

Bidirectional and Temporal Association Between Hypertension and Microalbuminuria: A Longitudinal Study in Chinese Adults

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Background—Although hypertension and microalbuminuria are closely interrelated, the magnitude and temporal sequence of the bidirectional association between hypertension and microalbuminuria are largely unknown. We aimed to delineate the bidirectional and temporal relationship between hypertension and microalbuminuria.

Methods and Results—Leveraging a longitudinal cohort of Chinese adults who had blood pressure and urinary albumin measured twice 4 years apart, we examined the temporal association between hypertension and microalbuminuria by bidirectional and cross-lagged panel analysis. All participants were free of cardiovascular disease and chronic kidney disease at baseline. Bidirectional association analysis found that baseline microalbuminuria predicted the risk of incident hypertension (odds ratio=1.75, $P=0.028$), and baseline blood pressure also significantly predicted the risk of microalbuminuria (odds ratios=1.27 and 1.21 for a per-SD increase in systolic and diastolic blood pressure, respectively; all $P<0.05$). Cross-lagged panel analysis demonstrated a bottom-line significant relationship of baseline systolic blood pressure to follow-up urinary albumin ($P=0.079$), which is significantly weaker than the other direction of the relationship of baseline urinary albumin to follow-up blood pressures (all $P<0.001$).

Conclusions—These findings indicate a significant bidirectional association between microalbuminuria and hypertension in Chinese adults. Elevated urinary albumin excretion is more likely to precede hypertension. The causality between microalbuminuria and hypertension needs further investigation. (*J Am Heart Assoc.* 2018;7:e010723. DOI: 10.1161/JAHA.118.010723)

Key Words: bidirectional association • cross-lagged panel analysis • hypertension • high blood pressure • kidney • longitudinal cohort study

Chronic kidney disease is frequently encountered among patients presenting with cardiovascular disease (CVD; eg, coronary heart disease,^{1,2} stroke,^{3–5} and heart failure^{6–8}). Microalbuminuria, an indicator and predictor of early kidney disease, has also been recognized as a marker of vascular

dysfunction^{9,10} and a predictor for morbidity and mortality of CVD.^{11–13} It is highly prevalent in individuals with cardiovascular risk factors, such as diabetes mellitus and hypertension,^{14–17} and the prevalence increases with disease duration.¹⁸ The associations between microalbuminuria and cardiovascular risk factors, including hypertension, have been extensively studied.¹⁹ For example, basic studies found that arterial blood pressure was dramatically elevated in mice with renal dysfunction presenting with microalbuminuria.²⁰ The prospective association between microalbuminuria and hypertension has also been reported in populations, although with inconsistent results. Some studies found that microalbuminuria related to the risk of hypertension,^{21–24} whereas others indicated that higher blood pressure predicted future risks of microalbuminuria.^{25–27} These findings may indicate that microalbuminuria and hypertension might interact with each other, but no study has examined such bidirectional effects. Moreover, because hypertension has been the most common and modifiable risk factor of cardiovascular and kidney disorders,^{16,17} a better understanding of the magnitude and temporal sequence of the association between hypertension and microalbuminuria would undoubtedly improve the management and prevention of cardiovascular and kidney diseases. However, existing data are mainly from cross-sectional

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Clinical Perspective

What Is New?

- This study systemically demonstrated the bidirectional association between hypertension and microalbuminuria.
- Elevated urinary albumin excretion is more likely to temporally precede hypertension.

What Are the Clinical Implications?

- Screening of microalbuminuria in a community population, nonhypertensive individuals, in particular, may promote prevention of cardiovascular disease.
- Whether personal treatment could prevent hypertension in participants with microalbuminuria only still needs to be confirmed by clinical trials.

or prospective study designs, which may not elucidate the magnitude of the biphasic effects between microalbuminuria and hypertension. Moreover, most prior studies are conducted in European populations. Therefore, we aimed to examine the temporal and bidirectional relationship between microalbuminuria and hypertension in a longitudinal cohort of Chinese adults.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure by contacting the corresponding author at penghao@suda.edu.cn.

Study Participants

Our study is a community-based longitudinal study of CVD and its risk factors in Chinese adults in 8 communities residing in a traditional but economically developed district of Suzhou, China. The study design, survey methods, and laboratory techniques have been described previously.²⁸ In brief, the first clinical examination was conducted in 2010 (phase 1) by enrolling 2706 community members aged >30 years. All surviving participants were reexamined in 2014 (phase 2) and are currently being followed up through 2020. The protocols of the current study were approved by the Soochow University Ethics Committee. Written informed consent was obtained from all study participants.

Figure 1 describes the selection of study participants included in the current analysis. Of 2706 participants participating in the phase 1 examination, 139 were excluded because of missing data on microalbuminuria at baseline. After further excluding 576 participants who denied

participation in the phase 2 examination, 1991 participants were included in the final data analysis. All participants in our study had not been diagnosed with CVD or chronic kidney disease at the phase 1 examination.

Measurement of Urinary Albumin/Creatinine Ratio and Definition of Incident Microalbuminuria

The methods of measurement and definition of microalbuminuria used in our study have been described elsewhere.²⁹ Briefly, a single first-morning void urine sample was obtained from every participant. Urine albumin was assessed using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and urine creatinine was assessed using the Jaffe method. The urinary albumin/creatinine ratio (UACR) was calculated as the following algorithm: UACR (mg/g)=urine albumin (mg/dL)/urine creatinine (g/dL). According to the recommendation of the National Kidney Foundation, women with a UACR >25 mg/g and men with a UACR >17 mg/g were treated as having microalbuminuria.³⁰ Incident microalbuminuria was defined as participants who were free of microalbuminuria in the phase 1 examination but had an abnormal level of UACR in the phase 2 examination.

Measurement of Blood Pressure and Definition of Incident Hypertension

Blood pressure was measured 3 times by trained staff using a standard mercury sphygmomanometer and a cuff of appropriate size, according to a standard protocol,³¹ after the participants had been resting for at least 5 minutes in a relaxed, sitting position. The first and fifth Korotkoff sounds were recorded as systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. The mean of the 3 measurements was used in statistical analyses. Hypertension was defined as SBP \geq 140 mm Hg and/or DBP \geq 90 mm Hg or use of antihypertensive medication in the past 2 weeks.³¹ Incident hypertension was defined as participants who were free of hypertension at baseline but initiated antihypertensive medications during follow-up or had an SBP of at least 140 mm Hg or a DBP of at least 90 mm Hg in the phase 2 examination.

Assessment of Cardiovascular Risk Factors

Cigarette smoking was classified as current smoking or not. Current smoking was defined as having smoked at least 100 cigarettes in the entire life, having smoked cigarettes regularly, and smoking currently. Alcohol consumption was classified as current drinkers or not. Current drinkers were those who had consumed any alcohol during the past year. Body weight (kg) and height (cm) were measured when participants wore light clothes and no shoes by trained staff.

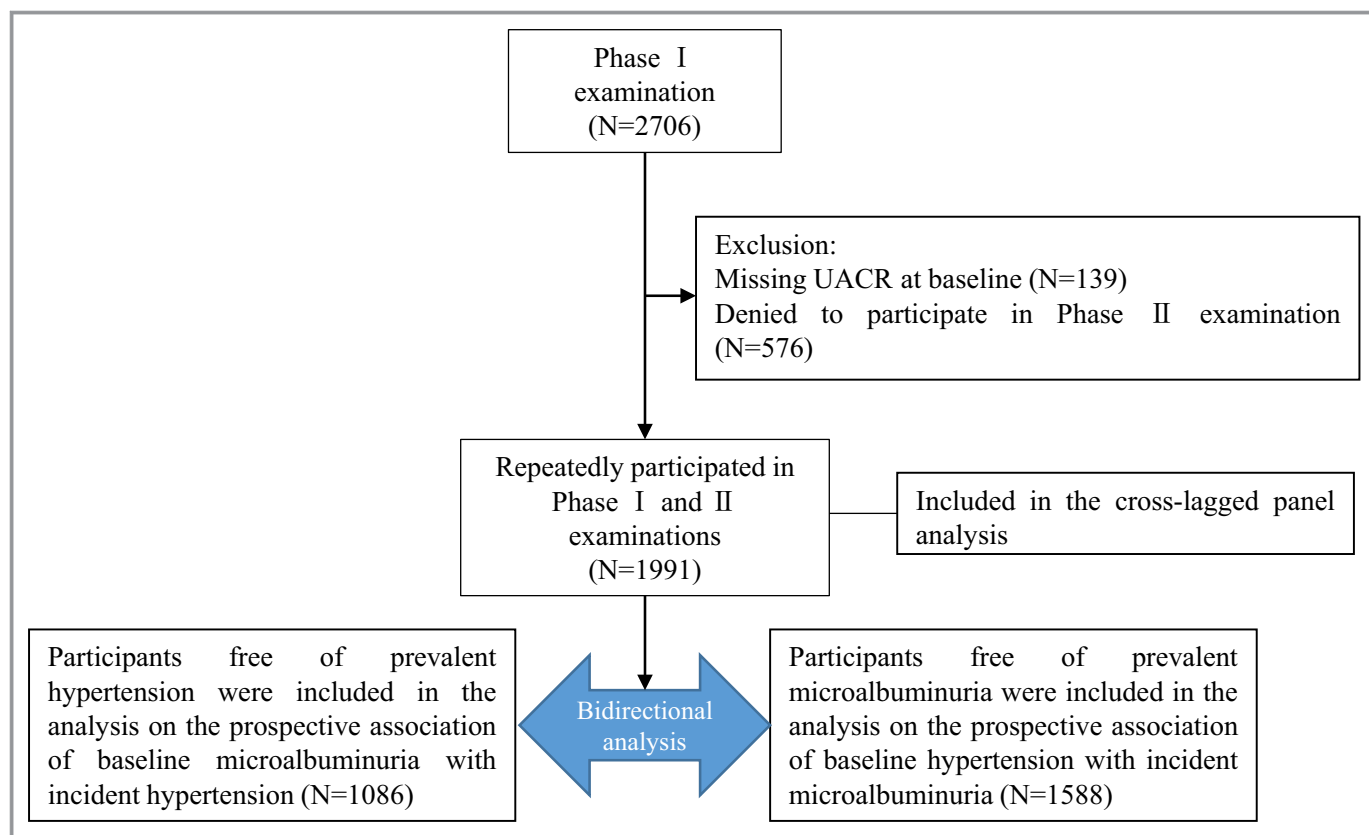


Figure 1. A flowchart illustrating the selection of study participants and the statistical plan. UACR indicates urinary albumin/creatinine ratio.

Body mass index (BMI) was calculated by dividing weight in kilograms by the height in meters squared (kg/m^2). Fasting glucose and blood lipids, including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured by standard laboratory methods.²⁸ Diabetes mellitus was defined as fasting glucose >7.0 mmol/L and/or receiving hypoglycemic medications in the past 2 weeks.³²

Statistical Analysis

To examine whether hypertension and microalbuminuria interact on each other to exacerbate cardiovascular risk, we conducted bidirectional and cross-lagged panel analysis to examine the mutual effects between hypertension and microalbuminuria, followed by conducting interaction analysis to examine their combined effects on cardiovascular risk. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). A 2-tailed $P < 0.05$ was considered statistically significant.

Bidirectional association analysis

To examine the 1-directional association of whether microalbuminuria at baseline predicted future risk of

hypertension, we constructed a logistic regression model in which incident hypertension was the dependent variable and baseline UACR (continuous log-transformed UACR or categorical variable: normal versus microalbuminuria) was the independent variable. We adjusted for potential baseline confounders, including age, sex, education level, cigarette smoking, alcohol consumption, BMI, LDL-C, HDL-C, fasting glucose, and follow-up months. In this model, participants who had been already diagnosed as having hypertension at baseline were excluded. The association between baseline microalbuminuria and blood pressure at follow-up was also examined by constructing a robust linear regression model further adjusting for blood pressure at baseline. To examine the other directional association that whether hypertension at baseline predicts future risk of microalbuminuria, we constructed a similar model with incident microalbuminuria as the dependent variable and blood pressure (continuous SBP/DBP or categorical variable: normal versus hypertension) as the independent variable. Participants who had already been diagnosed as having microalbuminuria at baseline were excluded in this model. The association between baseline hypertension and UACR at follow-up was also similarly examined.

Cross-lagged panel analysis

To examine the temporal relationship between hypertension and microalbuminuria, we constructed a cross-lagged panel analysis model on the basis of the 2–time points measurements of blood pressure and UACR at baseline and follow-up examinations. The rationale of using a cross-lagged panel analysis model herein is that this model can simultaneously examine reciprocal and longitudinal relationships among a series of interrelated variables. In this model, both the baseline and follow-up values of blood pressure and UACR were first standardized with Z-transformation (mean=0; SD=1), followed by estimating Pearson correlation coefficients and cross-lagged path coefficients (Figure 2, β_1 representing the effect of baseline blood pressure on subsequent UACR, and β_2 representing the effect of baseline UACR on subsequent blood pressure) among the Z-transformed quantitative variables, adjusting for confounding variables previously listed. The validity of model fitting was represented by the root mean square residual and comparative fit index. The cross-lagged panel analysis was performed by the “lavaan” R package.³³

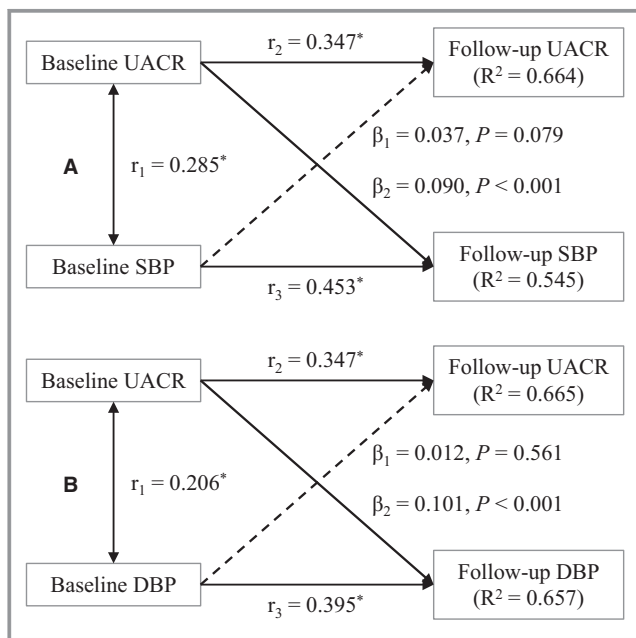


Figure 2. Cross-lagged panel analysis models of blood pressure and UACR, adjusting for age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low-density lipoprotein, high-density lipoprotein, fasting glucose, and follow-up months. Goodness of fit: root mean square residual (RMR) = 0.010 and comparative fit index (CFI) = 0.971 for systolic blood pressure (SBP; **A**); RMR = 0.008 and CFI = 0.981 for diastolic blood pressure (DBP; **B**). β_1 and β_2 indicate cross-lagged path coefficients; r_1 , synchronous correlation; r_2 and r_3 , tracking correlations; R^2 , variance explained; UACR, urinary albumin/creatinine ratio. * $P < 0.05$.

Sensitivity analysis

To examine whether sex influences our results, in addition to adjustment for sex, we repeated our analysis in men and women, respectively. To examine whether diabetes mellitus influences our results, participants with diabetes mellitus were excluded. To examine whether antihypertensive drugs affect our results, participants who took antihypertensive medicine at baseline were excluded.

Results

Baseline Characteristics of Study Participants

Our analysis included 1991 participants who received repeated measurements of blood pressure and UACR at baseline and follow-up examinations (mean age, 53 years; 61% women). Of them, 905 participants (45.45%), including 531 under antihypertensive treatment, had been diagnosed as having hypertension and 403 participants (20.24%) had an abnormal level of UACR. Several of 264 hypertensive participants also experienced microalbuminuria (29.17%), and ≈66% of individuals with microalbuminuria experienced hypertension. Baseline characteristics of study participants are shown in Table 1. The average levels of SBP and DBP in our study participants were 130.6 and 85.0 mm Hg. The median level of UACR was 8.38 mg/g in our study participants. There were significant sex differences in blood pressure and UACR, as well as other conventional risk factors (eg, age, cigarette smoking, alcohol consumption, BMI, and lipids).

Prospective Association of Baseline Microalbuminuria With Incident Hypertension

Of the 1086 participants free of hypertension at the phase 1 examination, 148 developed new hypertension during a median 4.05 years of follow-up. The incidence density of hypertension was 33.65 per 1000 person-years. Characteristics at baseline and follow-up were presented according to incident hypertension (Table 2). Participants who developed new hypertension were more likely to be older, men, current smokers, and current drinkers and to have higher levels of BMI, blood pressure, lipids, fasting glucose, and UACR at both baseline and follow-up than those remaining free of hypertension (all $P < 0.05$). The prospective associations of baseline microalbuminuria with incident hypertension and follow-up blood pressure are shown in Table 3.

Regression using log-transformed UACR as a continuous variable showed that a higher level of log-transformed UACR was significantly associated with a higher level of SBP ($\beta = 1.31$, $P < 0.001$), a higher level of DBP ($\beta = 1.16$, $P < 0.001$), and an increased risk of hypertension (odds ratio [OR] = 1.50,

Table 1. Baseline Characteristics of Study Participants (N=1991)

Characteristics	Total Participants	Men	Women	P Value
No.	1991	776	1215	...
Age, y	53 (9)	53 (9)	53 (9)	0.242
Current smoking	461 (23.15)	454 (58.51)	7 (0.58)	<0.001
Current drinking	375 (18.84)	339 (43.69)	36 (2.96)	<0.001
Education level, y*	9 (6–9)	8 (5–8)	5 (5–8)	<0.001
Body mass index, kg/m ²	24.81 (3.55)	25.25 (3.97)	24.53 (3.23)	<0.001
Systolic blood pressure, mm Hg	130.6 (17.0)	132.8 (16.8)	129.2 (17.0)	<0.001
Diastolic blood pressure, mm Hg	85.0 (9.4)	87.8 (10.0)	83.2 (8.6)	<0.001
Total cholesterol, mmol/L*	5.10 (4.54–5.76)	5.03 (4.53–5.64)	5.16 (4.54–5.82)	0.027
Triglycerides, mmol/L*	1.11 (0.78–1.64)	1.24 (0.84–1.86)	1.05 (0.75–1.52)	<0.001
HDL-C, mmol/L*	1.45 (1.23–1.71)	1.34 (1.15–1.58)	1.53 (1.31–1.78)	<0.001
LDL-C, mmol/L*	2.96 (2.51–3.46)	2.94 (2.49–3.37)	2.97 (2.52–3.48)	0.035
Fasting glucose, mmol/L*	5.2 (5.7–5.7)	5.2 (4.7–5.8)	5.2 (4.7–5.6)	0.301
UACR, mg/g*	8.38 (5.00–18.21)	6.26 (4.06–11.71)	10.40 (5.90–22.00)	<0.001

Data are given as mean (SD) or number (percentage). P value indicates the significance of sex differences in the characteristics. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UACR, urinary albumin/creatinine ratio.

*Presented as median (interquartile range).

$P<0.001$), after adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, BMI, LDL-C, HDL-C, fasting glucose, follow-up years, and baseline blood pressure. Results of regression on the basis of microalbuminuria

status also detected significant associations in the same direction. Compared with participants with a normal UACR at baseline, those with microalbuminuria had an elevated SBP ($\beta=2.79$, $P=0.005$), an elevated DBP ($\beta=2.50$, $P<0.001$), and a

Table 2. Characteristics According to Incident Hypertension in Participants Free of Prevalent Hypertension at Baseline (N=1086)

Characteristics	Baseline			Follow-Up		
	Without Incident Hypertension	With Incident Hypertension	P Value	Without Incident Hypertension	With Incident Hypertension	P Value
Age, y	50 (9)	53 (9)	0.001	55 (9)	58 (9)	0.001
Sex, men	264 (28.14)	75 (50.68)	<0.001
Current smoking	170 (18.12)	53 (35.81)	<0.001	169 (18.02)	52 (35.14)	<0.001
Current drinking	119 (12.69)	35 (23.65)	0.001	164 (17.48)	49 (33.11)	<0.001
Education level, y*	8 (5–8)	5 (5–8)	0.013
Body mass index, kg/m ²	23.74 (3.01)	25.35 (2.83)	<0.001	23.9 (3.02)	25.78 (3.07)	<0.001
SBP, mm Hg	119.4 (10.3)	127.3 (7.5)	<0.001	116.3 (11.0)	136.6 (13.6)	<0.001
DBP, mm Hg	79.0 (6.0)	83.3 (4.1)	<0.001	75.7 (7.23)	87.9 (8.3)	<0.001
Total cholesterol, mmol/L*	4.99 (4.42–5.6)	5.08 (4.48–5.77)	0.296	5.02 (4.49–5.62)	5.1 (4.4–5.71)	0.771
Triglycerides, mmol/L*	0.95 (0.69–1.41)	1.12 (0.81–1.69)	0.001	1.09 (0.79–1.54)	1.46 (0.98–1.97)	<0.001
HDL-C, mmol/L*	1.52 (1.30–1.75)	1.43 (1.19–1.69)	0.007	1.26 (1.08–1.46)	1.14 (0.99–1.38)	<0.001
LDL-C, mmol/L*	2.89 (2.45–3.34)	2.94 (2.46–3.48)	0.309	2.99 (2.59–3.45)	3.08 (2.64–3.57)	0.388
Fasting glucose, mmol/L*	5.0 (4.6–5.4)	5.2 (4.7–5.7)	0.007	5.2 (4.9–5.7)	5.4 (5.0–6.0)	0.001
UACR, mg/g*	6.80 (4.44–12.88)	9.13 (5.37–18.09)	0.001	18.36 (12.38–31.03)	21.42 (13.88–42.05)	0.002

Data are given as mean (SD) or number (percentage). DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Presented as median (interquartile range).

Table 3. Prospective Associations of Baseline Microalbuminuria With Follow-Up Blood Pressure and Incident Hypertension in Participants Free of Hypertension at Baseline (N=1086)

Baseline Microalbuminuria	Follow-Up SBP		Follow-Up DBP		Incident Hypertension	
	β (SE)	P Value	β (SE)	P Value	OR (95% CI)	P Value
Continuous						
Log-transformed UACR*	1.31 (0.40)	0.001	1.16 (0.27)	<0.001	1.50 (1.22–1.83)	<0.001
Categorical						
Normal	Reference	...	Reference	...	Reference	...
Microalbuminuria [†]	2.79 (1.00)	0.005	2.50 (0.68)	<0.001	1.75 (1.06–2.87)	0.028

CI indicates confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; SE, standard error of the regression coefficient; UACR, urinary albumin/creatinine ratio.

Adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, fasting glucose, and follow-up months.

*Increase in blood pressure or risk of hypertension per unit increase in log-transformed urinary albumin/creatinine ratio.

[†]Increase in blood pressure or risk of hypertension for participants with microalbuminuria at baseline compared with those without.

75% increased risk for developing hypertension (OR=1.75, $P=0.028$).

Prospective Association of Baseline Hypertension With Incident Microalbuminuria

Of the 1588 participants free of microalbuminuria at the phase 1 examination, 624 were identified to have microalbuminuria at the phase 2 examination. The incidence density of microalbuminuria was 90.7 per 1000 person-years. Their

median UACR levels elevated from 6.67 to 18.14 mg/g. Characteristics at baseline and follow-up were presented according to incident microalbuminuria (Table 4). Participants who developed new microalbuminuria were more likely to be older, men, current smokers, and current drinkers and to have higher levels of BMI, blood pressure, fasting glucose, and UACR at both baseline and follow-up than those remaining free of microalbuminuria (all $P<0.05$). The prospective associations of baseline hypertension with incident microalbuminuria and follow-up UACR are shown in Table 5.

Table 4. Characteristics According to Incident Microalbuminuria in Participants Free of Prevalent Microalbuminuria at Baseline (N=1588)

Characteristics	Baseline			Follow-Up		
	Without Incident Microalbuminuria	With Incident Microalbuminuria	P Value	Without Incident Microalbuminuria	With Incident Microalbuminuria	P Value
Age, y	51 (9)	54 (10)	<0.001	56 (9)	58 (10)	<0.001
Sex, men	313 (32.71)	328 (51.98)	<0.001
Current smoking	206 (21.53)	182 (28.84)	0.001	205 (21.44)	187 (29.64)	<0.001
Current drinking	146 (15.26)	157 (24.88)	<0.001	196 (20.50)	199 (31.54)	<0.001
Education level, y*	8 (5–8)	5 (5–8)	<0.001
Body mass index, kg/m ²	24.38 (3.15)	24.89 (3.66)	0.004	24.40 (3.18)	25.04 (3.09)	<0.001
SBP, mm Hg	126.6 (15.0)	131.5 (16.3)	<0.001	122.5 (15.0)	129.3 (17.0)	<0.001
DBP, mm Hg	83.6 (8.9)	84.9 (9.2)	0.005	79.2 (9.0)	81.8 (10.2)	<0.001
Total cholesterol, mmol/L*	5.05 (4.48–5.65)	5.07 (4.49–5.77)	0.444	4.99 (4.45–5.58)	5.07 (4.49–5.66)	0.171
Triglycerides, mmol/L*	1.09 (0.77–1.59)	1.08 (0.78–1.61)	0.892	1.18 (0.85–1.72)	1.24 (0.88–1.93)	0.065
HDL-C, mmol/L*	1.45 (1.22–1.71)	1.44 (1.23–1.72)	0.885	1.19 (1.04–1.39)	1.23 (1.02–1.45)	0.140
LDL-C, mmol/L*	2.92 (2.49–3.37)	2.94 (2.47–3.47)	0.331	3.00 (2.57–3.45)	3.04 (2.57–3.49)	0.393
Fasting glucose, mmol/L*	5.1 (4.7–5.6)	5.1 (4.7–5.7)	0.038	5.3 (4.9–5.7)	5.5 (5.1–6.0)	<0.001
UACR, mg/g*	5.86 (4.25–9.07)	8.33 (5.60–13.76)	<0.001	13.13 (9.87–16.92)	35.66 (26.71–51.13)	<0.001

Data are given as mean (SD) or number (percentage). DBP indicates diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Presented as median (interquartile range).

Table 5. Prospective Associations of Baseline Hypertension With Follow-Up UACR and Incident Microalbuminuria in Participants Free of Microalbuminuria at Baseline (N=1588)

Baseline Hypertension	Follow-Up Log-Transformed UACR		Incident Microalbuminuria	
	β (SE)	P Value	OR (95% CI)	P Value
Continuous				
1-SD increase in SBP*	0.04 (0.02)	0.032	1.27 (1.13–1.43)	<0.001
1-SD increase in DBP*	−0.00 (0.02)	0.926	1.21 (1.01–1.25)	0.040
Categorical				
Normal	Reference	...	Reference	...
Hypertension [†]	−0.02 (0.03)	0.612	1.26 (0.90–1.42)	0.305

Adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, fasting glucose, and follow-up months. CI indicates confidence interval; DPB, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Increase in log-transformed UACR at follow-up or risk of microalbuminuria per SD increase in blood pressure.

[†]Increase in log-transformed UACR at follow-up or risk of microalbuminuria for participants with hypertension at baseline compared with those without.

Regression using blood pressure as a continuous variable showed that a higher level of SBP was significantly associated with a higher level of log-transformed UACR at follow-up ($\beta=0.04$, $P=0.032$ for SBP) and an increased risk of microalbuminuria (OR=1.27, $P<0.001$) after adjustment for baseline age, sex, education level, cigarette smoking, alcohol consumption, BMI, LDL-C, HDL-C, fasting glucose, follow-up years, and baseline UACR. DBP presented a significant association with risk of microalbuminuria (OR =1.21, $P=0.040$) but not follow-up UACR. Further regression on the basis of hypertensive status did not find any significant associations with either follow-up UACR or risk of incident microalbuminuria.

on the basis of SBP showed that the path coefficient from baseline SBP to follow-up UACR (β_1) was 0.037 ($P=0.079$), which was significantly smaller than that from baseline UACR to follow-up SBP (β_2) of 0.090 ($P<0.001$), with a $P<0.001$ for the difference between β_1 and β_2 . Analysis on the basis of DBP revealed similar results. The path coefficient from baseline DBP to follow-up UACR was not significant ($\beta_1=0.012$, $P=0.561$) and also much smaller than that from baseline UACR to follow-up DBP ($\beta_2=0.101$, $P<0.001$), with a $P<0.001$ for difference between β_1 and β_2 . The models are relatively well fitted in our sample, as indicated by the root mean square residual and comparative fit index of 0.010 and 0.971 for SBP and 0.008 and 0.981 for DBP, respectively, referring to the criteria of root mean square residual <0.05 and comparative fit index >0.90.

Temporal Relationship Between Hypertension and Microalbuminuria

Figure 2 presents the results of cross-lagged panel analysis of blood pressure and UACR, adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, BMI, LDL-C, HDL-C, fasting glucose, and follow-up months. Analysis

Sensitivity Analysis

Although sex differences in UACR and cardiovascular risk have been demonstrated, sex may not influence our results because of a similar effect of baseline UACR on the risk of

Table 6. Bidirectional Associations Between Microalbuminuria and Hypertension in Men and Women

Baseline Predictors	Men		Women		P Value for Sex Difference
	OR (95% CI)	P Value	OR (95% CI)	P Value	
Baseline microalbuminuria*					
Log-transformed UACR	1.48 (1.06–2.07)	0.021	1.46 (1.12–1.88)	0.004	0.994
Baseline hypertension[†]					
1 SD of SBP	1.28 (1.07–1.52)	0.007	1.24 (1.06–1.44)	0.006	0.920
1 SD of DBP	1.06 (0.90–1.25)	0.502	1.13 (0.98–1.31)	0.084	0.302

CI indicates confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Baseline microalbuminuria predicting incident hypertension.

[†]Baseline hypertension predicting incident microalbuminuria.

Table 7. Bidirectional Associations Between Microalbuminuria and Hypertension After Excluding Participants Under Antihypertensive Medications at Baseline

Baseline Predictors	OR (95% CI)	P Value
Baseline microalbuminuria*		
Log-transformed UACR	1.50 (1.22–1.83)	<0.001
Baseline hypertension†		
1 SD of SBP	1.24 (1.09–1.41)	0.001
1 SD of DBP	1.11 (0.98–1.26)	0.096

Adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, fasting glucose, and follow-up months. CI indicates confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Baseline microalbuminuria predicting incident hypertension.

†Baseline hypertension predicting incident microalbuminuria.

hypertension identified in men and women (OR=1.48 versus 1.46, *P* for sex difference=0.994, Table 6). Excluding participants under antihypertensive treatment (Table 7) or with diabetes mellitus (Table 8) at baseline did not change our results a lot, indicating that the association between microalbuminuria and hypertension may unlikely be driven by these conditions.

Discussion

In a longitudinal cohort of Chinese adults, we examined, for the first time, the bidirectional and temporal sequence between microalbuminuria and hypertension. Our results showed that baseline microalbuminuria significantly predicted future risk of hypertension, but baseline hypertension appeared not to be robustly associated with risk of microalbuminuria. Furthermore, the relationship of baseline UACR to

Table 8. Bidirectional Associations Between Microalbuminuria and Hypertension After Excluding Participants With Diabetes Mellitus at Baseline

Baseline Predictors	OR (95% CI)	P Value
Baseline microalbuminuria*		
Log-transformed UACR	1.67 (1.00–2.78)	0.050
Baseline hypertension†		
1 SD of SBP	1.29 (1.15–1.46)	<0.001
1 SD of DBP	1.14 (1.02–1.28)	0.022

Adjusting for baseline age, sex, education level, cigarette smoking, alcohol consumption, body mass index, low- and high-density lipoprotein cholesterol, fasting glucose, and follow-up months. CI indicates confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; UACR, urinary albumin/creatinine ratio.

*Baseline microalbuminuria predicting incident hypertension.

†Baseline hypertension predicting incident microalbuminuria.

follow-up blood pressure was much stronger than that between baseline blood pressure and follow-up UACR. These findings indicate that elevated UACR may precede the elevation of blood pressure and these 2 conditions in combination boost cardiovascular risk.

In line with our study, one direction of the association between microalbuminuria and hypertension is that microalbuminuria predicts future risk of hypertension, which has also been found in prior studies. For example, a basic study found a dramatically elevated blood pressure in mice with microalbuminuria.²⁰ The Framingham Offspring Heart Study, including 1499 nonhypertensive individuals without diabetes mellitus, found that baseline UACR predicted future risk of hypertension over conventional risk factors.²⁴ A population study including 920 normotensive nondiabetic Indian adults found that elevated UACR at baseline was significantly associated with incident hypertension after 2 years of follow-up.²¹ Another study comprising 1173 Korean adults free of hypertension found a similar predicting effect of UACR on future risk of hypertension.²² In our study sample of 1086 Chinese adults free of hypertension, we found that participants with microalbuminuria at baseline had a 75% higher risk of hypertension 4 years later than those without microalbuminuria at baseline, and this association was independent of many conventional risk factors of hypertension, including obesity, lipids, and glucose. Our results suggest that elevated UACR may contribute to the development of hypertension through mechanisms beyond these traditional risk factors.

Although some prospective studies reported the other direction of the association between microalbuminuria and hypertension in European-original populations,^{25–27} the association of baseline hypertension with future risk of microalbuminuria lacks robustness in our study sample of 1588 Chinese adults free of microalbuminuria at baseline. Some factors, such as small sample size, use of antihypertensive drugs, and diabetes mellitus, may probably limit the robustness of our results, given that a decreasing trajectory of UACR has been observed in hypertensive patients receiving antihypertensive drugs (eg, olmesartan and losartan).^{23,34} To examine whether these conditions modify the effect of hypertension on the risk of microalbuminuria, we applied sensitivity analysis by excluding participants receiving antihypertensive medications or with diabetes mellitus at baseline. Results showed that the effect size of blood pressure at baseline on the prediction of incident microalbuminuria was unchanged, indicating that antihypertensive drugs and diabetes mellitus may not modify the effect of hypertension on microalbuminuria. Our findings somewhat indicate that hypertension, at least elevated SBP, may aggravate the development of microalbuminuria, given that the relationship of baseline SBP to incident microalbuminuria persisted in sensitivity analysis.

Together with existing data, our bidirectional association analysis uncovered a probably bidirectional association between microalbuminuria and hypertension, regardless of one delicate direction of this association. To further delineate the temporal sequence of this bidirectional association, we additionally conducted a cross-lagged panel analysis that can efficiently examine reciprocal and longitudinal relationships among a series of interrelated variables. Results showed that baseline elevated SBP was bottom line significantly associated with elevation of UACR at follow-up, but the effect size of this direction was significantly and drastically weaker than the other direction of the association between UACR and blood pressure, indicating that elevated UACR and microalbuminuria precede elevation of blood pressure and may contribute to hypertension. Given that hypertension is an important and modifiable risk factor for CVD, its contributors, including elevated albumin excretion and microalbuminuria, may enhance its contribution to CVD events. In support of this hypothesis, participants with hypertension complicated with microalbuminuria had a significantly higher CVD risk, measured by Framingham cardiovascular risk score,³⁵ than those with only hypertension ($P=0.006$, the result was not shown). In light of this result, screening and monitoring of urinary albumin is essential and of potential importance for prevention and control of CVD, particularly in hypertensive patients.

Mechanisms underlying the association between microalbuminuria and hypertension are not clear. One possibility is that they have a common pathogenesis, vascular endothelial dysfunction. The endothelium is the largest organ in our body linking almost all organs through vascularity. Microalbuminuria reflects dysfunction of glomerular endothelial cells, which may reflect wider endothelial dysfunction³⁶ presenting in any pathological conditions associated with hypertension, such as diabetes mellitus, aging, dyslipidemia, obesity, and cigarette smoking.³⁷ Therefore, microalbuminuria is not only considered an early marker of endothelial dysfunction in the glomeruli but also a marker of systemic vascular endothelial dysfunction, which is an established pathogenesis of hypertension.^{38,39} When endothelial dysfunction occurs in glomerular vessels, albumin begins to be excreted into the urine and ultimately microalbuminuria presents.⁴⁰ In contrast, only when increased stiffness and reduced elasticity after endothelial dysfunction present in arteries, blood pressure begins to elevate. Given that the glomerular vessel wall is thinner than systemic arteries, microalbuminuria may occur before the elevation of blood pressure, thereby serving as a potential indicator of hypertension risk. However, whether microalbuminuria is a risk factor for hypertension is still unknown and warrants further investigation.

To the best of our knowledge, our study represents the first to systemically examine the bidirectional and temporal association between hypertension and microalbuminuria in

Chinese adults. The strengths of our study include its longitudinal design, repeated measurements of blood pressure and UACR, and comprehensive adjustment for many possible confounding factors. Our study also applied the cross-lagged path analysis model, a powerful statistical approach to dissecting a temporal relationship between 2 interrelated variables.

However, the present study also had several limitations. First, although UACR in a spot urinary sample is widely used to diagnose microalbuminuria in various studies, UACR in a single morning void urine sample, used in our study, may lead to misclassification of microalbuminuria in some participants. Second, the sample size is relatively not large. The prospective association of baseline hypertension with incident microalbuminuria was not robust in our study. Third, like all other observational epidemiological studies, residual confounding may exist in our study. Interpretation of our results needs further cautions. Fourth, given the observational study design, we cannot establish the causality between hypertension and microalbuminuria. Last, we did not obtain data on medication class and thus cannot identify which class of antihypertensive medication could protect kidney function in hypertensive participants. However, sensitivity analysis found that excluding participants under antihypertensive treatment did not change our results, indicating that the association between hypertension and microalbuminuria may not be affected by antihypertensive medications.

In conclusion, our study demonstrates a significant bidirectional association between hypertension and microalbuminuria, and elevated urinary albumin excretion is more likely to precede hypertension among Chinese adults. Microalbuminuria may be an early marker, beyond hypertension, of cardiovascular risk. In light of our findings, screening of microalbuminuria in a community population of nonhypertensive individuals, in particular, may promote the prevention of CVD. Given the observational study design, we could not delineate the causality between hypertension and microalbuminuria. Clinical trials are warranted to test the causal contribution of microalbuminuria to hypertension.

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Disclosures

None.

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