, -0.24)	-0.95 (-1.35, -0.56)	-0.76 (-1.15, -0.37)*	-0.10 (-0.13, -0.06) [#]	0 (ref)	-0.63 (-0.89, -0.37) [#]
Model 2	0 (ref)	-0.21 (-0.60, 0.18)	-0.70 (-1.10, -0.30)	-1.18 (-1.57, -0.79)	-1.32 (-1.71, -0.94)*	-0.15 (-0.19, -0.11) [#]	0 (ref)	-0.95 (-1.21, -0.70) [#]
Model 3	0 (ref)	-0.23 (-0.62, 0.16)	-0.67 (-1.06, -0.28)	-1.11 (-1.50, -0.72)	-1.30 (-1.69, -0.92)*	-0.14 (-0.18, -0.10) [#]	0 (ref)	-0.92 (-1.18, -0.66) [#]

Model 1 was univariate analysis. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, educational level (primary, middle, or college), income level (<1,000 RMB/month, 1,000–3,000 RMB/month, or >3,000 RMB/month), physical activity (never, <4 times/week, 4 + times/week, or every time more than 20 min), smoking status (never, past smoker, or current smoker), drinking status (never, past drinker, or current drinker), MI history (no or yes), stroke history (no or yes), cancer history (no or yes), MAP (mm Hg), BMI (kg/m²), FBG (mmol/L), TG (mmol/L), TC (mmol/L), LDL (mmol/L), HDL (mmol/L), and C-reactive protein (<1 mg/L, 1–3 mg/L, or ≥3 mg/L). eGFR, estimated glomerular filtration rate; CI, confidence interval; baPWV, brachial-ankle pulse wave velocity; MAP, mean arterial blood pressure; MI, myocardial infarction; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein. * Means *p* value <0.0001. [#] Means *p* trend <0.0001.

Fig. 2. Time-dependent decrease rate and 95% CI in eGFR (mL/min/1.73 m² per year) by quintile groups of baseline baPWV. Model 1 was univariate analysis. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, educational level (primary, middle, and college), income level (<1,000 RMB/month, 1,000–3,000 RMB/month, and >3,000 RMB/month), physical activity (never, <4 times/week, 4 + times/week, and every time more than 20 min), smoking status (never, past smoker, and current smoker), drinking status (never, past drinker, and current drinker), MI history (no, yes), stroke history (no, yes), cancer history (no, yes), MAP (mm Hg), BMI (kg/m²), FBG (mmol/L), TG (mmol/L), TC (mmol/L), LDL (mmol/L), HDL (mmol/L), and C-reactive protein (<1 mg/L, 1–3 mg/L, and ≥3 mg/L). CI, confidence interval; baPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Results

The characteristics of the cohort based on the quintiles of baPWV at baseline are shown in Table 1. Compared with participants in the Q1 group of baPWV, participants in Q2–Q5 groups were older and tended to have higher SBP, DBP, MAP, FBG, TC levels, and lower baseline eGFR levels; they were more likely to be men, smokers or drinkers, with lower education levels, and had a higher prevalence of prior MI or stroke (Table 1).

Mean eGFR level decreased during 6 years of follow-up. In the GEE model, there was an inverse linear association between Q1–Q5 groups of baseline baPWV and eGFR change (Fig. 2). Compared with Q1 group, the mean differences and 95% CI in eGFR rate among Q2–Q5 groups were -0.23 (-0.62, 0.16), -0.67 (-1.06, -0.28), -1.11 (-1.50, -0.72), and -1.30 (-1.69, -0.92) mL/

min/1.73 m² per year, respectively (model 3, *p* trend <0.0001). For each 100 cm/s increase in baPWV at baseline, the fully adjusted mean difference in eGFR change was -0.14 mL/min/1.73 m² per year (95% CI -0.18, -0.10, *p* < 0.0001). Compared with the group of baPWV < 1,400

cm/s, the fully adjusted mean difference in eGFR decrease was -0.92 mL/min/1.73 m² per year (95% CI -1.18, -0.66) for the group of baPWV ≥ 1,400 cm/s (*p* difference < 0.0001) (Table 2).

There were significant interactions between baPWV and age, physical activity, and FBG (all *p* interaction <0.001), in relation to the change of eGFR. Participants aged ≤65 years, undertaking physical activities never or rarely, or with normal FBG level exhibited more pronounced inverse association between baseline baPWV and eGFR change (Fig. 3).

Sensitivity analyses generated similar results after separately excluding participants with hypertension, obesity (BMI ≥ 28 kg/m²), history of MI, stroke, or cancer, and mediations (antihypertensive drugs, hypoglycemic drugs, or hypolipemic drug) (see online suppl. Table 1; see www.karger.com/doi/10.1159/000510611 for all online suppl. material).

Discussion

To the best of our knowledge, this was the first large scale, longitudinal study with repeated measurements to investigate the association between baPWV and change in eGFR. We found an inverse dose-response relationship between baseline baPWV and eGFR change during 6-year follow-up. For each 100 cm/s increase in baseline baPWV, eGFR decreased by 0.13 mL/min/1.73 m² per year, reaching approximately 1 mL/min/1.73 m² after 8-year follow-up. This difference may have clinical significance when one considers that the risk of ESKD increases almost 2-fold for every 1 mL/min/1.73 m² decline in eGFR after adjustment for covariates [25]. In the present study,

Fig. 3. Time-dependent decrease rate and 95% CI in eGFR rate (mL/min/1.73 m² per year) by quintile groups of baseline baPWV in subgroups by age (a), physical activity (b), and diabetes status (c). The model was adjusted for age, sex, educational level (primary, middle, and college), income level (<1,000 RMB/month, 1,000–3,000 RMB/month, and >3,000 RMB/month), physical activity (never, <4 times/week, 4 + times/week, and every time more than 20 min), smoking status (never, past smoker, and current smoker), drinking status (never, past drinker, and current drinker), MI history (no, yes), stroke history (no, yes), cancer history (no, yes), MAP (mm Hg), BMI (kg/m²), FBG (mmol/L), TG (mmol/L), TC (mmol/L), LDL (mmol/L), HDL (mmol/L), and C-reactive protein (<1 mg/L, 1–3 mg/L, and ≥3 mg/L). baPWV, brachial-ankle pulse wave velocity; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

participants with arterial stiffness saw a decline in eGFR of 0.92 mL/min/1.73 m² per year, reaching 5.52 mL/min/1.73 m² after 6-year follow-up and so potentially increasing their risk of ESKD by as much as 10-fold.

Our results were consistent with previous work [11] associating baseline cfPWV with annual decrease in eGFR. Several other studies [8, 9, 26, 27] also linked the decline in kidney function to increase aortic stiffness and suggested that vascular stiffness could be a target for delaying loss of kidney function. Together, this suggests that arterial stiffness plays an important role in the development of renal damage. However, in contrast, renal hyperfiltration has also been associated with arterial stiffness among individuals with relatively normal kidney function [28]. Each 10 mL/min/1.73 m² increase in eGFR was associated with an 11–23% increased risk of elevated baPWV. Future prospective studies are warranted to clarify the temporal relationship between baPWV and eGFR, which may improve our understanding of the underlying causal mechanisms.

The association between higher baseline baPWV and faster decrease in eGFR was found to be more pronounced in Participants aged ≤65 year. Both arterial stiffness and eGFR decrease are age-related disorders [29], and as elastic artery stiffness may promote the development of systolic hypertension [30], one could infer that BP mediates the association between baPWV and eGFR in older people. Participants without regular physical activity also had a faster decrease in eGFR associated with arterial stiffness than those who have frequent physical activities. Arterial stiffness may be ameliorated or reversed through healthy lifestyle practices, such as aerobic exercise [31], weight loss [32], and dietary sodium restriction [33]. The observed association between baPWV and change in eGFR could also potentially be modified by lifestyle.

Several mechanisms might explain the relationship between arterial stiffness and kidney function. The kidney is a high-flow organ, and the special structure of the glomerular capillaries, with the pressure in the efferent artery being higher than that in the afferent artery, means the renal vasculature is relatively susceptible to hemodynamic stress. Increasing stiffness of the arterial vasculature reduces the pressure buffering capabilities of the vascular wall [34], leading to increased speed of the forward traveling pulse wave as well as in earlier pulse wave reflection that augments systolic pressure. Meanwhile, DBP falls with arterial stiffening, and the increased central pulse pressure contributes to a high pulsatile flow in the aorta and its branching arteries, including the renal vessels [34, 35]. The torrential pulsatile flow is transmitted to the vulnerable renal microvasculature [36], eventually causing either baro-

trauma, endothelial dysfunction, and oxidative stress [37, 38]. This may ultimately result in microvascular ischemia and kidney dysfunction [7]. Moreover, while the glomeruli and renal microcirculation are protected against BP variations by autoregulation of vascular tone in afferent and efferent arterioles [39, 40], sustained exposure to increased BP induces microvascular remodeling and blunts renal autoregulation [41]. This complex (and incompletely understood) pathway may explain our present findings.

Several limitations should be considered. In particular, we did not measure urinary albumin excretion in a quantitative way, given that urinary albumin excretion is a sensitive maker of renal microvascular dysfunction. In addition, the participants were all from the Kailuan community and they were not nationally representative of the Chinese population. Compared with the general Chinese adult population, the proportion of men is higher in our study. These factors may limit the generalization of our findings. Finally, without adjustment for multiple testing, the results of our subgroup analyses should be interpreted cautiously. The strengths of this study include the long follow-up duration, repeated measurements, and large sample size. In addition, the average eGFR in the study population was relatively high (>90 mL/min/1.73 m²), so while the relationship between decline in renal function and baPWV in CKD patients cannot be inferred from these data, this study shows that this association is not restricted to those who already have impaired kidney function.

In conclusion, we found that participants with higher baPWV at baseline had a faster decrease rate in eGFR during 6-year follow-up. BaPWV may become a novel marker of renal risk and perhaps intervention target for preventing kidney dysfunction. Future intervention studies are warranted to address whether there is a causal relationship and whether lowering the arterial stiffness can prevent or delay the onset of CKD and further contribute to a lower risk of ESKD.

Acknowledgements

The authors also thank the participants of the Kailuan study. The authors would also express their appreciation for the help from the laboratory staff of the Department of Cardiology of Kailuan Hospital.

Statement of Ethics

This study was approved by the Ethics Committee of the Kailuan General Hospital. All participants provided written informed consent.

Conflict of Interest Statement

All authors read and approved the final manuscript. All the authors have no conflicts of interest to declare.

Funding Sources

No finding sources.

Author Contributions

Junjuan Li and Liufu Cui searched the literature, conceived and designed the study, analyzed the data, interpreted the results, and drafted the manuscript. Jingli Gao and Shouling Wu organized and supervised the study, interpreted the results, and revised the manuscript. Other members collected and analyzed the data. Jingli Gao and Shouling Wu are the guarantor and take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

References

- 1 Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013 Jul 20;382(9888):260–72.
- 2 Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet*. 2012 Mar 3;379(9818):815–22.
- 3 Chronic Kidney Disease Prognosis Consortium; Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010 Jun 12;375(9731):2073–81.
- 4 Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL, et al. Kidney disease as a risk factor for recurrent cardiovascular disease and mortality. *Am J Kidney Dis*. 2004 Aug;44(2):198–206.
- 5 Meisinger C, Döring A, Löwel H, KORA Study Group. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. *Eur Heart J*. 2006 May; 27(10):1245–50.
- 6 Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, et al. Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. *Hypertension*. 2006 Oct;48(4): 616–21.
- 7 Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, et al. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. *Hypertension*. 2015 Aug;66(2): 294–300.
- 8 Sedaghat S, Dawkins Arce FG, Verwoert GC, Hofman A, Ikram MA, Franco OH, et al. Association of renal function with vascular stiffness in older adults: the Rotterdam study. *Age Ageing*. 2014 Nov;43(6):827–33.
- 9 Sedaghat S, Mattace-Raso FU, Hoorn EJ, Uitterlinden AG, Hofman A, Ikram MA, et al. Arterial stiffness and decline in kidney function. *Clin J Am Soc Nephrol*. 2015 Dec 7; 10(12):2190–7.
- 10 Elias MF, Davey A, Dore GA, Gillespie A, Abhayaratna WP, Robbins MA. Deterioration in renal function is associated with increased arterial stiffness. *Am J Hypertens*. 2014 Feb; 27(2):207–14.
- 11 van Varik BJ, Vossen LM, Rennenberg RJ, Stoffers HE, Kessels AG, de Leeuw PW, et al. Arterial stiffness and decline of renal function in a primary care population. *Hypertens Res*. 2017 Jan;40(1):73–8.
- 12 Madero M, Peralta C, Katz R, Canada R, Fried L, Najjar S, et al. Association of arterial rigidity with incident kidney disease and kidney function decline: the Health ABC study. *Clin J Am Soc Nephrol*. 2013 Mar;8(3):424–33.
- 13 Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int*. 2006 Jan;69(2):350–7.
- 14 Upadhyay A, Hwang SJ, Mitchell GF, Vasan RS, Vita JA, Stantchev PI, et al. Arterial stiffness in mild-to-moderate CKD. *J Am Soc Nephrol*. 2009 Sep;20(9):2044–53.
- 15 Jia L, Zhang W, Ma J, Chen X, Chen L, Li Z, et al. Pulse pressure, instead of brachial-ankle pulse wave velocity, is associated with reduced kidney function in a Chinese Han population. *Kidney Blood Press Res*. 2017;42(1): 43–51.
- 16 Oliver JJ, Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. *Arterioscler Thromb Vasc Biol*. 2003 Apr 1;23(4):554–66.
- 17 Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res*. 2002 May;25(3):359–64.
- 18 Youn JC, Kim JY, Park S, Kwon J, Lee HS, Shin DH, et al. Comparison of arterial stiffness indices measured by the Colins and SphygmoCor systems. *Hypertens Res*. 2012 Dec;35(12):1180–4.
- 19 Nowak KL, Rossman MJ, Chonchol M, Seals DR. Strategies for achieving healthy vascular aging. *Hypertension*. 2018 Mar;71(3):389–402.
- 20 Gavish B, Izzo JL Jr. Arterial stiffness: going a step beyond. *Am J Hypertens*. 2016 Nov 1; 29(11):1223–33.
- 21 Wu Y, Zhang Y, Gao J, Man S, Xing J, Cao Z, et al. Effect of brachial-ankle pulse wave velocity combined with blood pressure on cardio-cerebrovascular events. *Exp Ther Med*. 2019 Dec;18(6):4555–66.
- 22 Li J, Huang Z, Hou J, Sawyer AM, Wu Z, Cai J, et al. Sleep and CKD in Chinese adults: a cross-sectional study. *Clin J Am Soc Nephrol*. 2017 Jun 7;12(6):885–92.
- 23 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009 May 5;150(9):604–12.
- 24 Yamashina A, Tomiyama H, Arai T, Hirose K, Koji Y, Hirayama Y, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res*. 2003;26(8):615–22.
- 25 Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013 Jun 4;158(11):825–30.
- 26 Elias MF, Davey A, Dore GA, Gillespie A, Abhayaratna WP, Robbins MA. Deterioration in renal function is associated with increased arterial stiffness. *Am J Hypertens*. 2014 Feb; 27(2):207–14.
- 27 Kim ED, Tanaka H, Ballew SH, Sang Y, Heiss G, Coresh J, et al. Associations between kidney disease measures and regional pulse wave velocity in a large community-based cohort: the atherosclerosis risk in communities (ARIC) study. *Am J Kidney Dis*. 2018 Nov; 72(5):682–90.
- 28 Lin L, Peng K, Du R, Huang X, Sun W, Ding L, et al. High glomerular filtration rate is associated with arterial stiffness in Chinese population. *J Hypertens*. 2017 Feb;35(2):385–91.
- 29 Wu S, Jin C, Li S, Zheng X, Zhang X, Cui L, et al. Aging, arterial stiffness, and blood pressure association in Chinese adults. *Hypertension*. 2019 Apr;73(4):893–9.
- 30 Weisbrod RM, Shiang T, Al Sayah L, Fry JL, Bajpai S, Reinhart-King CA, et al. Arterial stiffening precedes systolic hypertension in diet-induced obesity. *Hypertension*. 2013 Dec;62(6):1105–10.

- 31 Tanaka H, Dinunno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. [Circulation](#). 2000 Sep 12;102(11):1270–5.
- 32 Dengo AL, Dennis EA, Orr JS, Marinik EL, Ehrlich E, Davy BM, et al. Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. [Hypertension](#). 2010 Apr;55(4):855–61.
- 33 He FJ, Marciniak M, Visagie E, Markandu ND, Anand V, Dalton RN, et al. Effect of modest salt reduction on blood pressure, urinary albumin, and pulse wave velocity in white, black, and Asian mild hypertensives. [Hypertension](#). 2009 Sep; 54(3):482–8.
- 34 Mitchell GF. Increased aortic stiffness: an unfavorable cardiorenal connection. [Hypertension](#). 2004 Feb;43(2):151–3.
- 35 Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Hanges in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham heart study. [Hypertension](#). 2004 Jun; 43(6):1239–45.
- 36 Fesler P, du Cailar G, Ribstein J, Mimran A. Glomerular hemodynamics and arterial function in normal individuals. [J Hypertens](#). 2010 Dec;28(12):2462–7.
- 37 Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. [J Appl Physiol](#). 2008 Nov;105(5): 1652–60.
- 38 Hashimoto J, Ito S. Central pulse pressure and aortic stiffness determine renal hemodynamics: pathophysiological implication for microalbuminuria in hypertension. [Hypertension](#). 2011 Nov;58(5):839–46.
- 39 Loutzenhiser R, Bidani A, Chilton L. Renal myogenic response: kinetic attributes and physiological role. [Circ Res](#). 2002 Jun 28; 90(12):1316–24.
- 40 Bidani AK, Griffin KA, Williamson G, Wang X, Loutzenhiser R. Protective importance of the myogenic response in the renal circulation. [Hypertension](#). 2009 Aug;54(2): 393–8.
- 41 Hultström M. Development of structural kidney damage in spontaneously hypertensive rats. [J Hypertens](#). 2012 Jun;30(6):1087–91.