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ORIGINAL RESEARCH

Causal Association of Arterial Stiffness With the Risk of Chronic Kidney Disease

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ABSTRACT

BACKGROUND Previous studies on the direction of the association between arterial stiffness (AS) and chronic kidney disease (CKD) were inconsistent, leaving a knowledge gap in understanding the temporal sequence of the association.

OBJECTIVES This study sought to assess the temporal and longitudinal relationship between AS and CKD.

METHODS The temporal relationship between AS measured by brachial ankle pulse wave velocity and CKD measured by estimated glomerular filtration rate (eGFR) was analyzed among 7,753 participants with repeated examinations in the Kailuan study using cross-lagged panel analysis. The longitudinal associations of AS status and vascular aging (VA) phenotype with incident CKD were analyzed among 10,535 participants.

RESULTS The adjusted cross-lagged path coefficient ($\beta_1 = -0.03$; 95% CI: −0.06 to −0.01; $P < 0.0001$) from baseline brachial ankle pulse wave velocity to follow-up eGFR was significantly greater than the path coefficient ($\beta_2 = -0.01$; 95% CI: −0.02 to 0.01; $P = 0.6202$) from baseline eGFR to follow-up brachial ankle pulse wave velocity ($P < 0.0001$ for the difference). During a median follow-up of 8.48 years, 953 cases of incident CKD (9.05%) occurred. After adjustment for confounders, borderline (HR: 1.17; 95% CI: 1.08-1.38) and elevated AS (HR: 1.39; 95% CI: 1.12-1.72) was associated a higher risk of CKD, compared with normal AS. Consistently, supernormal VA (HR: 0.76; 95% CI: 0.66-0.86) was associated with a decreased and early VA (HR: 1.36; 95% CI: 1.29-1.43) was associated with an increased risk of CKD, compared with normal VA.

CONCLUSIONS AS appeared to precede the decrease in eGFR. Additionally, increased AS and early VA were associated with an increased risk of incident CKD. (JACC: Asia 2024;4:444-453) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Chronic kidney disease (CKD) is a major global health burden due to the high prevalence and its association with the risk of cardiovascular disease.[1] This cardiorenal relationship has raised increasing interest in terms of its vast and complex interaction that has significant impacts on health.[2,3] Arterial stiffness (AS) has been considered a potentially important mediator of cardiorenal interaction.[4] From the pathophysiological prospectives, AS has an important impact on pulsatile

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hemodynamics, and increased AS can promote excessive penetration of pressure and flow pulsatility into the kidney, leading to damage on kidney function.[5-7] On the contrary, CKD also could increase AS through inducing premature vascular aging (VA), increasing the vascular tone, wall thickening, and favoring calcium deposits in the arterial wall.[8-10]

Results of cross-sectional or longitudinal researches on this issue have also been inconsistent. Some studies supported the direction that increased AS may predict CKD,[11-17] alternatively, a lower eGFR was also reported to be associated with increased AS.[18-22] These findings suggest that the dynamic of the temporal relationship between AS and CKD is probably far from straightforward because changes in either one may precede changes in the other. Whereas previous epidemiological evidence on the association of AS and CKD were merely focused in 1 direction, which one is the precursor or whether the association between AS and CKD is bidirectional remains unclear. Modeling the temporal relationship between AS and CKD may offer an opportunity to improve understanding of the temporal sequence of AS and CKD, which in turn could highlight potential targets for early intervention.

Using data from a large community-based population study, initially, our study aimed to explore the temporal relationship between AS measured by brachial ankle pulse wave velocity (baPWV) and CKD measured by estimated glomerular filtration rate (eGFR) with the approach of cross-lagged path analysis. Once the temporal relationship was established (we hypothesized that AS was the precursor), we further aimed to investigate the longitudinal risk of incident CKD, with AS status and VA phenotype measured by baPWV, and these cardiovascular risk factors as the exposure.[23]

METHODS

STUDY POPULATION. The Kailuan study is an ongoing prospective cohort study conducted biennially since 2006 in Tangshan, northern China. Starting in 2010 (the third survey), AS was assessed among participants who consented to join nested studies on vascular health using baPWV, as described previously.[24-26] In the current study, we included participants who participated in the baPWV measurement prior to 2014 (the fifth survey) and had data on eGFR at the same time period. Among 13,073 participants who met the criteria, we further excluded participants without follow-up health examination, with a history of cardiovascular disease or death, or a history of CKD (eGFR <60 mL/min/1.73 m^2) at baseline, leaving 7,753 participants with repeated measurement in baPWV in the cross-lagged analysis and 10,535 participants in the longitudinal analysis for the risk of incident CKD (Supplemental Figure 1). A comparison in the baseline characteristics between included and excluded participants was presented in Supplemental Table 1. The study was performed according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Kailuan General Hospital (approval 2006-05) and Beijing Tiantan Hospital (approval 2010-014-01). All participants provided written informed consent.

ABBREVIATIONS AND ACRONYMS

AS = arterial stiffness

baPWV = brachial ankle pulse wave velocity

cfPWV = carotid-femoral aortic pulse wave velocity

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

EVA = early vascular aging

SCr = serum creatinine

SUPERNOVA = supernormal vascular aging

VA = vascular aging

MEASUREMENT OF baPWV AND CALCULATION OF VA. BaPWV was measured by a BP-203 RPE III networked arterial stiffness detection device (Omron Health Medical [China] Co, LTD) following the recommended standard procedures, as reported previously.[24-26] All subjects were called and asked to refrain from alcohol or caffeine consumption or from smoking at least 12 hours prior to their appointment. Before the assessment, subjects rested for least 5 minutes in a supine position in a room with 22-25°C temperature. Electrodes of the electrocardiograph were placed on both wrists, a microphone was placed on the left edge of the sternum to detect heart sounds, and pneumatic cuffs were placed on both the brachia and ankles. The lower edge of the arm cuff was positioned 2 to 3 cm above the transverse striation of the cubital fossa, and the lower edge of the ankle cuff was positioned 1 to 2 cm above the superior aspect of the medial malleolus. The maximum value of left- and right-sided baPWV measurements was used for the analysis, and the same methodology for baPWV measurement was available for all participants.

Normal AS was defined as baPWV $<1,400$ cm/s; borderline AS was defined as $1,400 \leq$ baPWV $<1,800$ cm/s; and elevated AS was defined as baPWV $\geq 1,800$ cm/s.[24] Because arterial stiffness is highly correlated with age and blood pressure, we further used age- and blood pressure-specific cutoff points.[27]

Vascular age was defined as the predicted age in a multivariable regression model including classical cardiovascular risk factors (age, blood pressure, glucose, body mass index, total cholesterol), treatment, and baPWV using generalized additive models, as previous reported.[23] The model fit and diagnostics was provided in Supplemental Figure 2. VA was calculated as chronological age minus vascular age,

and the 10th and 90th percentiles of VA were used as cutoffs to defined early VA (EVA) (<10th percentiles), normal VA (10th-90th percentiles), and supernormal VA (SUPERNOVA) (>90th percentiles).[23] Additionally, we also calculated VA as the residual resulting from a linear model when regression vascular age on chronological age.[28] Then VA presented vascular age after accounting for chronological age, with a positive (negative) value indicating a person appears older (younger) than expected, physiologically, based on chronological age.[28]

DEFINITION OF INCIDENT CKD. Fasting blood samples were collected from cubital veins and transfused into vacuum tubes containing EDTA after 8 hours of fasting. Serum creatinine (SCr) was measured by using chemistry autoanalyzer (Hitachi 747, Hitachi). eGFR was calculated from creatinine following the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula:[29] $\text{eGFR} = 141 \times \min(\text{SCr}/k,1)^{\alpha} \times \max(\text{SCr}/k,1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if women), where k is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min is the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1. The CKD-EPI China equation was calculated with a coefficient of 1.1.[30] Incident CKD was characterized with eGFR <60 mL/min/1.73 m^2.[31-33]

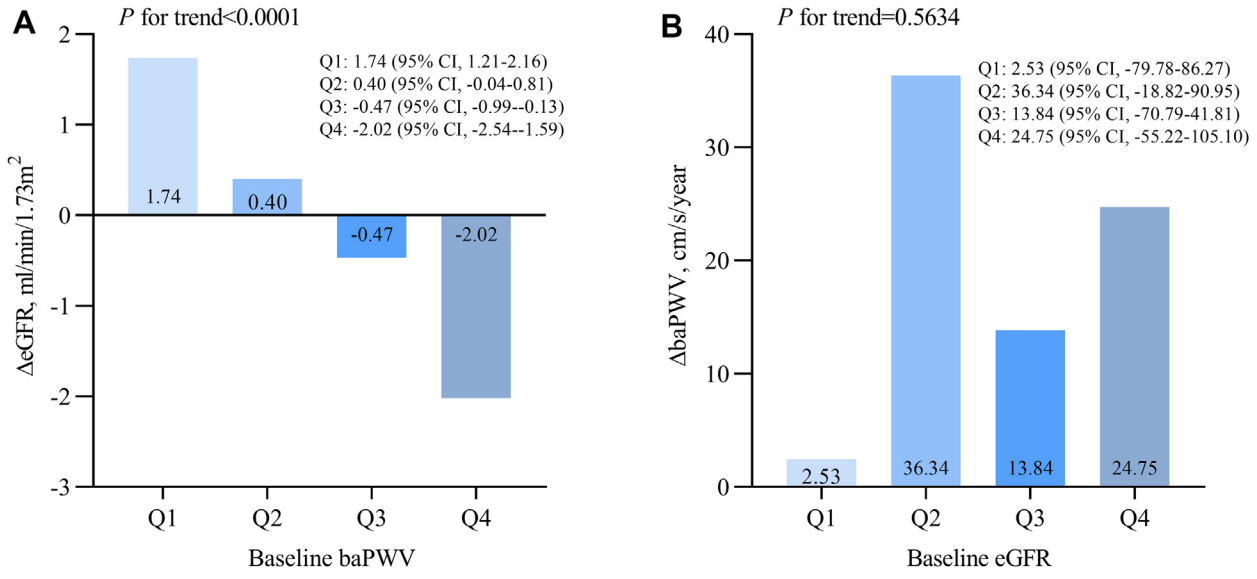
COVARIATES COLLECTION. Demographic information, lifestyle, medical history, and medication usages were collected via standardized questionnaires at baseline and during the follow-up. Educational levels were categorized as illiteracy or primary school, middle school, and high school or above. Income levels were categorized as <800 and ≥800 yuan. Smoking status and drinking status were classified as never, former, or current. Physical activity was classified as inactive activity (<80 minutes activity per week) and active activity (≥80 minutes activity per week). Smoking and drinking statuses were classified as never, former, or current. Heart rate, height, and weight were measured by trained nurses, then body mass index was calculated by dividing body weight (kg) by the square of height (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured 3 times with the participants in the seated position using a mercury sphygmomanometer, and the average of 3 readings was used in the analyses. Mean arterial pressure was calculated as: 1/3 SBP + 2/3 DBP. All blood samples were tested using a Hitachi 747 auto-analyzer at the central laboratory of the Kailuan Hospital. The biochemical indicators tests included fasting blood glucose, lipid profiles, and high-sensitivity C-reactive protein.

STATISTICAL ANALYSIS. Continuous variables were described as mean ± SD or median (Q1-Q3) according to the distributions, and categorical variables were described as frequencies and percentages. One-way analysis of variance, Kruskal-Wallis test, and chi-square test were used to compare the differences in characteristics across baseline groups, as appropriate.

CROSS-LAGGED ANALYSIS. Participants with repeated measurement of baPWV and eGFR constituted a typical cross-lagged panel design, which measured the effect size of baseline baPWV on subsequent eGFR (β_1) and the effect of baseline eGFR on subsequent baPWV (β_2) simultaneously. Before the cross-lagged path analysis, the baseline and subsequent baPWV and eGFR were adjusted for variables in using a regression residual analysis and then were standardized by z transformation. Three models were constructed progressively. Model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was further adjusted for smoking status, alcohol drinking, antihypertensive agents, antidiabetic agents, lipid-lowering agents, mean arterial pressure, heart rate, body mass index, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein. The difference between β_1 and β_2 derived from the standardized variable was tested with Fisher z test. Several sensitivity analyses were performed to validate the temporal relationship shown in the cross-lagged path analysis. First, eGFR levels were recalculated by using the CKD-EPI China equation. Second, to address unequal time interval between follow-up across participants, we also calculated the annual changes in baPWV and eGFR and re-estimated the cross-lagged model. Annual change in eGFR = (follow-up eGFR − baseline eGFR) / follow-up time, and annual change of baPWV = (follow-up baPWV − baseline baPWV) / follow-up time. Third, we examined annual change in in baPWV and eGFR according to quartiles of their baseline values using general linear models.

LONGITUDINAL ANALYSIS FOR INCIDENT CKD. Person-years were calculated from baseline to the first occurrence of CKD, death, or the end of the study (December 31, 2019), whichever came first. The incidence rate of CKD was calculated by dividing the number of incident cases by the total follow-up duration (person-years). Cox proportional hazards models were used to analyze the association of AS status and VA phenotype with the risk of incident CKD, HRs, and

FIGURE 1 **Annual Changes in baPWV and eGFR by Baseline Values**



(A) Baseline brachial-ankle pulse wave velocity (baPWV) and change in estimated glomerular filtration rate (eGFR). (B) Baseline eGFR and change in baPWV. Adjusted for age, sex, smoking status, alcohol drinking, antihypertensive agents, antidiabetic agents, lipid-lowering agents, mean arterial pressure, heart rate, body mass index, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein.

95% CIs were reported. The models were adjusted for the same variables in the cross-sectional analysis. Schoenfeld residuals were investigated to verify the proportionality of hazards. There were no indications that the proportional hazards assumption was violated. Both baPWV and VA were also treated as continuous variables, and the restricted cubic splines analysis with 5 knots at the 5th, 25th, 50th, 75th, and 95th percentiles of baPWV (reference point: 1,400 cm/s) and VA (reference point: 0 years) were performed to capture the dose-response associations, with adjustment for variables in model 3.

To test the robustness of the findings, sensitivity analyses were performed as follows. First, eGFR levels and CKD status were redefined using the CKD-EPI China equation. Second, we excluded participants who developed incident CKD within the first year of follow-up to explore the potential impact of reverse causality. Third, the competing risk model was applied by considering non-CKD death as a competing risk event. Fourth, AS was redefined by using age- and blood pressure-specific cutoffs. Finally, missing data were imputed using multiple imputations by chained equations in both cross-sectional and longitudinal analysis. In addition, subgroup analysis stratified by age and sex was also performed to test the interaction between stratified variables and AS.

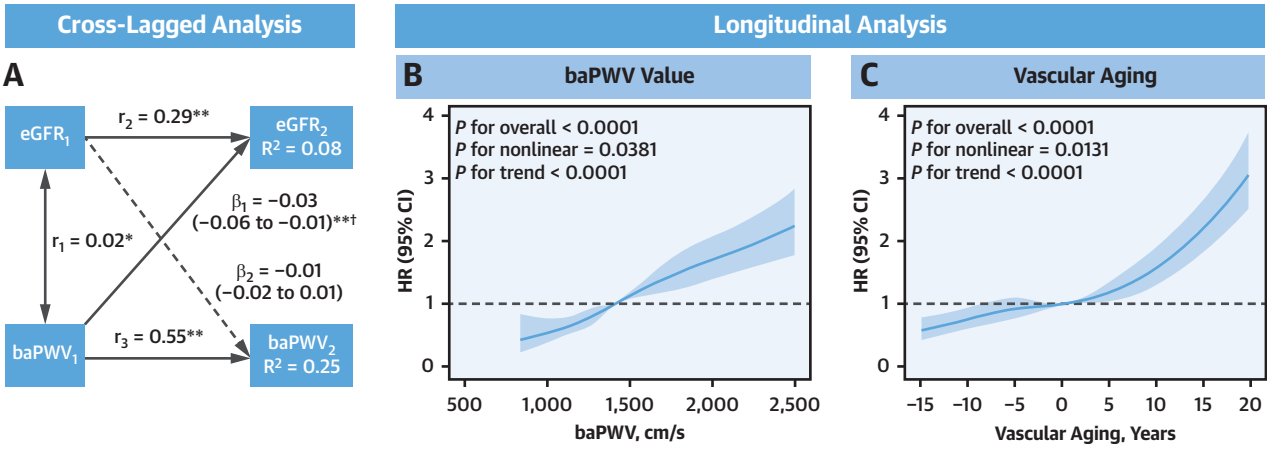
All analyses were conducted using SAS (version 9.4, SAS Institute Inc). Cross-lagged analysis was performed with SAS Proc Calis procedure. A 2-sided $P < 0.05$ was considered statistically significant.

DATA SHARING STATEMENT. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

CROSS-LAGGED PATH ANALYSIS. The mean age of the 7,753 participants with repeated baPWV and eGFR in the cross-lagged path analysis was 55.14 ± 11.05 years, and 3,864 participants (49.84%) were men (Supplemental Table 1). The median interval between eGFR measurement and baPWV measurement was 2.09 years (Q1-Q3: 1.94-2.49) and 3.23 years (Q1-Q3: 2.34-5.13). The distribution of baPWV measurement times is shown in Supplemental Figure 3. **Figure 1** presented cross-lagged path analysis of baPWV and eGFR. After adjustment for potential covariables, the significant path coefficient from baseline baPWV to follow-up eGFR ($\beta_1 = -0.03$; 95% CI: −0.06 to −0.01; $P < 0.0001$) was significantly greater than the nonsignificant path coefficient from baseline eGFR to the follow-up baPWV ($\beta_2 = -0.01$; 95% CI: −0.02 to 0.01; $P = 0.6202$), with $P = 0.0112$ for difference between β_1

CENTRAL ILLUSTRATION **Cross-Sectional and Longitudinal Association of Brachial-Ankle Pulse Wave Velocity and Estimated Glomerular Filtration Rate**



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(A) Cross-lagged path analysis of brachial-ankle pulse wave velocity (baPWV) and estimated glomerular filtration rate (eGFR). (B) Restricted cubic splines for the association of baPWV with chronic kidney disease. (C) Restricted cubic splines for the association of vascular aging with chronic kidney disease. Adjusted for age, sex, smoking status, alcohol drinking, antihypertensive agents, antidiabetic agents, lipid-lowering agents, mean arterial pressure, heart rate, body mass index, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein. β_1 indicates the path coefficient from baseline baPWV to follow-up eGFR; β_2 indicates path coefficient from baseline eGFR to follow-up baseline; r_1 represents synchronous correlations; r_2 and r_3 represent tracking correlations; R^2 variance explained. $^{**}P < 0.01$, $^{*}P < 0.05$ for coefficients being different from 0; †difference between $\beta 1$ and $\beta 2$ for being different from 0.

and β_2 (**Central Illustration 1A**, Supplemental Table 2). Similar results were observed for the temporal relationship between baPWV and eGFR measured by the CKD-EPI China equation (Supplemental Table 3), as well as annual changes in baPWV and eGFR (Supplemental Table 4). The yearly rates of change in eGFR during the follow-up period significantly varied across increasing quartiles of baseline baPWV ($P < 0.0001$); however, the yearly rate of change in baPWV did not show a significantly varying trend across quartiles of baseline baPWV ($P = 0.5634$) (**Figure 1**).

LONGITUDINAL ANALYSIS. Baseline characteristics. Among 10,535 enrolled participants (mean age: 55.93 ± 11.30 years, 5,445 [51.68%] were men), 5,138 participants had normal AS, 3,824 participants had borderline AS, and 1,573 participants had elevated AS. Baseline characteristics among the 3 groups are presented in **Table 1**. Compared with participants with normal AS, participants with borderline or elevated AS tended to be older; men; more likely to be current smokers and heavy drinkers; more likely to take antihypertensive agents, antidiabetic agents, and lipid-lowering agents; have a higher level of blood pressure, heart rate, fasting blood glucose, lipid profiles, and high-sensitivity C-reactive protein; and have a lower level of eGFR. When participants were stratified by VA phenotype, more cardiovascular risk profiles were observed in participants with EVA, compared with participants with normal VA or SUPERNOVA (Supplemental Table 5).

ANALYSIS FOR THE RISK OF INCIDENT CKD. During a median follow-up of 8.48 years (Q1-Q3: 4.75-9.17), a total of 953 participants (9.05%) developed incident CKD. The incidence rate of CKD increased with the magnitude of baPWV, from 9.35 (95% CI: 8.38-10.40) per 1,000 person-years in the normal AS group to 21.60 (95% CI: 19.00-24.50) per 1,000 person-years in the elevated AS group. The associations remain after adjustment for potential variables: participants in the borderline AS group had a 54% higher risk of developing CKD (HR: 1.54; 95% CI: 1.31-1.81) and participants in the elevated AS group had a 120% higher risk of developing CKD (HR: 2.20; 95% CI: 1.81-2.69) (**Table 2**), compared with those in the normal AS group. The restricted cubic splines showed a nonlinear association between baPWV and the risk of incident CKD increased (**Central Illustration B**).

In terms of VA phenotype, SUPERNOVA had a decreased rate (49 cases [4.64%]; HR: 0.53; 95% CI: 0.41-0.72) and EVA had an increased rate (198 cases

TABLE 1 Baseline Characteristics According to AS Status

	Overall (N = 10,535)	Normal AS (n = 5,138)	Borderline AS (n = 3,824)	Elevated AS (n = 1,573)	*P* Value
baPWV, cm/s	1,472.17 ± 337.41	1,216.83 ± 120.07	1,564.26 ± 110.95	2,082.36 ± 282.02	<0.0001
Age, y	55.93 ± 11.30	50.73 ± 8.76	58.71 ± 10.27	66.14 ± 11.70	<0.0001
Men	5,445 (51.68)	1,897 (36.92)	2,470 (64.59)	1,078 (68.53)	<0.0001
Smoking status					
Never	7,179 (72.01)	4,008 (81.73)	2,271 (62.87)	900 (61.90)	<0.0001
Former smoker	302 (3.03)	87 (1.77)	140 (3.88)	75 (5.16)	
Current smoker	2,489 (24.96)	809 (16.50)	1,201 (33.25)	479 (32.94)	
Alcohol drinking					
Never	7,810 (74.13)	4,185 (81.45)	2,586 (67.63)	1,039 (66.05)	<0.0001
Former	58 (0.55)	17 (0.33)	29 (0.76)	12 (0.76)	
Light	1,903 (18.06)	714 (13.90)	837 (21.89)	352 (22.38)	
Moderate	643 (6.10)	197 (3.83)	308 (8.05)	138 (8.77)	
Heavy	96 (0.91)	16 (0.31)	54 (1.41)	26 (1.65)	
Antihypertensive agents	329 (8.00)	51 (2.00)	164 (14.46)	114 (26.39)	<0.0001
Antidiabetic agents	312 (2.96)	38 (0.74)	153 (4.00)	121 (7.69)	<0.0001
Lipid-lowering agents	82 (0.78)	19 (0.37)	40 (1.05)	23 (1.46)	<0.0001
Systolic BP, mm Hg	126.87 ± 19.72	116.53 ± 14.77	133.25 ± 17.19	145.17 ± 19.74	<0.0001
Diastolic BP, mm Hg	82.42 ± 11.52	77.57 ± 9.74	86.19 ± 10.81	89.09 ± 11.79	<0.0001
MAP, mm Hg	97.24 ± 13.47	90.56 ± 10.84	101.88 ± 12.04	107.78 ± 13.03	<0.0001
Heart rate, beats/min	73.21 ± 9.53	71.80 ± 8.64	73.93 ± 9.75	76.04 ± 10.86	<0.0001
BMI, kg/m^2	25.57 ± 2.61	25.45 ± 2.39	25.72 ± 2.79	25.59 ± 2.80	<0.0001
FBG, mmol/L	5.52 ± 1.32	5.21 ± 0.87	5.71 ± 1.48	6.07 ± 1.78	<0.0001
TC, mmol/L	5.02 ± 1.28	4.85 ± 1.21	5.11 ± 1.00	5.32 ± 1.86	<0.0001
TG, mmol/L	1.87 ± 1.99	1.57 ± 1.53	2.14 ± 2.44	2.23 ± 1.95	<0.0001
LDL-C, mmol/L	2.56 ± 0.85	2.44 ± 0.87	2.66 ± 0.80	2.72 ± 0.84	<0.0001
HDL-C, mmol/L	1.54 ± 0.44	1.56 ± 0.45	1.51±0.43	1.53±0.44	<0.0001
eGFR, mL/min/1.73 m^2	92.54 ± 17.69	95.41 ± 17.82	90.72 ± 17.15	87.59 ± 16.85	<0.0001
hs-CRP, mg/L	2.07 ± 4.10	1.72 ± 2.62	2.28 ± 5.33	2.71 ± 4.52	<0.0001

Values are mean ± SD or n (%).

AS = arterial stiffness; baPWV = brachial-ankle pulse wave velocity; BP = blood pressure; BMI = body mass index; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; HDL-C = high density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MAP = mean arterial pressure; TC = total cholesterol; TG = triglyceride.

[18.58%]; HR: 2.41; 95% CI: 2.05-2.84) of incident CKD as compared to normal VA (708 cases [8.40%]) (**Table 2**). The restricted cubic splines showed that the risk of CKD nonlinearly increased with increasing VA (**Central Illustration C**). Similar results were observed for VA calculated as the residual; results showed that participants with younger VA was associated with a 40% (HR: 0.60; 95% CI: 0.52-0.68) lower risk of CKD, compared to those with older VA (**Table 2**).

Sensitivity analysis by using the CKD-EPI China equation (Supplemental Table 6), excluding incident CKD within 1 year of follow-up (Supplemental Table 7), using competing risk model (Supplemental Table 8), using age- and blood pressure-specific definition of AS, and using imputation on missing data (Supplemental Tables 9 to 11) yielded similar results with the primary analysis. Subgroup analysis showed that the association of AS status with incident CKD was consistent across different age and sex groups ($P_{\text{interaction}} > 0.05$) (Supplemental Table 12).

DISCUSSION

In this study, using longitudinal population-based data in China, temporal analysis showed a unidirectional relationship from increased AS to CKD. Consistently, the longitudinal analysis showed that elevated AS status and EVA were associated with a substantially increased risk of incident CKD. The results indicated that increase in AS might precede the decline in eGFR.

Although the single directional association between AS and CKD has been vastly demonstrated, the temporal relationship between baPWV and eGFR is completely elucidated. A review paper[34] provided a comprehensive ideal of the 2-way path between AS and renal dysfunction. In this study, we examined this chicken-and-egg question using cross-lagged path analysis, which is a powerful statistical approach in dissecting a causal relationship between intercorrelated variables. One unidirectional

TABLE 2 Association of Incident CKD in Relation to AS Status and VA

	N	Cases, n (%)	Incidence Rate, per 1,000 Person-Years	Model 1	Model 2	Model 3
AS status						
Normal AS	5,138	319 (6.21)	9.35 (8.38-10.40)	Reference	Reference	Reference
Borderline AS	3,824	394 (10.30)	14.20 (12.80-15.60)	1.54 (1.33-1.79)	1.66 (1.43-1.93)	1.54 (1.31-1.81)
Elevated AS	1,573	240 (15.26)	21.60 (19.00-24.50)	2.29 (1.94-2.71)	2.48 (2.09-2.95)	2.20 (1.81-2.69)
Per 1-SD increase				1.36 (1.29-1.43)	1.33 (1.27-1.40)	1.33 (1.25-1.42)
P for trend				<0.0001	<0.0001	<0.0001
VA with difference						
SUPERNOVA	1,055	49 (4.64)	6.68 (5.05-8.83)	0.53 (0.39-0.71)	0.54 (0.40-0.73)	0.53 (0.41-0.72)
NVA	8,425	708 (8.40)	12.00 (11.20-12.90)	Reference	Reference	Reference
EVA	1,055	196 (18.58)	28.90 (25.10-33.20)	2.38 (2.03-2.78)	2.44 (2.08-2.86)	2.41 (2.05-2.84)
Per 5-y increase				1.26 (1.21-1.30)	1.26 (1.22-1.31)	1.24 (1.20-1.28)
P for trend				<0.0001	<0.0001	<0.0001
VA with residuals						
Older	5,123	585 (11.42)	16.60 (15.30-18.00)	Reference	Reference	Reference
Younger	5,412	368 (6.80)	9.75 (8.80-10.80)	0.59 (0.52-0.67)	0.59 (0.52-0.67)	0.60 (0.52-0.68)
Per 1-U decrease				0.96 (0.95-0.96)	0.95 (0.95-0.96)	0.95 (0.95-0.96)
P for trend				<0.0001	<0.0001	<0.0001

Values are HR (95% CI) unless otherwise indicated. VA was calculated as the difference between chronological age and vascular age, lowest and highest deciles identifying SUPERNOVA and EVA, respectively. Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 is further adjusted for smoking status, alcohol drinking, antihypertensive agents, antidiabetic agents, lipid-lowering agents, mean arterial pressure, heart rate, body mass index, fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and high-sensitivity C-reactive protein.

AS = arterial stiffness; CKD = chronic kidney disease; EVA = early vascular aging; NVA = normal vascular aging; SUPERNOVA = supernormal vascular aging; VA = vascular aging.

relationship from baseline AS to follow-up eGFR decline was confirmed in our analyses, providing evidence that increased AS was probable a causal factor for CKD.

The unidirectional relationship from AS to CKD in our study was supported by the majority of, but not all, conclusions from community-based cohorts. Actually, current evidence regarding whether increased AS is associated either cross-sectionally with kidney function or longitudinally with decline in kidney function has been controversial. Some studies suggested that increased AS was independently associated with the levels of eGFR cross-sectionally, and greater baseline AS could longitudinally predict eGFR decline or the risk of incident CKD.[11-17] Oppositely, some studies failed to demonstrated a significant association between AS and CKD after adjustment for potential covariates or including individuals with diabetes or with different eGFR levels.[35-38] Except for population characteristics and study design, other reasons underlying the inconsistencies may be the relatively small sample size in these studies and the different parameters of AS, such as carotid-femoral aortic pulse wave velocity (cfPWV) or baPWV. Anatomically, cfPWV was considered as the measure of central arterial stiffness, whereas baPWV was considered to reflect both central and peripheral stiffness.[39] In our longitudinal analysis, elevated AS measured by baPWV was significantly associated with a higher risk of incident CKD among 10,535 participants. Furthermore, when combining baPWV and other risk factors, results of the association of VA phenotype with incident CKD showed that EVA, a status reflecting premature alterations in artery structure and function, could increase the risk of incident CKD; SUPERNOVA, the result of the body's intrinsic and extrinsic protective factors against the risk factors of AS, could decrease the risk of CKD. The results of VA phenotype further confirmed the pathway from AS to the CKD. Our findings added evidence to expand our knowledge on the hazardous effect of AS on the occurrence of CKD.

It has been reported that AS caused by vascular calcification was found to occur frequently in patients with CKD and the incidence increased as renal function progressively declined.[40] The ARIC (Atherosclerosis Risk In Communities) study and several other studies showed that lower eGFR was also associated with AS.[18-21] However, these studies were designed to be cross-sectional, which does not allow investigators to establish whether kidney function decline contributes to or is the consequence of AS. This knowledge gap has been filled up by the findings of cross-lagged path analysis, showing no significant

association from decline eGFR to subsequent AS, indicating that kidney function decline was the consequence of increased AS. This finding was supported by the results in the Systolic Blood Pressure Intervention Trial, demonstrating that baseline cfPWV was not associated with eGFR decline in the longitudinal analysis.[41]

There were several mechanisms underlying the unidirectional relationship from AS to CKD. First, increased AS can reduce the central arteries' buffering capacity and generate high pulsatility stress at the microvasculature level, which then is introduced into the organs with high viscous components.[5-7] The kidney has the highest flow rate and lowest vascular resistance of any large organ.[42] This low-resistance/high-blood flow state renders the kidneys highly susceptible to trauma from pulsatile pressure and blood flow. The main consequences of these events would be the functional deterioration with the development of acceleration of renal function impairment. Second, AS can increase both circumferential and shear stresses via increasing pressure and speed of blood flow in the arterial lumen, which results in endothelial dysfunction and microvascular ischemic leading to kidney injury.[35,43] Additionally, endothelial function damage may cause capillary diastolic dysfunction, shrinkage, or sparse distribution, and in turn can aggravate stiffening of artery wall and cause a vicious cycle. Other possible mechanisms underlying the association include chronic inflammation, oxidative stress, and activation of the renin-angiotensin system that could reduce eGFR.[43,44] AS was associated with a series of metabolic diseases, such as hypertension, insulin resistance, and diabetes, that could also contribute to the development of CKD.[24,37,45] More precise mechanisms are needed further investigations.

The clinical implications on therapeutic approaches should be noted. Studies suggested that antihypertensive medications of renin-angiotensin-aldosterone system blockers can lower AS through changing the intrinsic material properties of the arterial wall, and other standard medications can reduce vascular resistance or cardiac output to lower AS.[42] Additionally, interruption of the renin-angiotensin-aldosterone system blockers with angiotensin converting enzyme inhibitors and angiotensin-receptor blockers, alone or in combination, has become a leading therapeutic strategy to slow down the progression of CKD.[46] These findings indicated that use of these types of drugs in hypertensive patients may bring additional beneficial effect for reducing the development of CKD at the same time of preventing AS and lowering blood pressure.

STUDY LIMITATIONS. First, data on the urinary albumin and urinary creatinine were unavailable, thus CKD was defined by using eGFR only with the CKD-EPI equation, which might misclassify CKD status. However, eGFR was recalculated by using the CKD-EPI China equation, which yielded consistent conclusions. We additionally excluded participants with <1 year's interval between visits to avoid misclassification at baseline and increase specificity of CKD diagnosis. Second, we did not measure cfPWV, although it was considered the gold standard to assess the status of AS. The accuracy of baPWV vs cfPWV has been validated in previous studies, and the American Heart Association also recommended baPWV as a common indicator for AS, especially for central and peripheral stiffness.[47] Third, participants in our study were from a community-based cohort, so the generalization of the findings may be limited. However, the constitution of the population was complex, including individuals from all levels of society and across various occupations, study of such a geographically confined and controlled population greatly reduces residual confounding factors because of diverse socioeconomic factors and lifestyle patterns. Fourth, although the temporal relationship between eGFR and baPWV was established based on 2 waves of measurements, the findings still needed to be validated with multiple waves of data and more accurate methods, such as the random-intercept cross-lagged panel model. The final limitations are the reliance on self-reported data and the lack of information on the treatment of CKD, thus the findings need to be interpreted with caution.

CONCLUSIONS

Our results of causal inference analysis of AS and CKD showed that AS preceded the development of CKD. Additionally, increased AS was longitudinally associated with the risk of incident CKD. These findings could improve our understanding of the pathobiology and mechanisms of CKD and facilitate selection of potential therapeutic and intervention strategies at AS for delaying the decline in kidney function in primary prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is a unidirectional relationship between baPWV and eGFR, and arterial stiffness measured by baPWV appeared to precede the decrease in eGFR levels. Consistently, longitudinal analysis showed that elevated AS status and early VA were associated with a substantially increased risk of incident CKD.

TRANSLATIONAL OUTLOOK: These findings could improve our understanding of the pathobiology and mechanisms of CKD and facilitate selection of potential therapeutic and intervention strategies at AS for delaying the decline in kidney function in primary prevention.

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KEY WORDS arterial stiffness, chronic kidney disease, cohort study, cross-lagged panel analysis, vascular aging

APPENDIX For supplemental figures and tables, please see the online version of this paper.