Hypertension

ORIGINAL ARTICLE

Blood Pressure Levels, Cardiovascular Events, and Renal Outcomes in Chronic Kidney Disease Without Antihypertensive Therapy: A Nationwide Population-Based Cohort Study

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BACKGROUND: High blood pressure (BP) is highly prevalent in patients with chronic kidney disease. However, the thresholds to initiate BP-lowering treatment in this population are unclear. We aimed to examine the associations between BP levels and clinical outcomes and provide evidence on potential thresholds to initiate BP-lowering therapy in people with chronic kidney disease.

METHODS: This nationwide, multicenter, prospective cohort study included 12 523 chronic kidney disease participants without antihypertensive therapy in mainland China. Participants were followed up during 2011 to 2016 for cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, hospitalized or treated heart failure, and cardiovascular death) and renal events (≥20% decline in the estimated glomerular filtration rate, end-stage kidney disease, and renal death).

RESULTS: Overall, 652 cardiovascular events and 1268 renal events occurred during 43 970 person-years of follow-up. We observed a positive and linear relationship between systolic BP and risks of cardiovascular and renal events down to 90 mm Hg, as well as between diastolic BP and risks of renal events down to 50 mm Hg. A J-shaped trend was noted between diastolic BP and risks of cardiovascular events, but a linear relationship was revealed in participants <60 years (*P* for interaction <0.001). A significant increase in the risk of cardiovascular and renal outcomes was observed at systolic BP ≥130 mm Hg (versus 90–119 mm Hg) and at diastolic BP ≥90 mm Hg (versus 50–69 mm Hg).

CONCLUSIONS: In people with chronic kidney disease, a higher systolic BP/diastolic BP level (≥130/90 mm Hg) is significantly associated with a greater risk of cardiovascular and renal events, indicating potential thresholds to initiate BP-lowering treatment.
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Key Words: blood pressure ■ cardiovascular disease ■ chronic kidney disease ■ end-stage renal disease ■ hypertension

High blood pressure (BP) is one of the most important modifiable risk factors for cardiovascular disease (CVD), renal dysfunction, and mortality.[1] Although studies have shown that BP reduction can decrease the disease risk, subpopulations such as those with chronic kidney disease (CKD) may benefit from

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

In community adults with chronic kidney disease (CKD),
a linear association between systolic blood pressure (SBP) and risks of cardiovascular and renal events was observed to a level as low as 90 mm Hg;
a J-shaped association between diastolic blood pressure (DBP) and cardiovascular outcomes was observed with the lowest risk at 80 mm Hg and a linear association between DBP and renal outcomes to a level as low as 50 mm Hg;
a significant increase in the risk of cardiovascular and renal outcomes was observed at SBP ≥130 mm Hg (versus 90–119 mm Hg) and at DBP ≥90 mm Hg (versus 50–69 mm Hg).

What Is Relevant?

Blood pressure (BP) level ≥130/90 mm Hg, which is below the commonly recognized threshold for hypertension diagnosis, was associated with significantly increased risks of cardiovascular and renal outcomes in people with CKD.

Clinical/Pathophysiological Implications?

BP level ≥130/90 mm Hg can be potential thresholds for the initiation of BP-lowering treatment in people with CKD to prevent cardiovascular and renal events.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
ACR	albumin-to-creatinine ratio
AHA	American Heart Association
BP	blood pressure
CKD	chronic kidney disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
4C	China Cardiometabolic Disease and Cancer Cohort
KDIGO	Kidney Disease Improving Global Outcomes
SBP	systolic blood pressure

BP management differently.[2,3] Because hypertension is highly prevalent in patients with CKD, which affects 697.5 million people globally,[4,5] appropriate BP management in this population has large clinical and public health impacts. However, consensus on the associations between BP levels and cardiovascular and renal outcomes in CKD patients remains elusive. Findings from previous studies were controversial, demonstrating either linear, J-shaped, or U-shaped relationships, in which the specific BP component and the type of CVD may play a part.[6–9] A few studies also revealed that patients' characteristics (eg, age and stages of CKD) can be relevant.[6,7,10] These findings were mostly from studies in treated hypertensive patients to examine BP-lowering targets, while evidence from CKD patients without antihypertensive treatment to examine initiation thresholds for BP-lowering therapy is limited.[11]

The Kidney Disease Improving Global Outcomes (KDIGO) 2012 clinical practice guideline recommended to initiate BP-lowering therapy when systolic BP (SBP) >130 mm Hg or diastolic BP (DBP) >80 mm Hg among CKD patients with albuminuria, or when SBP >140 mm Hg or DBP >90 mm Hg among those without albuminuria.[12] The recently updated KDIGO 2021 guideline did not make recommendations on thresholds for initiation of BP-lowering therapy but tightened BP-lowering target to an SBP <120 mm Hg in CKD patients.[11] Using data from a large, nationwide, multicenter, prospective cohort of community adults, we defined CKD participants according to the KDIGO guideline and excluded those taking antihypertensive medications. We aimed to provide evidence on potential thresholds to initiate BP-lowering therapy in CKD patients by investigating the relationships of SBP and DBP levels with the risks of cardiovascular and renal events in the overall study population and in patients within different age and KDIGO risk categories.[12]

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The 4C study (The China Cardiometabolic Disease and Cancer Cohort) is a nationwide, multicenter, population-based, prospective cohort study of cardiometabolic diseases and risk factors in Chinese adults.[13–15] In 2011 to 2012, a total of 193 846 participants aged ≥40 years from 20 community sites located in 16 provinces, autonomous regions, or municipalities across mainland China were recruited using the local resident registration system to undergo a comprehensive evaluation of cardiometabolic characteristics, among whom 19 451 participants had CKD. Participants taking antihypertensive drug therapy, with a previous diagnosis of CVD

or cancer, with an SBP level <90 mm Hg or a DBP level <50 mm Hg, with missing data on baseline BP levels, or with missing data on cardiovascular and renal outcomes during follow-up were excluded. Therefore, a total of 12 523 participants were included in the current analysis (Figure S1).

This study was approved by the Medical Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. All study participants provided written informed consent before data collection.

Data Collection

At each study site, trained staff collected data according to a standard protocol at local health stations or community clinics. Information on sociodemographic characteristics, lifestyle factors, and medical history was collected by using a standard questionnaire. Smoking and drinking habits at present as well as in the past were recorded. Physical activity was assessed using the International Physical Activity Questionnaire[16] and physical activity per week was evaluated based on the intensity (vigorous/intermediate/mild), frequency (days per week), and average duration (minutes per day).

Body weight and height measurements were performed according to a standard protocol and body mass index was calculated as weight in kilograms divided by height in meters squared. Three BP measurements were obtained by trained observers from each participant using a calibrated automatic electronic device (OMRON Model HEM-752 FUZZY) with 1 of 4 cuff sizes (pediatric, regular adult, large, or thigh) chosen on the basis of each participant's arm circumference in a separate examination room after at least 5-minute sitting rest with 1-minute intervals, with an observer present. Both the participant and the observer were required to remain quiet during the rest period and the measurement. Participants were advised to avoid alcohol, coffee, tea, smoking, and exercise at least 30 minutes before BP measurement. The average of 3 readings was used for analysis.

Blood samples were collected from each participant in the morning after an overnight fast for at least 10 hours. Fasting plasma glucose levels were measured locally using a glucose oxidase or hexokinase method. Fasting serum samples were aliquoted into 0.5-mL Eppendorf tubes within 2 hours after collection and were then frozen at −80 °C at local hospitals. All samples were shipped in dry ice to the central laboratory accredited by the College of American Pathologists at Shanghai National Clinical Research Center for Metabolic Diseases, where levels of serum creatinine, low-density lipoprotein cholesterol, and triglycerides were measured on an auto-analyzer (ARCHITECT ci16200 analyzer, Abbott Laboratories, Illinois, USA). Serum creatinine concentrations were measured using the kinetic Jaffé method with calibration traceable to an isotope dilution mass spectrometry reference measurement. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation.[17]

The first void urine samples were collected from each participant in early morning, and were frozen at −80 °C at local hospitals before shipment. Urinary albumin concentrations were measured at the central laboratory by immunonephelometry using Siemens BNII nephelometers (Siemens Healthcare Diagnostics, Marburg, Germany). The intra-assay and interassay coefficients of variation for urinary albumin were 2.1% and 2.3%, respectively. Urinary creatinine concentrations were measured at the central laboratory by an enzymatic method (ADVIA Chemistry XPT System, Siemens Healthcare, Erlangen, Germany). The intra-assay and interassay coefficients of variation for urinary creatinine were 1.1% and 1.3%, respectively. The urinary albumin-to-creatinine ratio (ACR) was calculated in milligrams per grams.

Definition

According to the KDIGO criteria,[12] CKD was defined by eGFR <60 mL/min per 1.73 meter square or urinary ACR ≥30 mg/g. The KDIGO risk categories were defined as follows: intermediate risk is defined by eGFR <60 mL/min per 1.73 meter square and urinary ACR 30 to 299 mg/g, or eGFR 45 to 59 mL/min per 1.73 meter square and urinary ACR <30 mg/g; high risk is defined by eGFR<60 mL/min per 1.73 meter square and urinary ACR ≥300 mg/g, eGFR 45 to 59 mL/min per 1.73 meter square and urinary ACR 30 to 299 mg/g, or eGFR 30 to 44 mL/min per 1.73 meter square and urinary ACR ≥30 mg/g; very high risk is defined by eGFR<30 mL/min per 1.73 meter square, eGFR 30 to 44 mL/min per 1.73 meter square and urinary ACR ≥30 mg/g, or eGFR 45 to 59 mL/min per 1.73 meter square and urinary ACR ≥300 mg/g.

Outcomes

During 2014 to 2016, participants were asked to return for a follow-up examination, during which the occurrence of cardiovascular and renal events was obtained. Incident cardiovascular event was defined as the first occurrence of myocardial infarction, stroke, hospitalization or treatment for heart failure, and cardiovascular death during follow-up. As described previously,[15] myocardial infarction was defined by characteristic changes in levels of troponin T and creatine-kinase-MB isoform, symptoms of myocardial ischemia, changes in electrocardiogram results, or a combination of them. Stroke was defined as a fixed neurologic deficit for at least 24 hours because of a presumed vascular cause. Heart failure was identified by hospitalization or an emergency department visit requiring a treatment with infusion therapy for a clinical syndrome presenting with multiple signs and symptoms consistent with cardiac decompensation or inadequate cardiac pump function. Blood samples were obtained at the follow-up visit and serum creatinine concentrations were measured at the central laboratory using the same protocol as that used at the baseline examination. Incident renal event was defined as a composite of ≥20% reduction in eGFR levels during follow-up, end-stage renal disease reaching eGFR <15 mL/min per 1.73 meter square or requiring dialysis or kidney transplantation, and death due to renal causes.[18] Reduction in eGFR was calculated as $(eGFR_{baseline}-eGFR_{follow\text{-}up})/eGFR_{baseline}\times100\%$.[19] Annual eGFR change was calculated as $(eGFR_{follow\text{-}up}-eGFR_{baseline})$/follow-up time in years.[20] Information on vital status and clinical outcomes was also obtained from the local death and disease registries of the National Disease Surveillance Point System and the National Health Insurance System. Throughout the study period, medical records of participants who visited an emergency department or were hospitalized were collected and adjudicated centrally. Two members of the outcome adjudication committee independently verified each clinical event and discrepancies were resolved by discussion involving other

members of the committee. All members of the committee were unaware of the baseline risk factors of study participants.

Statistical Analysis

Participants were categorized according to SBP levels 90 to 119, 120 to 129, 130 to 139, 140 to 159, 160 to 179, and ≥180 mm Hg, or according to DBP levels 50 to 69, 70 to 79, 80 to 89, 90 to 99, and ≥100 mm Hg. Baseline characteristics of participants by SBP and DBP categories were presented as means (SDs) or medians (interquartile ranges) for continuous variables and numbers (proportions) for categorical variables. The 1-way ANOVA was used to compare continuous variables and the χ^2 test was used to compare categorical variables across BP categories.

Incidence rates of cardiovascular and renal events were described as number of events per 1000 person-years. To evaluate the association between SBP and DBP as continuous variables and the risks of cardiovascular and renal events, covariate-adjusted restricted cubic splines with 3 knots at 5th, 50th, and 95th percentiles were constructed, with reference values at 120 mm Hg for SBP and 80 mm Hg for DBP. We tested for nonlinearity model fit in the relationship between BP levels and clinical outcomes by comparing a model with the linear term of BP to a model with the linear and restricted cubic spline terms of BP using the likelihood ratio test.[21–23] If a test for nonlinearity model fit was not significant, a test for linearity was conducted comparing a model with the linear term of BP to a model with only covariates. These analyses were repeated in participants with age <60 and ≥60 years, and participants with intermediate KDIGO risk and high/very high KDIGO risk, separately because age-specific analyses in our previous study[24] and others[25] indicated differences in the association between BP levels and clinical outcomes in adults aged <60 versus ≥60 years and the KDIGO guideline recommended the KDIGO risk categories to predict prognosis in CKD patients.[26] Interactions between BP levels and age or KDIGO risk categories in associations with cardiovascular and renal events were estimated by including the product term in the models. Cox proportional hazards models were used to calculate hazard ratios and 95% CIs for cardiovascular and renal events by BP groups, as compared with an SBP level of 90 to 119 mm Hg or a DBP level of 50 to 69 mm Hg, respectively. Restricted cubic splines and cox proportional hazards models were adjusted for age, sex, educational attainment (with/without high school education or above), current smoking (yes/no), current drinking (yes/no), body mass index, physical activity, triglycerides, low-density lipoprotein cholesterol, fasting plasma glucose, eGFR, urinary ACR, and residual systolic or DBP. In addition, a sensitivity analysis was conducted using ≥40% reduction in eGFR levels during follow-up as one of the components to define renal events.

Due to the strong correlation between SBP and DBP levels (Figure S2A), we did not mutually adjust SBP or DBP in the models. We ran a single-linear regression model in which the DBP was the dependent variable, and the SBP was the independent variable.[27–29] Ordinary least square residuals (called residual DBP) was the proportion of DBP that was entirely not related to SBP (Figure S2B). In the analysis between SBP levels and clinical outcomes, the models were adjusted for the residual DBP to exclude the effect of multicollinearity on the regression coefficients. Residual SBP was used in the analyses between DBP levels and clinical outcomes (Figure S2C).

All the tests were 2-tailed, with a P value <0.05 considered to indicate statistical significance. Statistical analyses were performed using R version 3.6.3 (R Project for Statistical Computing, http://www.r-project.org).

RESULTS

Distributions of BP levels in study participants are shown in Figure S3 and baseline characteristics of study participants by BP levels are presented in Tables 1 and 2. In this study population of Chinese community residents with CKD, the overall mean SBP/DBP levels were 127.1/64.3 mm Hg and ≈56.3% and 26.2% participants had an SBP ≥140 mm Hg or DBP ≥90 mm Hg, respectively. Age increased with an increasing SBP level whereas decreased with an increasing DBP level. The proportion of men increased with an increasing SBP or DBP level. Generally, cardiometabolic risk factors such as fasting plasma glucose, lipids, and urinary ACR increased across BP groups (all P values for trend <0.001).

During 43 970 person-years of follow-up, 652 participants developed cardiovascular events and 1268 participants developed renal events. The event numbers and incidence rates in each SBP and DBP groups are shown in Table 3. The incidence rates of both cardiovascular and renal events were the lowest in participants with SBP 90 to 119 mm Hg and increased steadily across SBP groups. In contrast, the incidence rates were the lowest in participants with DBP 80 to 89 mm Hg and increased in both lower and higher DBP levels.

The multivariable-adjusted restricted cubic spline analyses suggested no evidence of a nonlinear relationship between SBP and cardiovascular or renal events. There was evidence of a significant linear relationship between SBP and cardiovascular (Figure 1A) or renal events (Figure 1B). Subgroup analysis of SBP levels revealed generally similar and positive relationships with cardiovascular and renal outcomes in participants with age <60 or ≥60 years, and in participants with intermediate or high/very high KDIGO risks (Figure 2 and Figure S4). When MI and stroke were examined separately, the linear relationship was more evident for stroke than MI in association with SBP levels (Figure S6A through S6B and Table S1). When annual eGFR reduction was examined, evidence of a significant linear relationship was also observed (Figure S7A).

There was evidence that a higher DBP at ≥80 mm Hg was associated with a higher cardiovascular risk but not at <80 mm Hg (Figure 1C), while we observed evidence of a significant linear association between DBP and renal events (Figure 1D). Similar relationships were observed in participants with age ≥60 years, with intermediate, or high/very high KDIGO risks (Figure 3 and Figure S5). However, DBP levels were linearly associated with cardiovascular risks in participants <60 years and age significantly modified the association between

Table 1. Characteristics of Participants by Levels of Systolic Blood Pressure

Characteristics	All participants	Baseline systolic blood pressure, mm Hg						*P* value for trend
		90–119	120–129	130–139	140–159	160–179	≥180	
No. of participants (%)	12 523 (100)	1705 (13.6)	1704 (13.6)	2060 (16.4)	3886 (31.0)	2041 (16.3)	1127 (9.0)	
Age, y	59.9±10.1	55.7±9.9	57.5±10.0	58.9±10.0	60.9±9.7	62.4±9.7	63.2±9.5	<0.001
Men, n (%)	4115 (32.9)	421 (24.7)	519 (30.5)	673 (32.7)	1313 (33.8)	758 (37.1)	431 (38.2)	<0.001
High school education or above, n (%)	2903 (23.2)	565 (33.1)	476 (27.9)	488 (23.7)	835 (21.5)	379 (18.6)	160 (14.2)	<0.001
Current smokers, n (%)	1689 (13.5)	236 (13.8)	256 (15.0)	275 (13.3)	523 (13.5)	261 (12.8)	138 (12.2)	<0.001
Current drinkers, n (%)	1257 (10.0)	104 (6.1)	159 (9.3)	194 (9.4)	412 (10.6)	248 (12.2)	140 (12.4)	<0.001
PA >600 MET-min/wk, n (%)	6970 (55.7)	1022 (59.9)	959 (56.3)	1128 (54.8)	2183 (56.2)	1106 (54.2)	572 (50.8)	<0.001
BMI, kg/m^2	25.0±3.7	23.6±3.4	24.7±3.6	25.1±3.6	25.5±3.7	25.5±3.8	25.4±3.7	<0.001
SBP, mm Hg	145.2±23.6	111.1±6.6	124.8±2.9	134.7±2.9	148.9±5.7	168.3±5.8	192.3±11.1	<0.001
DBP, mm Hg	82.3±12.5	70.4±7.7	76.1±8.4	79.5±9.1	84.3±10.4	88.7±11.9	96.2±14.0	<0.001
TG, mg/dL	130.1 (90.3–193.8)	112.4 (80.5–169)	124.8 (88.5–185)	131.0 (91.2–194.7)	136.3 (94.7–203.5)	131.9 (94.7–194.7)	133.6 (92.9–197.3)	<0.001
LDL-c, mg/dL	115.2±35.1	107.3±33.8	111.0±33.4	114.6±34.8	117.1±35.9	118.8±35.0	121.3±34.2	<0.001
FPG, mg/dL	119.0±45.5	114.5±48.8	116.0±43.2	120.1±45.9	121.0±46.0	120.9±45.0	117.7±40.9	<0.001
eGFR, mL/min per 1.73 meter square	85.4±20.2	86.7±22.4	87.1±21.0	85.5±20.9	84.8±19.6	84.8±18.7	84.5±18.3	<0.001
UACR, mg/g	54.3 (36.0–111.0)	46.9 (33.0–83.2)	48.8 (34.4–97.1)	50.7 (34.8–95.2)	54.2 (36–109.6)	63.8 (39.6–150)	75.6 (43.0–178.0)	<0.001

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; LDL-c, low-density lipoprotein cholesterol; MET, metabolic equivalent; PA, physical activity; SBP, systolic blood pressure; TG, triglycerides; and UACR, urinary albumin-to-creatinine ratio.

DBP and CVD (*P* value for interaction <0.001). When MI and stroke were examined separately, evidence of a possible U-shaped relationship for MI and a significant linear relationship for stroke was observed (Figure S6C and S6D, Table S2). When annual eGFR reduction was examined, evidence of a significant linear relationship was observed (Figure S7B).

The hazard ratios and 95% CIs of developing cardiovascular and renal outcomes in each SBP and DBP groups are shown in Table 3. Compared to participants

Table 2. Characteristics of Participants by Levels of Diastolic Blood Pressure

Characteristics	Baseline diastolic blood pressure, mm Hg					*P* value for trend
	50–69	70–79	80–90	90–99	≥100	
No. of participants (%)	1856 (14.8)	3662 (29.2)	3721 (29.7)	2186 (17.5)	1098 (8.8)	
Age, y	62.3±11.0	60.7±10.4	59.6±9.7	58.5±9.1	56.2±9.0	<0.001
Men, n (%)	481 (25.9)	1080 (29.5)	1197 (32.2)	858 (39.2)	499 (45.4)	<0.001
High school education or above, n (%)	462 (24.9)	863 (23.6)	805 (21.6)	508 (23.2)	265 (24.1)	0.002
Current smokers, n (%)	248 (13.4)	473 (12.9)	479 (12.9)	322 (14.7)	167 (15.2)	<0.001
Current drinkers, n (%)	118 (6.4)	284 (7.8)	376 (10.1)	295 (13.5)	184 (16.8)	<0.001
PA >600 MET-min/wk, n (%)	1075 (57.9)	2119 (57.9)	2030 (54.6)	1220 (55.8)	526 (47.9)	<0.001
BMI, kg/m^2	23.5±3.5	24.7±3.6	25.3±3.6	25.9±3.6	26.3±3.8	<0.001
SBP, mm Hg	127.1±20.2	136.2±19.7	146.9±18.8	158.2±18.9	174.4±21.2	<0.001
DBP, mm Hg	64.3±4.2	75.0±2.9	84.3±2.9	94.0±2.8	107.0±7.4	<0.001
TG, mg/dL	109.3 (78.8–158.4)	125.7 (88.5–182.3)	131.9 (93.8–202.7)	146.0 (100.0–216.4)	143.4 (97.3–212.4)	<0.001
LDL-c, mg/dL	110.8±35.0	114.3±34.6	115.1±35.0	117.9±35.6	120.5±34.9	<0.001
FPG, mg/dL	115.4±44.5	118.8±46.3	120.0±45.8	120.2±44.8	119.4±44.5	0.005
eGFR, mL/min per 1.73 meter square	81.8±22.2	84.4±20.4	86.1±19.9	87.4±18.6	89.2±18.7	<0.001
UACR, mg/g	48.4 (33.4–95.8)	50.7 (34.3–97.3)	55.5 (36.5–110.5)	58.2 (38.3–127.8)	69.9 (41.8–165.8)	<0.001

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; LDL-c, low-density lipoprotein cholesterol; MET-min/wk, metabolic equivalent minutes per week; PA, physical activity; SBP, systolic blood pressure; TG, triglycerides; and UACR, urinary albumin-to-creatinine ratio.

Table 3. Hazard Ratios (95% CIs) for Incident Cardiovascular and Renal Events by Systolic and Diastolic Blood Pressure Levels

Characteristics	Cardiovascular events				Renal events			
	No. of events/no. of participants	Incidence rate per 1000 person-years	Model 1	Model 2	No. of events/no. of participants	Incidence rate per 1000 person-years	Model 1	Model 2
Baseline systolic blood pressure, mm Hg								
90–119	39/1590	6.85	1 [reference]	1 [reference]	131/1291	31.64	1 [reference]	1 [reference]
120–129	57/1604	9.97	1.46 (0.97–2.20)	1.40 (0.89–2.20)	145/1279	35.55	1.19 (0.94–1.51)	1.16 (0.90–1.50)
130–139	83/1898	12.39	1.82 (1.24–2.60)	1.60 (1.06–2.43)	200/1549	40.85	1.41 (1.13–1.76)	1.35 (1.05–1.74)
140–159	208/3558	16.78	2.47 (1.76–3.48)	1.86 (1.27–2.73)	415/2974	44.15	1.59 (1.30–1.93)	1.45 (1.16–1.81)
160–179	154/1836	24.53	3.68 (2.59–5.23)	2.58 (1.72–3.86)	240/1532	50.11	1.93 (1.56–2.39)	1.73 (1.35–2.22)
≥180	111/1006	33.12	4.86 (3.37–7.00)	3.64 (2.33–5.70)	137/847	51.82	2.04 (1.60–2.60)	2.04 (1.50–2.76)
Baseline diastolic blood pressure, mm Hg								
50–69	105/1691	17.6	1 [reference]	1 [reference]	177/1350	41.17	1 [reference]	1 [reference]
70–79	183/3371	15.42	0.88 (0.69–1.12)	0.99 (0.76–1.30)	357/2733	41.38	1.08 (0.90–1.29)	1.22 (1.00–1.49)
80–89	166/3435	13.9	0.80 (0.63–1.02)	1.03 (0.78–1.36)	359/2885	39.24	1.01 (0.84–1.21)	1.11 (0.90–1.36)
90–99	124/1993	17.98	1.04 (0.80–1.34)	1.51 (1.10–2.06)	244/1674	46.31	1.24 (1.02–1.50)	1.40 (1.11–1.76)
≥100	74/1002	21.39	1.23 (0.92–1.66)	1.90 (1.29–2.81)	131/830	50.28	1.32 (1.05–1.66)	1.45 (1.07–1.95)

Model 1 was unadjusted; model 2 was adjusted for age, sex, educational attainment, smoking and drinking status, body mass index, physical activity, levels of residual diastolic blood pressure (only for systolic blood pressure categories), levels of residual systolic blood pressure (only for diastolic blood pressure categories), triglycerides, low-density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio.

with an SBP of 90 to 119 mm Hg, the risk of incident cardiovascular events increased by 40%, 60%, 86%, 158%, and 264%, and the risk of incident renal events increased by 16%, 35%, 45%, 73%, and 104% in participants with an SBP 120 to 129, 130 to 139, 140 to 159, 160 to 179, or ≥180 mm Hg, respectively (Table 3). The increase in risks of cardiovascular and renal outcomes was significant at SBP ≥130 mm Hg. Compared to participants with a DBP of 50 to 69 mm Hg, risks of cardiovascular and renal outcomes significantly increased at DBP ≥90 mm Hg (Table 3; cardiovascular events: hazard ratio, 1.51 [95% CI, 1.10–2.06]; renal events: hazard ratio, 1.40 [95% CI, 1.11–1.76]). The sensitivity analysis using ≥40% reduction in eGFR levels during follow-up as the component of the composite renal outcome revealed similar findings (Figure S8 and Table S3).

DISCUSSION

Using data from a nationwide, multicenter, prospective cohort study of 12 523 Chinese community residents with CKD, we observed evidence of a significant linear association between SBP and risks of cardiovascular and renal events to an SBP level as low as 90 mm Hg. The relationship between DBP and clinical outcomes was more complicated and we found evidence of a possible J-shaped association with cardiovascular outcomes whereas a linear association with renal outcomes. Using SBP of 90 to 119 mm Hg as the reference, risks of cardiovascular and renal events increased significantly at SBP ≥130 mm Hg. Using DBP of 50 to 69 mm Hg as the reference, risks of cardiovascular and renal events increased significantly at DBP ≥90 mm Hg. Therefore, pharmacological treatment might be initiated when SBP is >130 mm Hg or DBP is >90 mm Hg in CKD patients.

The linear, J-curve or U-shaped relationship between BP levels and risks of clinical outcomes has been debated during the past decades, and this relationship can differ in different populations with hypertension. In line with the recent evidence from general population,[30,31] we found evidence of a significant linear relationship between SBP and cardio-renal events beginning at an SBP level as low as 90 mm Hg in CKD patients not initially taking antihypertensive medications. In general, hypertension guidelines recommend a more aggressive BP-lowering threshold and target in younger adults, as compared with older patients. However, emerging evidence supports lowering SBP to <140 mm Hg in the elderly and found that a SBP target of <130 mm Hg or even <120 mm Hg was associated with significant cardiovascular benefits.[32,33] Adding to the previous evidence, we found evidence of a positive and linear relationship between SBP and cardio-renal events in CKD patients aged ≥60 years. In addition, although previous guidelines make recommendations of BP-lowering therapy depending on patients with or without albuminuria, the KDIGO risk category defined by both urinary ACR and eGFR levels was proved to stratify and predict CVD risk well.[34] Therefore, we grouped participants into KDIGO risk categories and found similar results.

There is no consensus on the J-shaped relationship between DBP and cardiovascular and renal outcomes

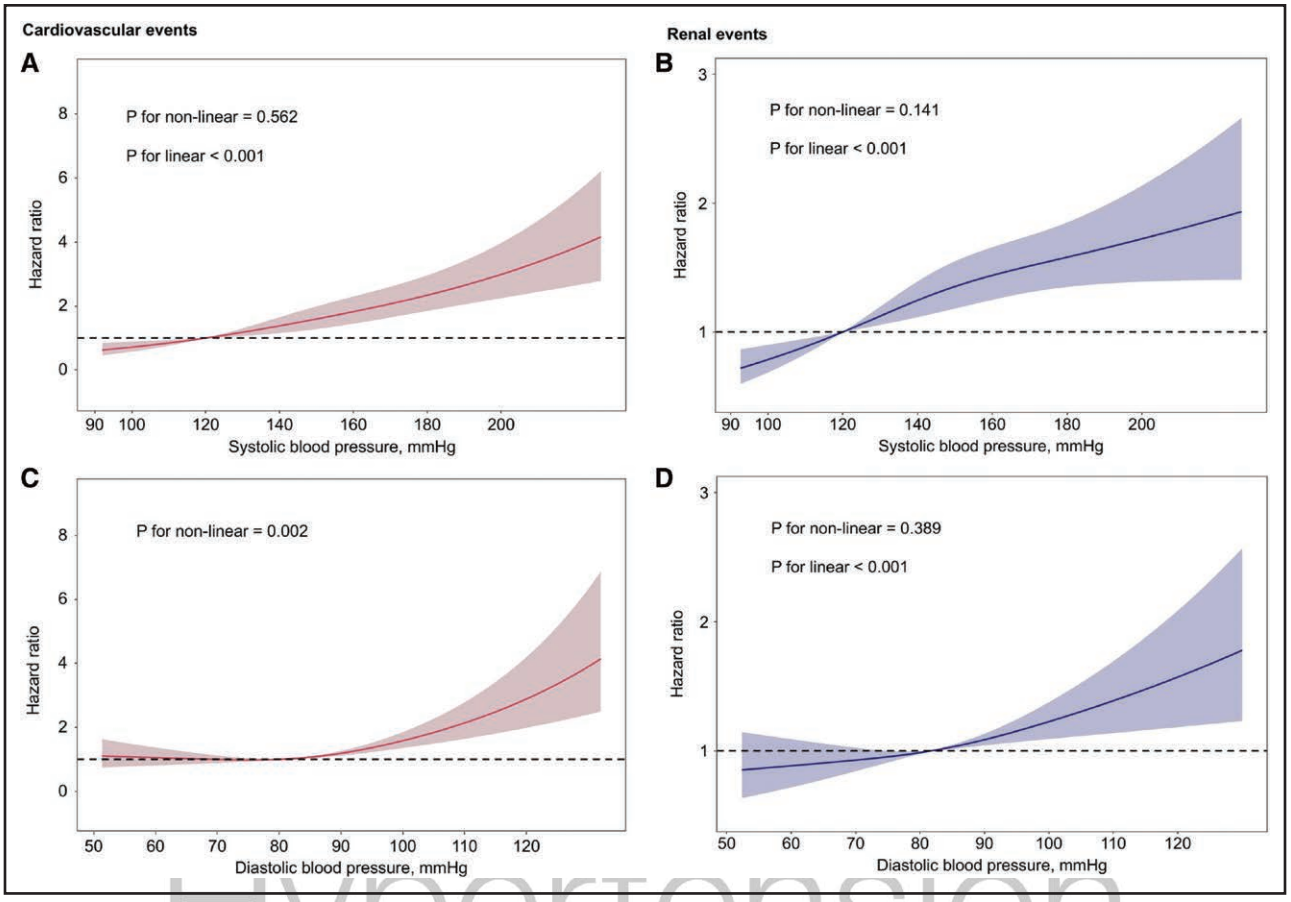

Figure 1. Adjusted cubic splines for the hazard ratios of incident cardiovascular and renal events by systolic and diastolic blood pressure levels.

Models were adjusted for age, sex, educational attainment, smoking and drinking status, body mass index, physical activity, triglycerides, low-density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and residual diastolic blood pressure (**A** and **B**), or residual systolic blood pressure (**C** and **D**).

in CKD patients. In a cohort study of 339 887 CKD patients mostly taking antihypertensive medications, while SBP displayed a linear association with CVD and end-stage renal disease, DBP showed no consistent association with either outcome.[7] A retrospective cohort study using data from 1.3 million adults in a US outpatient population found a J-shaped relation between DBP and CVD, which might be attributed in part to age.[35] However, a Mendelian randomization study from UK Biobank demonstrated a linear, positive, and causal association between DBP and CVD in the UK general population.[27] In the current study, the relationship between DBP and CVD components (ie, MI and stroke), as well as the relationship in younger and older adults, tended to be different. While DBP was found to be linearly associated with stroke, a U-shaped relationship between DBP and MI was demonstrated, which might be explained, in hypothesis, by coronary perfusion depending on DBP. In addition, the relationship between DBP and cardio-renal events in adults aged <60 years was found to be linear in CKD patients, in consistent with the recent findings from observational studies in general population.[36–38] Therefore, the relationship between DBP and cardio-renal outcomes may depend on CVD components and population subgroups.

The updated KDIGO BP guideline recommended an SBP treatment target of <120 mm Hg based on standardized office BP measurement in CKD patients with hypertension.[11] However, recommendation was not made regarding BP levels above which pharmacological treatment should be initiated. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommended BP ≥130/80 mm Hg as thresholds for BP-lowering treatment in patients with CKD.[2] The 2018 European Society of Cardiology/European Society of Hypertension guideline recommended ≥140/90 mm Hg in patients with CKD aged 18 to 79 years.[3] A meta-analysis demonstrated reduced risks of death and CVD events by BP-lowering treatment in patients with baseline SBP ≥140 mm Hg, but not in patients with lower baseline SBP levels in the general hypertension population.[39] Data were limited in CKD patients with hypertension and one meta-analysis demonstrated reduced risks of death by BP-lowering

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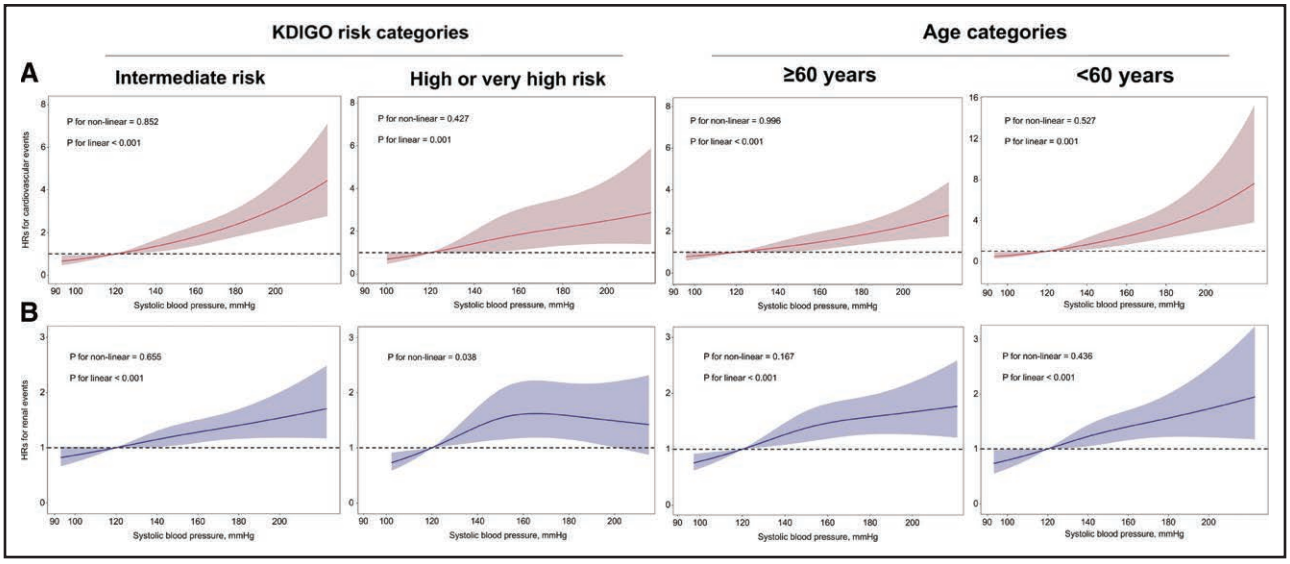

Figure 2. Adjusted cubic splines for the hazard ratios of incident cardiovascular (A) and renal (B) events by systolic blood pressure levels, according to the Kidney Disease Improving Global Outcomes (KDIGO) risk and age categories.
Models were adjusted for age, sex, educational attainment, smoking and drinking status, body mass index, physical activity, triglycerides, low-density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and residual diastolic blood pressure. Interaction between systolic blood pressure and KDIGO risk categories in associations with cardiovascular and renal events: *P* for interaction=0.138 (**A**); *P* for interaction=0.307 (**B**). Interaction between systolic blood pressure and age categories in associations with cardiovascular and renal events: *P* for interaction=0.001 (**A**); *P* for interaction=0.171 (**B**).

treatment in those with CKD stages 3 to 5 and baseline SBP >140 mm Hg, but there was less evidence in CKD patients with baseline SBP <140 mm Hg.[40] In the current study, we found that a baseline SBP ≥130 mm Hg or a baseline DBP ≥90 mm Hg was significantly associated with higher risks of cardiovascular and renal events, indicating that 130/90 mm Hg might be considered a potential threshold for initiating pharmacological treatment in CKD. Although there are randomized controlled trials showing benefits from treating patients with BP levels of ≥130/90 mm Hg,[41] there are few randomized controlled trial data for antihypertensive drug treatment of patients with untreated BP levels of <130/90 mm Hg. More evidence, especially from randomized controlled

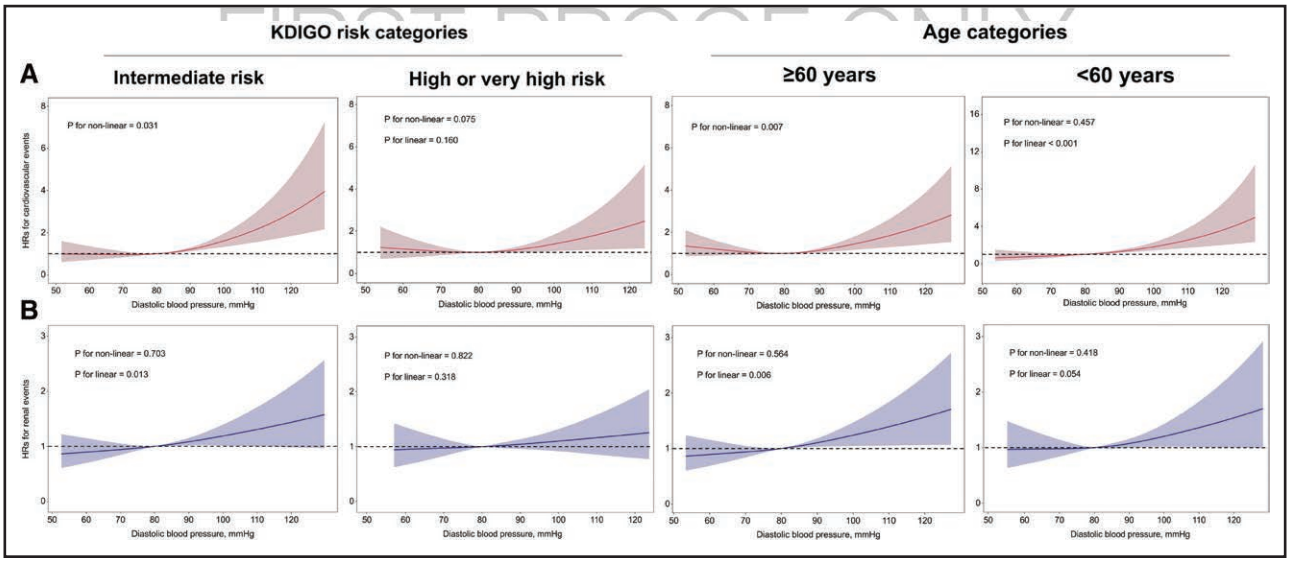

Figure 3. Adjusted cubic splines for the hazard ratios of incident cardiovascular (A) and renal (B) events by diastolic blood pressure levels, according to the Kidney Disease Improving Global Outcomes (KDIGO) risk and age categories.
Models were adjusted for age, sex, educational attainment, smoking and drinking status, body mass index, physical activity, triglycerides, low-density lipoprotein cholesterol, fasting blood glucose, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and residual systolic blood pressure. Interaction between diastolic blood pressure and KDIGO risk categories in associations with cardiovascular and renal events: *P* for interaction=0.025 (**A**); *P* for interaction=0.887 (**B**). Interaction between diastolic blood pressure and age categories in associations with cardiovascular and renal events: *P* for interaction <0.001 (**A**); *P* for interaction=0.243 (**B**).

trials, is needed to identify thresholds to initiate BP-lowering treatment in the CKD population, although such studies might prove to be challenging given that recent guidelines diverge at BP thresholds for drug initiation.

The current study has several limitations. First, serum creatinine and urinary ACR were measured once at the baseline examination and serum creatinine was measured again at the follow-up examination without subsequent confirmation. Although the confirmation of a persistent eGFR decline is important to exclude the acute fluctuation in eGFR levels, it proves difficult in a large and multicenter cohort population with serum creatinine levels measured centrally. Therefore, misclassification of renal events might exist. Second, the relatively short duration of follow-up limited the number of incident cardio-renal events and prevented further analysis based on individual components. In addition, hard renal outcomes such as end-stage renal disease and death due to renal causes were limited and ≥20% reduction in eGFR levels was added to define renal events. A more substantial reduction in eGFR levels should have been used but this was again prevented by a limited statistical power. Third, changes in BP levels and initiation of antihypertensive medications were not accounted for in this study. Fourth, despite the adjustment for multiple covariates in the Cox models, residual confounding is still a possibility. Fifth, although excluding participants with antihypertensive drug therapy was necessary in the current study to examine BP thresholds for drug initiation, this might have introduced selection bias. Finally, our findings may not be generalizable to other populations.

PERSPECTIVES

An SBP level ≥130 mm Hg and a DBP level ≥90 mm Hg were associated with significantly increased risks of cardiovascular and renal events in this nationwide, community-based, prospective cohort study of CKD participants. SBP/DBP >130/90 mm Hg might be considered as thresholds to initiate BP-lowering treatment in adults with CKD. More evidence is needed from large and long-term cohort studies to confirm the current findings and clinical trials testing different BP thresholds for treatment initiation in people with CKD are most warranted.

ARTICLE INFORMATION

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S. Wu, Y. Xu, Y. Bi, W. Wang, and G. Ning conceived and designed the study. S. Wu analyzed the data. M. Li and J. Lu verified the data. S. Wu, X. Tang, and G. Wang drafted the article. J. Lu, Y. Xu, M. Li, Y. Bi, and W. Wang revised the article. R. Zheng, J. Niu, L. Chen, Y. Huo, M. Xu, T. Wang, Z. Zhao, S. Wang, H. Lin, G. Qin, L. Yan, Q. Wan, L. Chen, L. Shi, R. Hu, X. Tang, Q. Su, X. Yu, Y. Qin, G. Chen, Z. Gao, G. Wang, F. Shen, Z. Luo, Y. Chen, Y. Zhang, C. Liu, Y. Wang, S. Wu, T. Yang, Q. Li, Y. Mu, J. Zhao, and Y. Bi collected the data and critical revised the article for important intellectual content. All authors agreed to be held accountable for all aspects of this work and approved the final version of the article. S. Wu and Y. Xu are guarantors of this work and take responsibility for the integrity of the data and accuracy of the data analysis. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors are grateful to all the staff members and participants from participating centers in the 4C study for data collection.

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Disclosures

None.

Supplemental Material

Figures S1–S8.
Tables S1–S3.

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