Hypertension

ORIGINAL ARTICLE

Associations of Long-Term Visit-to-Visit Blood Pressure Variability With Subclinical Kidney Damage and Albuminuria in Adulthood: a 30-Year Prospective Cohort Study

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BACKGROUND: Recent evidence indicates that long-term visit-to-visit blood pressure variability (BPV) may be associated with risk of cardiovascular disease. We, therefore, aimed to determine the potential associations of long-term BPV from childhood to middle age with subclinical kidney damage (SKD) and albuminuria in adulthood.

METHODS: Using data from the ongoing cohort of Hanzhong Adolescent Hypertension study, which recruited children and adolescents aged 6 to 18 years at baseline, we assessed BPV by SD and average real variability (ARV) for 30 years (6 visits). Presence of SKD was defined as estimated glomerular filtration rate between 30 and 60 mL/min per 1.73 m^2 or elevated urinary albumin-to creatinine ratio at least 30 mg/g. Albuminuria was defined as urinary albumin-to creatinine ratio ≥30 mg/g.

RESULTS: During 30 years of follow-up, of the 1771 participants, 204 SKD events occurred. After adjustment for demographic, clinical characteristics, and mean BP during 30 years, higher SD_{SBP}, ARV_{SBP}, SD_{DBP}, ARV_{DBP}, SD_{MAP}, ARV_{MAP}, and ARV_{PP} were significantly associated with higher risk of SKD. When we used cumulative exposure to BP from childhood to adulthood instead of mean BP as adjustment factors, results were similar. In addition, greater long-term BPV was also associated with the risk of albuminuria. Long-term BPV from childhood to middle age was associated with higher risk of SKD and albuminuria in adulthood, independent of mean BP or cumulative exposure to BP during follow-up.

CONCLUSIONS: Identifying long-term BPV from early age may assist in predicting kidney disease and cardiovascular disease in later life. **(*Hypertension*. 2022;79:1247–1256. DOI: 10.1161/HYPERTENSIONAHA.121.18658.)** • **Supplemental Material**

Key Words: albuminuria ■ blood pressure ■ cardiovascular diseases ■ cohort studies ■ kidney

Chronic kidney disease (CKD) is now recognized as a worldwide public health problem.[1,2] Patients with early stage CKD are generally asymptomatic, and most remain undiagnosed even in developed countries.[3] From its earliest stages and as it progressed to end-stage kidney disease, CKD is associated with an increasing risk of cardiovascular events and mortality.[1] Albuminuria is an early marker of vascular endothelial dysfunction

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NOVELTY AND RELEVANCE

What Is New?

Higher long-term blood pressure (BP) variability from childhood to adulthood is significantly associated with higher risk of subclinical kidney damage and albuminuria in adulthood.

What Is Relevant?

Long-term visit-to-visit BP variability is associated with the risk of cardiovascular disease, independent of mean BP levels.

Clinical/Pathophysiological Implications?

Long-term BP variability for 30 years from childhood to adulthood is associated with higher risk of subclinical kidney damage and albuminuria in adulthood, independent of mean BP or cumulative exposure to BP during follow-up. Identifying long-term BP variability from early age may assist in predicting kidney disease and cardiovascular disease in later life.

Nonstandard Abbreviations and Acronyms

ARV	average real variability
BPV	blood pressure variability
CKD	chronic kidney disease
CUM	cumulative exposure
CV	coefficient of variation
eGFR	estimated glomerular filtration rate
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MMD	maximum and minimum BP difference
ORs	odds ratio
PP	pulse pressure
SKD	subclinical kidney damage
uACR	urinary albumin-to creatinine ratio
VIM	BP variability independent of the mean

and kidney disease, which has been linked to progression to end-stage kidney disease, and increased cardiovascular complications and mortality.[4–7] Albuminuria is common in persons with specific diseases, such as diabetes or hypertension, and can also be detected those without these conditions.[8] Therefore, early detection and management of albuminuria and kidney dysfunction are of utmost importance.

The association between higher blood pressure (BP) and CKD has been well established.[9–11] In addition to average BP values, BP variability (BPV) may be associated with CKD.[12–14] BPV refers to the diurnal BP rhythm with nocturnal dipping, the pseudoperiodic variability, and the variability between BP measurements separated by minutes, hours, weeks, months, or years. The intraindividual fluctuation of BP is physiologically attributed to baroreflex, autonomic function, and response to challenge.[15,16] Several streams of evidence suggest that short-term BPV (eg, beat-to-beat and within 24 hours) is independently associated with end-organ damage and cardiovascular events.[17–19] However, the implications of long-term BPV (eg, day-by-day and visit-to-visit BPV) are less defined, particularly as it may affect kidney function.

Early life risk factors can increase the risk of CKD from childhood, independent of the risk profile of late adulthood.[20–22] Beginning in childhood, oscillations in BP may influence kidney function and initiate processes that result in subclinical kidney damage (SKD). A few studies have suggested that higher long-term visit-to-visit BPV is significantly associated with greater decline in kidney function.[14,23,24] However, this conclusion is based on cross-sectional studies conducted on middle-aged/older persons or on high-risk populations. Most importantly, little is known about the impact of long-term BPV—from childhood to adulthood—on the risk of developing SKD in later life.

In this study, we examine data obtained during a 30-year prospective cohort to determine long-term BPV from childhood to adulthood and to evaluate its association with the risk of developing SKD—including albuminuria—later in life.

METHODS

Study Cohort

The data that support the findings of this study are available from the corresponding author upon reasonable request. This cohort study used data from the Hanzhong Adolescent Hypertension Study; the design and participant selection of that study has been previously published.[20,21,25,26] Briefly, the study began in 1987 when 4623 school children were enrolled from 26 rural sites of 3 towns (Qili, Laojun, and Shayan) in Hanzhong, Shaanxi, China. During the baseline survey, the inclusion criteria were as follows: aged 6 to 18 years old; no chronic disease by medical records; the ability to communicate frequently in Mandarin; and volunteered to participate in this study. Participants were excluded if the participants or their parents/guardians were unwilling to participate, or if they had a chronic disease according to the clinical data or self-report. Follow-up examinations were conducted in 1989, 1992, 1995, 2005, 2013, and 2017, resulting in a maximum follow-up time of 30 years. Among those follow-up activities, we selected several participants to visit in 2005 and obtained BP and other

data from 436 individuals. Except for the visit in 2005, other follow-ups were large in scale and aimed to visit each individual who was enrolled in 1987. In this study, we used data at baseline and follow-up of 5 large follow-ups. The response rate was 77.7% (n=3592) in 1989 (visit 2), 84.8% (n=3918) in 1992 (visit 3), 82.1% (n=3794) in 1995 (visit 4), 65.3% (n=3018) in 2013 (visit 5), and 60.1% (n=2780) in 2017 (visit 6). No significant difference was observed between those who were followed and lost to follow-up (Table S1).

The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Code: XJTU1AF2015LSL-047). All participants in this study signed informed consent for each visit, and for those <18 years of age at baseline, consent of a parent/guardian was obtained. This study adheres to the principles of the Declaration of Helsinki, and all studies procedures were performed in accordance with institutional guidelines (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02734472).

Visit-to-Visit BP Variability

Participants were required to avoid coffee/tea, alcohol, cigarette smoking, and strenuous exercise for at least 30 minutes before BP measurement. BP was measured 3 times in a seated position on the right upper arm after a 5-minute rest, with a 2-minute interval between measurements. The average of 3 BP values was used in the analyses. BP was measured by trained and certified observers using standard mercury sphygmomanometer for the first 6 visits and electronic sphygmomanometer (Omron HBP-1100, Kyoto, Japan) in 2017 follow-up as previously described.[27–30] The mean arterial pressure (MAP) was calculated as DBP + (1/3×[SBP−DBP]). Pulse pressure (PP) was calculated as SBP−DBP.

For different BP phenotypes (SBP, DBP, MAP, and PP), we calculated the following indicators as BPV index: SD (SD_{SBP}, SD_{DBP}, SD_{MAP}, and SD_{PP}), BPV independent of the mean (VIM_{SBP}, VIM_{DBP}, VIM_{MAP}, and VIM_{PP}), coefficient of variation (CV_{SBP}, CV_{DBP}, CV_{MAP}, and CV_{PP}), maximum and minimum BP difference (MMD_{SBP}, MMD_{DBP}, MMD_{MAP}, and MMD_{PP}), and average real variability (ARV_{SBP}, ARV_{DBP}, ARV_{MAP}, and ARV_{PP}) across 6 visits. All of these measures have been used in previous studies of BPV.[12,23,31,32] ARV is the average absolute difference between successive BP measurements, and in contrast with SD and CV, it takes the order of the BP measurements into account.[33] Here, we only report BPV using SD and ARV because CV and MMD are strongly correlated with SD (r=0.87–0.98; both P<0.05, Tables S2 and S3). In addition, we also calculated mean BP from visit 1 to visit 6 ($mean_{SBP}$, $mean_{DBP}$, $mean_{MAP}$, and $mean_{PP}$) and cumulative exposure to BP from visit 1 to visit 6 (mm Hg×year; CUM_{SBP}, CUM_{DBP}, CUM_{MAP}, and CUM_{PP}) to use as adjusted variables. Figure 1 illustrates how each BP pattern is calculated.

Data on other factors, including social demographic survey, medical and family history, physical activity, and anthropometric measurements, were collected using standardized protocols described previously.[30,34–36]

Blood Biochemical Analyses

At the latest follow-up examination in 2017, fasting blood samples were obtained on the last day of each intervention period through peripheral venous puncture. Total cholesterol, triglycerides, LDL (low-density lipoprotein), HDL (high-density lipoprotein), serum uric acid, alanine aminotransferase, aspartate aminotransferase, serum creatinine, and fasting glucose levels were measured using an automatic biochemical analyzer (Hitachi, Tokyo, Japan) as described previously.[30,34–36]

Assessment of Albuminuria and Kidney Function

At the last follow-up in 2017, kidney function was assessed with estimated glomerular filtration rate (eGFR) and urinary albumin-to creatinine ratio (uACR). eGFR was calculated using the formula adapted from the Modification of Diet in Renal Disease equation on the basis of data from Chinese patients with CKD.[20,21,29] The specific formula is as follows: $eGFR=175\times serum\ creatinine^{-1.234}\times age^{-0.179}$ (×0.79 for girls/women), where serum creatinine concentration is in milligrams per deciliter and age is in years. Presence of SKD was defined as eGFR between 30 and 60 mL/min per 1.73 m^2 or elevated uACR of at least 30 mg/g as previously described.[20,21,29] Albuminuria was defined as uACR ≥30 mg/g.[37]

Definitions

Participants who reported continuous or cumulative smoking for 6 months or more during their lifetime were defined as cigarette smokers.[27] Physical inactivity was defined as having mild to moderate physical activity <3 hours per week. Hypertension was defined as SBP of ≥140 mm Hg, DBP ≥90 mm Hg or as the use of antihypertensive drugs according to participants' clinical data or self-report.[38] Diabetes was defined as fasting blood glucose at least 7.0 mmol/L, current use of antidiabetic medications or a previous history of diabetes.[39] Hyperlipidemia was defined as the occurrence of any one of the following 4 situations: hypertriglyceridemia (triglycerides ≥2.26 mmol/L), hypercholesterolemia (total cholesterol ≥6.22 mmol/L), high levels of LDL (≥4.14 mmol/L), or low levels of HDL (≤1.04 mmol/L).[40]

Statistical Analyses

All statistical analyses were performed with *R* statistical package (version 3.0.2). Data are expressed as means±SD for normally distributed values, as median (25th and 75th percentile) for non-normally distributed values, and as percentages. Differences between continuous variables were analyzed by Mann-Whitney *U* test and Kruskal-Wallis test. Categorical variables were analyzed by χ^2 tests. Correlation analysis was determined with the Pearson correlation coefficient.

Unadjusted and multivariable-adjusted logistic regression models were used to assess the association between long-term BPV and risk for new-onset SKD/albuminuria at visit 6. In the first step, we performed unadjusted analyses (model 1). In the second step, we added age (visit 1), sex, body mass index (BMI) as adjustment covariates (model 2). In the next step, we further adjusted for clinical characteristics at visit 6 (ie, smoking, physical activity level, heart rate, fasting glucose, serum uric acid, triglyceride, and total cholesterol) plus mean BP from visit 1 to visit 6 (model 3). In the last step, we further added cumulative exposure to BP through visit 1 to visit 6 (model 4). Two-side P values of <0.05 were considered significant in all analyses.

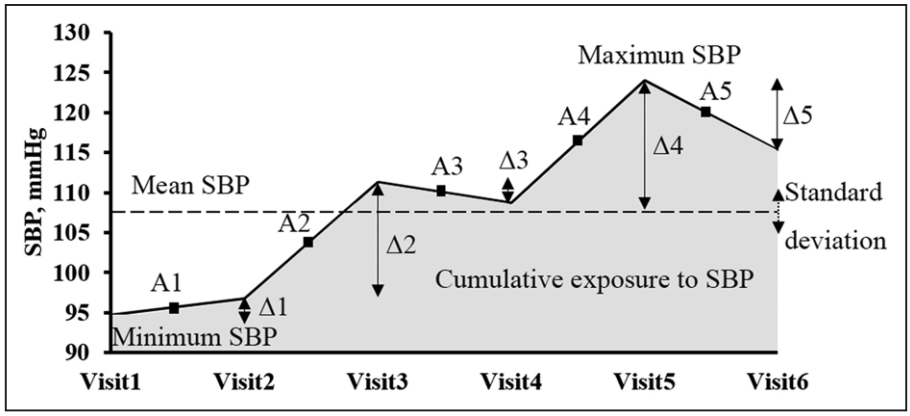

Figure 1. The example of individual follow-up data of systolic blood pressure (SBP) across 6 visits (Y_0–Y_{30}).
The absolute differences of BP between successive SBP measurements are shown as Δ1—Δ5. For example, Δ1 represents the difference in SBP between visit 1 and visit values. Average real variability is calculated as (Δ1+Δ2+Δ3+Δ4+Δ5)/5. The mean BP between successive BP measurements is shown as A1—A5. Cumulative exposure to BP was calculated as (A1×2 y+A2×3 y+A3×3 y+A4×18 y+A5×4) and is shown by the dotted area, representing in mm Hg×y. Mean SBP and SD were calculated from all 6 BP values from visit 1 to visit 6 for each individual, and coefficient of variation was calculated as SD/mean BP. The variability independent of the mean (VIM) of SBP was defined as the intraindividual SD of SBP across examinations $(M/x)^p$, where x is individual mean SBP across visits, M is the mean of individual mean SBP in the overall population, and p is the regression coefficient on the basis of regressing the natural logarithm of SD on the natural logarithm of the multiplication of x and M.

RESULTS

Association of Long-Term BPV From Childhood to Middle Age With SKD in Adulthood

Among the 2780 participants enrolled as of 2017, 1771 were selected for final analysis because we excluded those with at least 2 missing BP measurements (n=447), or missing outcome measures and other critical covariates at visit 6 (n=562; a flowchart of the participants' inclusion is shown in Figure 2). No significant differences regarding baseline characteristics were observed between those who included and excluded in the final

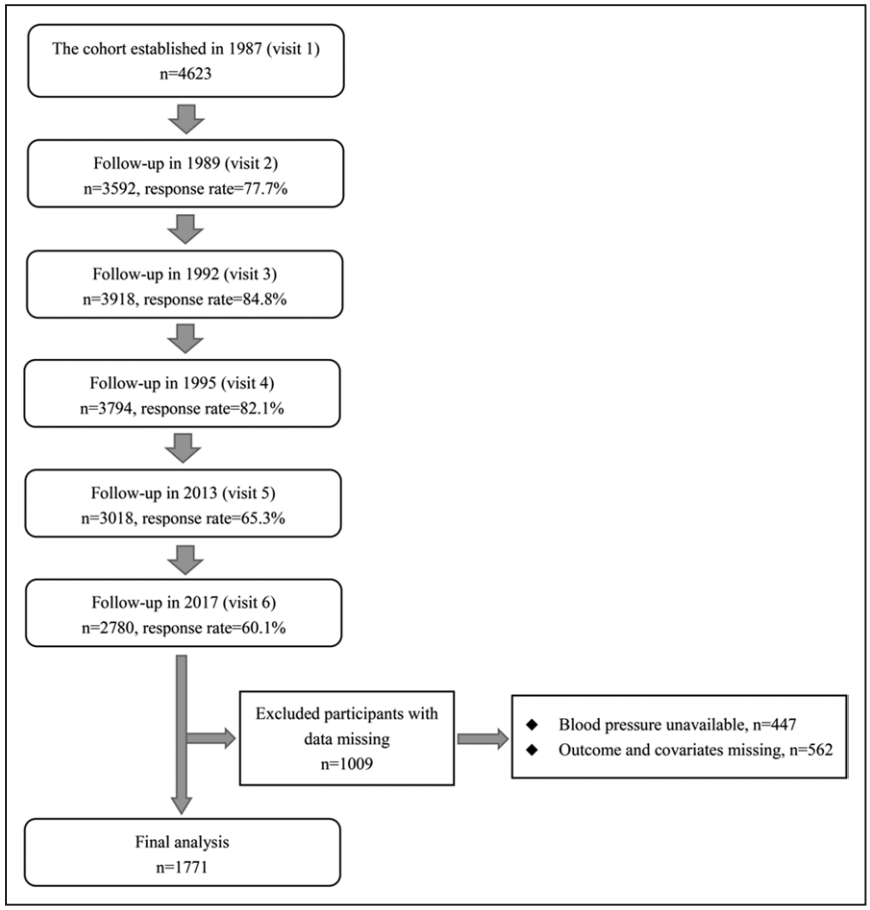

Figure 2. Flow diagram showing the selection of the study population.

analysis (Table S4). As shown in Table 1, no significant differences were observed in the age, BMI, bust, heart rate, SBP, DBP, and MAP in 1987 between participants with and without SKD (P>0.05). In comparison to participants without SKD, SKD participants had higher BMI, WHR, heart rate, fasting glucose, triglycerides, total cholesterol, serum uric acid, uACR, and visit-to-visit BPV, and the prevalence of hypertension, diabetes, hyperlipidemia, and smoking was also higher in middle age (Table 1). Similar tendencies were observed for eGFR categories (30–59, 60–89, ≥90 mL/min per 1.73 m^2) and CKD risk stratification (low risk, moderately increased risk and high risk) based on the KDIGO 2020 clinical practice guideline for CKD (Tables S5 and S6).[41]

Over a follow-up period of 30 years, 204 participants developed SKD and the incident rate was 11.5%. Table 2 shows the associations of SD_{BP} and ARV_{BP} from childhood to adulthood with risk for SKD in adulthood. Higher SD_{BP} and ARV_{BP} were associated with higher risk of SKD (model 1). Adjustment for demographic variables did not change the associations (model 2), with adjustment also for clinical characteristics at visit 6, and mean BP from (visit 1–6; model 3; odds ratio [ORs] [95% CIs] were 1.14 [1.06–1.23] for SD_{SBP}, 1.15 [1.08–1.21] for ARV_{SBP}, 1.12 [1.06–1.17] for SD_{DBP} and 1.16 [1.08–1.25] for ARV_{DBP}, 1.12 [1.07–1.17] for SD_{MAP} and 1.18 [1.10–1.27] for ARV_{MAP}; model 3). When we used cumulative exposure to BP (visit 1–6) instead of mean BP (visit 1–6) as adjustment factors, results were similar (model 4).

Association of Long-Term BPV From Childhood to Middle Age With Albuminuria in Adulthood

Albuminuria is a marker of early kidney damage and is associated with the development of CKD and increases cardiovascular complications and mortality.[4–7] We examined the association of long-term BPV from childhood to middle age with the risk of albuminuria. Of the 2780 participants followed up in 2017 (visit 6), 441 were excluded because of 2 or more missing BP measurements during the earlier follow-ups and 662 because of missing outcome or adjustment variables at visit 6, leaving 1671 for this analysis. No significant differences in baseline characteristics were noted between those who included and excluded in this study (Table S7). As shown in Table S8, no significant difference was observed between the participants with and without albuminuria in age, BMI, bust, heart rate, HDL and BP in 1987 (P>0.05). In 2017, participants with albuminuria had higher BMI, heart rate, fasting glucose, total cholesterol, triglycerides, serum uric acid, uACR, and visit-to-visit BPV. Diabetes, hypertension, hyperlipidemia were more common in those with albuminuria compared with those without albuminuria (Table S8).

At the year 30 follow-up visit, 189 participants (11.3%) had developed albuminuria. As presented in Table 3, after adjusting for demographic, clinical characteristics at visit 6 and mean BPs from visit 1 to visit 6, higher SD_{SBP}, ARV_{SBP}, SD_{DBP}, ARV_{DBP}, ARV_{MAP}, and ARV_{PP} were significantly associated with higher risk of albuminuria (ORs [95% CIs] were 1.07 [1.03–1.10], 1.13 [1.06–1.20], 1.11 [1.06–1.17], 1.14 [1.06–1.23], 1.18 [1.09–1.27], and 1.08 [1.01–1.17], respectively; model 3). Similar results were obtained when we used cumulative exposure to BP (visit 1–6) instead of mean BP (visit 1–6) as adjustment factors (model 4).

Sensitivity Analysis

Several sensitivity analyses were performed. First, when we excluded individuals with antihypertensive, hypoglycemic, and lipid-lowering medications for SKD (n=367) and albuminuria (n=334), similar results were obtained (Tables S9 and S10). In addition, to further examine the effects of BPV in early life on kidney function in midlife, we identified BPV from childhood to adolescence (1987–1995) and BPV from adolescence to youth (1989–2005), and the associations of SD_{BP} and ARV_{BP} with SKD or albuminuria remained significant (Tables S11 through S14).

DISCUSSION

In a 30-year prospective cohort from childhood to adulthood, we found that greater long-term visit-to-visit SBP, DBP, and MAP variability was associated with SKD incidence in adulthood independent of the mean BP levels or cumulative BP exposure. Our study observations lend support to a distinct association of visit-to visit BP variability with increased risk for developing CKD because of the associations with adverse kidney function.

To our knowledge, this study is the first to comprehensively investigate the association between long-term BPV and SKD incidence. SKD is considered to be an early stage of CKD, although previous studies have shown strong associations between long-term BPV and the risk of CKD, the results are inconsistent. In a large cohort of Japanese adults aged 40 to 74 years, higher long-term BPV during 3 years was found to be associated with risk of onset of CKD (ORs, 1.06–1.15).[23] Whittle et al[12] also showed that higher visit-to-visit BPV was associated with higher risk of end-stage kidney disease and a 50% eGFR decline in a large cohort of hypertensive adults aged ≥55 years old over 3.5 years of follow-up (hazard ratio [95% CI] was 2.05 [1.25–3.36]). In addition, Chia et al[14] conducted a relatively long duration of follow-up of 15 years and showed that higher long-term visit-to-visit BPV was significantly associated with greater decline in kidney function in 825 hypertensive patients aged ≥30 years at baseline (SD: r=−0.16; CV: r=−0.14).[14] By contrast, Yokota et al[13] failed to show the relationship between long-term BPV over 32 months

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Table 1. Demographic and Clinical Characteristics Categorized by SKD Status

Characteristics	Total (n=1771)	Participants without SKD (n=1567)	Participants with SKD (n=204)	*P* value
Age in 1987, y	13.0 (10.0–15.0)	13.0 (10.0–15.0)	12.0 (10.0–15.0)	0.771
BMI in 1987, kg/m^2	16.1 (14.9–18.0)	16.1 (14.9–18.1)	15.9 (15.0–18.0)	0.853
Bust in 1987, cm	62.0 (58.0–70.0)	63.0 (58.0–70.0)	61.0 (56.3–69.6)	0.134
Heart rate in 1987, beats/min	78.0 (72.0–84.0)	78.0 (72.0–84.0)	80.0 (72.0–84.0)	0.066
SBP in 1987, mm Hg	103.3 (96.7–110.7)	103.3 (96.7–110.7)	104.6 (98.2–111.1)	0.198
DBP in 1987, mm Hg	64.7 (60.0–71.0)	64.7 (60.0–70.7)	64.7 (60.0–72.0)	0.796
MAP in 1987, mm Hg	78.0 (71.87–84.2)	77.8 (71.8–84.2)	79.1 (72.2–84.1)	0.552
BMI in 2017, kg/m^2	23.8 (21.9–26.0)	23.6 (21.8–25.7)	25.4 (23.0–27.5)	<0.001
WHR in 2017	0.92 (0.87–0.97)	0.92 (0.87–0.96)	0.95 (0.89–0.99)	<0.001
Heart rate in 2017, beats/min	73.0 (67.0–80.0)	73.0 (66.0–80.0)	77.0 (71.0–85.0)	<0.001
Female (%)	762 (43.0)	666 (42.5)	96 (47.1)	0.245
Hypertension (%)	213 (12.1)	161 (10.3)	52 (25.6)	<0.001
Diabetes (%)	55 (3.1)	37 (2.4)	18 (8.9)	<0.001
Hyperlipidemia (%)	171 (9.7)	141 (9.0)	30 (14.8)	0.013
Smoking (%)	770 (43.6)	676 (43.2)	94 (46.3)	0.448
Marital status (%)				0.27
Unmarried or other	26 (1.5)	25 (1.7)	1 (0.5)	
Married	1639 (97.0)	1454 (96.8)	185 (98.9)	
Divorced	24 (1.4)	23 (1.5)	1 (0.5)	
Physical activities (%)				0.715
Vigorous physical activity	43 (2.4)	36 (2.3)	7 (3.5)	
Moderate physical activity	65 (3.7)	59 (3.8)	6 (3.0)	
Mild physical activity	948 (53.9)	838 (53.8)	110 (54.5)	
No activity	704 (40.0)	625 (40.1)	79 (39.1)	
Fasting glucose, mmol/L	4.57 (4.28–4.91)	4.56 (4.27–4.88)	4.68 (4.30–5.16)	<0.001
Triglycerides, mmol/L	1.35 (0.96–1.95)	1.33 (0.94–1.89)	1.64 (1.06–2.48)	<0.001
Total cholesterol, mmol/L	4.50 (4.04–4.99)	4.48 (4.03–4.97)	4.63 (4.13–5.16)	0.008
LDL, mmol/L	2.50 (2.12–2.90)	2.49 (2.12–2.88)	2.54 (2.15–3.00)	0.246
HDL, mmol/L	1.14 (0.99–1.33)	1.14 (0.99–1.33)	1.12 (0.95–1.27)	0.019
Serum uric acid, mmol/L	280.7 (225.9–336.0)	278.8 (225.5–333.0)	292.0 (232.8–359.56)	0.016
Serum creatinine, mmol/L	76.0 (67.1–86.3)	76.0 (67.1–86.2)	76.2 (67.4–89.9)	0.181
eGFR, mL/min per 1.73 m^2	96.9 (86.6–110.1)	97.1 (87.6–110.0)	93.9 (80.5–111.2)	0.016
uACR, mg/g	8.73 (5.70–15.4)	7.97 (5.37–12.3)	51.7 (35.0–134.7)	<0.001
Blood pressure variability				
SD_{SBP}, mm Hg	11.3 (8.6–15.1)	11.0 (8.43–14.6)	14.6 (10.5–19.4)	<0.001
ARV_{SBP}, mm Hg	3.54 (1.73–5.86)	3.40 (1.61–5.61)	5.21 (2.70–7.31)	<0.001
VIM_{SBP}, mm Hg	1.79×10^{-6} (9.0×10^{-7}–3.25×10^{-6})	1.71×10^{-6} (9.22×10^{-7}–3.05×10^{-6})	2.71×10^{-6} (1.49×10^{-6}–4.95×10^{-6})	<0.001
MMD_{SBP}, mm Hg	29.3 (21.4–38.7)	28.7 (21.2–37.7)	36.5 (27.3–50.8)	<0.001
$Mean_{SBP}$, mm Hg/y	112.8 (106.9–119.2)	112.4 (106.6–118.6)	117 (111.0–124.6)	<0.001
CUM_{SBP}, mm Hg×y	6960.0 (6560.1–7382.5)	6930.7 (6542.1–7351.3)	7151.4 (6777.2–7781.5)	<0.001
SD_{DBP}, mm Hg	9.10 (6.89–11.8)	8.92 (6.75–11.3)	12.1 (8.52–15.6)	<0.001
ARV_{DBP}, mm Hg	2.40 (0.67–3.94)	2.21 (0.61–3.71)	3.60 (2.01–5.97)	<0.001
VIM_{DBP}, mm Hg	3.14×10^{-4} (2.02×10^{-4}–4.66×10^{-4})	2.99×10^{-4} (1.93×10^{-4}–4.42×10^{-4})	4.57×10^{-4} (2.69×10^{-4}–6.77×10^{-4})	<0.001
MMD_{DBP}, mm Hg	22.7 (17.0–30.6)	22.6 (16.7–29.3)	29.7 (19.6–40.2)	<0.001
$Mean_{DBP}$, mm Hg/y	71.2 (67.1–75.7)	70.8 (66.9–75.1)	75.2 (69.5–80.5)	<0.001
CUM_{DBP}, mm Hg×year	4438.2 (4162.2–4731.0)	4413.1 (4146.5–4691.3)	4681.6 (4364.1–5040.9)	<0.001
SD_{MAP}, mm Hg	9.21 (6.92–12.2)	8.93 (6.73–11.6)	12.5 (9.22–16.3)	<0.001
ARV_{MAP}, mm Hg	2.72 (1.07–4.42)	2.59 (0.98–4.21)	4.23 (2.27–6.39)	<0.001

(*Continued*)

Table 1. Continued

Characteristics	Total (n=1771)	Participants without SKD (n=1567)	Participants with SKD (n=204)	*P* value
VIM_{MAP}, mm Hg	4.53×10^{-6} (2.45×10^{-6}–8.22×10^{-6})	4.29×10^{-6} (2.34×10^{-6}–7.54×10^{-6})	7.57×10^{-6} (4.18×10^{-6}–1.45×10^{-5})	<0.001
MMD_{MAP}, mm Hg	23.4 (17.3–31.0)	22.9 (17.0–30.0)	29.6 (20.0–40.4)	<0.001
$Mean_{MAP}$, mm Hg/y	85.1 (80.7–89.7)	84.8 (80.5–89.1)	89.4 (83.6–94.4)	<0.001
CUM_{MAP}, mm Hg×y	5278.9 (4977.6–5614.3)	5243.4 (4965.0–5559.7)	5532.1 (5177.2–5905.0)	<0.001
SD_{PP}, mm Hg	7.38 (5.66–9.60)	7.30 (5.64–9.50)	8.10 (6.01–10.2)	0.014
ARV_{PP}, mm Hg	1.40 (0.19–2.79)	1.33 (0.20–2.73)	1.87 (0.04–3.10)	0.264
VIM_{PP}, mm Hg	1.29×10^{-2} (9.63×10^{-3}–1.74×10^{-2})	1.29×10^{-2} (9.55×10^{-3}–1.74×10^{-2})	1.37×10^{-2} (1.07×10^{-2}–1.85×10^{-2})	0.035
MMD_{PP}, mm Hg	19.3 (14.5–25.4)	19.3 (14.3–25.3)	20.7 (15.3–28.9)	0.002
$Mean_{PP}$, mm Hg/y	41.3 (38.1–45.3)	41.2 (38.0–45.2)	42.0 (39.0–45.8)	0.091
CUM_{PP}, mm Hg×y	2497.7 (2259.0–2752.3)	2498.3 (2259.1–2754.8)	2472.1 (2258.3–2708.1)	0.932

Non-normally distributed variables are expressed as the median (interquartile range). All other values are expressed as mean±SD or n, %. ARV indicates average real variability; BMI, body mass index; CUM, cumulative exposure to BP from visit 1 to visit 6; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; mean, mean BP from visit 1 to visit 6; MMD, maximum and minimum BP difference; SBP, systolic blood pressure; SKD, subclinical kidney damage; uACR, urinary albumin-to-creatinine ratio; VIM, BP variability independent of the mean; and WHR, waist-to-hip ratio.

and kidney function decline in 69 diabetic nephropathy patients with mean age of 66.9 years. Meanwhile in an elderly population (median age: 66.3 years), Mancia et al[42] showed that visit-to-visit SBP variability had no major predictive value for the risk of renal outcomes over 2 years of follow-up. However, these prior studies were conducted on middle-aged/older persons or high-risk populations, suggesting that BPV itself could be influenced substantially by comorbidities. Our prospective cohort study provides a unique opportunity to study these issues, because it enrolled only children and adolescents (6–18 years) without comorbidities, which representing the BP change of the population in the 30 years of reform and opening up in China. Furthermore, these studies have a shorter duration of follow-up and small sample size, which may not adequately show the effect of BPV on kidney function decline. In our analysis, we noted associations between greater visit-to-visit BP variability and incident SKD (ORs, 1.06–1.18), which may precede CKD.

To our knowledge, this is the first study to investigate the relationship between early life BPV and albuminuria in adulthood. We found that greater long-term visit-to-visit SBP variability through childhood and into adulthood was associated with a higher risk for albuminuria by middle age. In 3 small studies that focused on day-to day home BP variability, higher home BP variability was associated with increased uACR.[43–45] Taking this finding a step further, Noshad et al[46] showed that visit-to-visit variability of SBP was an independent risk factor for development of albuminuria in 194 diabetic patients with a mean age of 51.7 years after 2.6 years of follow-up

Table 2. Unadjusted and Multivariable-Adjusted Linear Regression Models to Examine the Relationship Between Long-Term BPV and Risk of SKD (n=1771)

	Model 1 (unadjusted)	Model 2	Model 3	Model 4
Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
SD_{SBP}	1.16 (1.11–1.20)*	1.14 (1.08–1.20)*	1.14 (1.06–1.23)*	1.16 (1.08–1.26)*
ARV_{SBP}	1.21 (1.16–1.26)*	1.18 (1.12–1.25)*	1.15 (1.08–1.21)*	1.15 (1.09–1.22)*
SD_{DBP}	1.15 (1.11–1.19)*	1.15 (1.10–1.20)*	1.12 (1.06–1.17)*	1.11 (1.06–1.17)*
ARV_{DBP}	1.24 (1.18–1.31)*	1.22 (1.14–1.31)*	1.16 (1.08–1.25)*	1.15 (1.07–1.24)*
SD_{MAP}	1.15 (1.12–1.18)*	1.15 (1.10–1.19)*	1.12 (1.07–1.17)*	1.12 (1.07–1.18)*
ARV_{MAP}	1.26 (1.20–1.33)*	1.24 (1.16–1.33)*	1.18 (1.10–1.27)*	1.18 (1.10–1.27)*
SD_{PP}	1.08 (1.04–1.13)*	1.06 (1.01–1.12)*	1.06 (1.00–1.12)	1.06 (1.01–1.12)†
ARV_{PP}	1.15 (1.08–1.23)*	1.12 (1.03–1.21)*	1.11 (1.03–1.21)*	1.11 (1.03–1.21)*

As adjustment factors, model 2 includes demographic variables (age and sex at visit 1, and BMI in visit 6); model 3 includes clinical characteristics at visit 6 (ie, smoking, physical activity level, heart rate, fasting glucose, SUA, triglyceride, and total cholesterol) plus mean BP from visit 1 to visit 6; and model 4 includes demographic variables + clinical characteristics at visit 6 + cumulative exposure to BP from visit 1 to visit 6. ARV indicates average real variability; BMI, body mass index; BPV, blood pressure variability; DBP, diastolic blood pressure; MAP, mean blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; SKD, subclinical kidney damage; and SUA, serum uric acid.

Statistical significance was defined as

*$P<0.001$

†$P<0.05$.

Table 3. Unadjusted and Multivariable-Adjusted Linear Regression Models to Examine the Relationship Between Long-Term BPV and Risk of Albuminuria (n=1671)

	Model 1 (unadjusted)	Model 2	Model 3	Model 4
Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
SD_{SBP}	1.11 (1.08–1.14)*	1.09 (1.05–1.12)*	1.07 (1.03–1.10)*	1.07 (1.03–1.11)*
ARV_{SBP}	1.21 (1.16–1.27)*	1.17 (1.11–1.23)*	1.13 (1.06–1.20)*	1.13 (1.07–1.20)*
SD_{DBP}	1.16 (1.11–1.19)*	1.14 (1.09–1.20)*	1.11 (1.06–1.17)*	1.11 (1.05–1.17)*
ARV_{DBP}	1.25 (1.18–1.32)*	1.21 (1.12–1.30)*	1.14 (1.06–1.23)*	1.14 (1.05–1.23)*
SD_{MAP}	1.09 (1.05–1.13)*	1.06 (1.01–1.12)*	1.05 (0.99–1.11)	1.04 (0.99–1.10)
ARV_{MAP}	1.27 (1.21–1.34)*	1.23 (1.14–1.31)*	1.18 (1.09–1.27)*	1.16 (1.07–1.25)†
SD_{PP}	1.15 (1.11–1.18)*	1.14 (1.09–1.18)*	1.10 (1.05–1.16)	1.12 (1.07–1.17)
ARV_{PP}	1.16 (1.09–1.24)*	1.10 (1.01–1.19)†	1.08 (1.01–1.17)†	1.10 (1.01–1.20)†

As adjustment factors, model 2 includes demographic variables (age and sex at visit 1, and BMI in visit 6); model 3 includes clinical characteristics at visit 6 (ie, smoking, physical activity level, heart rate, fasting glucose, SUA, triglyceride, and total cholesterol) plus mean BP from visit 1 to visit 6; and model 4 includes demographic variables + clinical characteristics at visit 6 + cumulative exposure to BP from visit 1 to visit 6. ARV indicates average real variability; BMI, body mass index; BPV, blood pressure variability; DBP, diastolic blood pressure; MAP, mean blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure; and SUA, serum uric acid.

Statistical significance was defined as

*$P<0.001$

†$P<0.05$.

(hazard ratio, 2.40 [95% CI, 1.07–5.38]). Our observations add to the scientific literature by providing data on long-term BP variability in a community-based sample of detailed assessment of uACR. In the present study, we confirmed the importance of BPV and showed that the BP variations originating from childhood, puberty, adulthood, to middle age was associated with albuminuria risk in later life (ORs, 1.04–1.16). Albuminuria is a marker not only for deterioration of kidney function but also for the risk of endothelial dysfunction. It has been established to provide incremental prognostic value for cardiovascular outcomes.[4,5] Our study observations are notable because albuminuria is a strong predictor of CKD and cardiovascular complications.[4,47,48]

The biological mechanisms underlying the association of long-term BPV with SKD remain uncertain. Higher BPV may lead to increased oscillatory shear stress to the vascular endothelium, potentially contributing to early atherosclerosis (eg, increased expression of adhesion molecules, prooxidant processes, and NO synthase reduction) more than steady blood flow.[49,50] Some experimental studies have suggested that higher BPV with unchanged average BP induced afferent and intralobular arteriole remodeling (eg, vascular smooth muscle cells proliferation and extracellular matrix deposition) and resultant patchy and focal sclerotic lesions consisting of glomerular and tubular atrophy and surrounding interstitial fibrosis.[51,52] In our study, higher long-term BPV was associated with risk of both albuminuria and SKD, this may indicate that higher BPV is an initiating factor precipitating kidney injury. Reverse causality, that is, kidney dysfunction preceding higher BPV, should also be a consideration. In the present study, we further showed that the strength of relationships (odds ratios) between BPV and kidney damage in our young cohort was similar to that of older populations with relatively short follow-ups in previous studies.[12,14,23,46] Therefore, metabolic abnormalities coexisting with higher BPV (eg, obesity and glycometabolic decompensation) may contribute to hyperfiltration and, finally, to incidence of SKD (primarily albuminuria) and its progression.[53] Further etiopathological studies of long-term BPV are warranted.

The current study has several strengths. First, a large prospective cohort were followed over 30 years, which represented the BP changes after China's reform and opening up. This cohort includes children and adolescents longitudinally followed as they transitioned from childhood to middle age, which provided us unique opportunity to investigate the effect of long-term BPV on premature kidney damage. Second, subclinical kidney outcomes were collected by a panel of physicians using detailed evaluation criteria, high retention, and the standardized data collection protocols and rigorous quality control. Several limitations are worth noting. Antihypertensive medication use, drug dose or type, and medication nonadherence may be associated with BP variability. This concern is partially mitigated since the associations remained significant when participants receiving BP-lowering medications were excluded. Due to the relatively small number of mid-life CKD events, we were not able to assess associations with CKD. Last, our findings may not be applicable to all groups because all the participants were Han Chinese from northern China and the cohort lacked ethnic and racial heterogeneity.

PERSPECTIVES

The present study provided a clinical implication of BPV throughout early life on kidney function in adulthood. Our results emphasize the importance of focusing not only on

BP values alone but also on visit-to-visit BPV to identify children and adolescents who may be at risk for developing worse kidney function later. CKD is often asymptomatic but progressive, and thus we need to pay attention to those who have higher long-term BPV to detect SKD as early as possible and to prevent its adverse consequences, such as cardiovascular disease and end-stage kidney disease.

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Disclosures

None.

REFERENCES

1. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol.* 2004;15:1307–1315. doi: 10.1097/01.asn.0000123691.46138.e2
2. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, Levin A. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet.* 2013;382:158–169. doi: 10.1016/S0140-6736(13)60439-0
3. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications. *Kidney Int Suppl.* 2005;(98):S7–S10. doi: 10.1111/j.1523-1755.2005.09801.x
4. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ; European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol.* 2004;33:189–198. doi: 10.1093/ije/dyh008
5. Vlek AL, van der Graaf Y, Spiering W, Algra A, Visseren FL; SMART study group. Cardiovascular events and all-cause mortality by albuminuria and decreased glomerular filtration rate in patients with vascular disease. *J Intern Med.* 2008;264:351–360. doi: 10.1111/j.1365-2796.2008.01970.x
6. Martens RJH, Houben AJHM, Kooman JP, Berendschot TTJM, Dagnelie PC, van der Kallen CJH, Kroon AA, Leunissen KML, van der Sande FM, Schaper NC, et al. Microvascular endothelial dysfunction is associated with albuminuria: the Maastricht Study. *J Hypertens.* 2018;36:1178–1187. doi: 10.1097/HJH.0000000000001674
7. Huang MJ, Wei RB, Zhao J, Su TY, Li QP, Yang X, Chen XM. Albuminuria and Endothelial Dysfunction in Patients with Non-Diabetic Chronic Kidney Disease. *Med Sci Monit.* 2017;23:4447–4453. doi: 10.12659/msm.903660
8. Sarafidis PA, Bakris GL. Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. *Nephrol Dial Transplant.* 2006;21:2366–2374. doi: 10.1093/ndt/gfl309
9. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. *N Engl J Med.* 1996;334:13–18. doi: 10.1056/NEJM199601043340103
10. Yano Y, Fujimoto S, Sato Y, Konta T, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, et al. Association between prehypertension and chronic kidney disease in the Japanese general population. *Kidney Int.* 2012;81:293–299. doi: 10.1038/ki.2011.346
11. Hill GS. Hypertensive nephrosclerosis. *Curr Opin Nephrol Hypertens.* 2008;17:266–270. doi: 10.1097/MNH.0b013e3282f88a1f
12. Whittle J, Lynch AI, Tanner RM, Simpson LM, Davis BR, Rahman M, Whelton PK, Oparil S, Muntner P. Visit-to-visit variability of BP and CKD outcomes: results from the ALLHAT. *Clin J Am Soc Nephrol.* 2016;11:471–480. doi: 10.2215/CJN.04660415
13. Yokota K, Fukuda M, Matsui Y, Kario K, Kimura K. Visit-to-visit variability of blood pressure and renal function decline in patients with diabetic chronic kidney disease. *J Clin Hypertens (Greenwich).* 2014;16:362–366. doi: 10.1111/jch.12293
14. Chia YC, Lim HM, Ching SM. Long-term visit-to-visit blood pressure variability and renal function decline in patients with hypertension over 15 years. *J Am Heart Assoc.* 2016;5:e003825. doi: 10.1161/JAHA.116.003825
15. Armitage P, Fox W, Rose GA, Tinker CM. The variability of measurements of casual blood pressure. II. Survey experience. *Clin Sci.* 1966;30:337–344.
16. Clark EG, Glock CY, Schweitzer MD, Vought RL. Studies in hypertension. II. Variability of daily blood pressure measurements in the same individuals over a three-week period. *J Chronic Dis.* 1956;4:469–476.
17. Palatini P, Saladini F, Mos L, Fania C, Mazzer A, Cozzio S, Zanata G, Garavelli G, Biasion T, Spinella P, et al. Short-term blood pressure variability outweighs average 24-h blood pressure in the prediction of cardiovascular events in hypertension of the young. *J Hypertens.* 2019;37:1419–1426. doi: 10.1097/HJH.0000000000002074
18. Chowdhury EK, Wing LMH, Jennings GLR, Beilin LJ, Reid CM; ANBP2 Management Committee. Visit-to-visit (long-term) and ambulatory (short-term) blood pressure variability to predict mortality in an elderly hypertensive population. *J Hypertens.* 2018;36:1059–1067. doi: 10.1097/HJH.0000000000001652
19. Hsu PF, Cheng HM, Wu CH, Sung SH, Chuang SY, Lakatta EG, Yin FC, Chou P, Chen CH. High short-term blood pressure variability predicts long-term cardiovascular mortality in untreated hypertensives but not in normotensives. *Am J Hypertens.* 2016;29:806–813. doi: 10.1093/ajh/hpw002
20. Zheng W, Mu J, Chu C, Hu J, Yan Y, Ma Q, Lv Y, Xu X, Wang K, Wang Y, et al. Association of blood pressure trajectories in early life with subclinical renal damage in middle age. *J Am Soc Nephrol.* 2018;29:2835–2846. doi: 10.1681/ASN.2018030263
21. Yuan Y, Chu C, Zheng WL, Ma Q, Hu JW, Wang Y, Yan Y, Liao YY, Mu JJ. Body mass index trajectories in early life is predictive of cardiometabolic risk. *J Pediatr.* 2020;219:31–37.e6. doi: 10.1016/j.jpeds.2019.12.060
22. Silverwood RJ, Pierce M, Hardy R, Thomas C, Ferro C, Savage C, Sattar N, Kuh D, Nitsch D; National Survey of Health and Development Scientific and Data Collection Teams. Early-life overweight trajectory and CKD in the 1946 British birth cohort study. *Am J Kidney Dis.* 2013;62:276–284. doi: 10.1053/j.ajkd.2013.03.032
23. Yano Y, Fujimoto S, Kramer H, Sato Y, Konta T, Iseki K, Iseki C, Moriyama T, Yamagata K, Tsuruya K, et al. Long-term blood pressure variability, new-onset diabetes mellitus, and new-onset chronic kidney disease in the Japanese general population. *Hypertension.* 2015;66:30–36. doi: 10.1161/HYPERTENSIONAHA.115.05472
24. McMullan CJ, Lambers Heerspink HJ, Parving HH, Dwyer JP, Forman JP, de Zeeuw D. Visit-to-visit variability in blood pressure and kidney and cardiovascular outcomes in patients with type 2 diabetes and nephropathy:

a post hoc analysis from the RENAAL study and the Irbesartan Diabetic Nephropathy Trial. *Am J Kidney Dis.* 2014;64:714–722. doi: 10.1053/j.ajkd.2014.06.008
25. Yan Y, Zheng W, Ma Q, Chu C, Hu J, Wang K, Liao Y, Chen C, Yuan Y, Lv Y, et al. Child-to-adult body mass index trajectories and the risk of subclinical renal damage in middle age. *Int J Obes (Lond).* 2021;45:1095–1104. doi: 10.1038/s41366-021-00779-5
26. Liao YY, Chu C, Wang Y, Zheng WL, Ma Q, Hu JW, Yan Y, Wang KK, Yuan Y, Chen C, et al. Sex differences in impact of long-term burden and trends of body mass index and blood pressure from childhood to adulthood on arterial stiffness in adults: A 30-year cohort study. *Atherosclerosis.* 2020;313:118–125. doi: 10.1016/j.atherosclerosis.2020.10.003
27. Wang Y, Hu JW, Qu PF, Wang KK, Yan Y, Chu C, Zheng WL, Xu XJ, Lv YB, Ma Q, et al. Association between urinary sodium excretion and uric acid, and its interaction on the risk of prehypertension among Chinese young adults. *Sci Rep.* 2018;8:7749. doi: 10.1038/s41598-018-26148-3
28. Wang Y, Chu C, Wang KK, Hu JW, Yan Y, Lv YB, Cao YM, Zheng WL, Dang XL, Xu JT, et al. Effect of salt intake on plasma and urinary uric acid levels in chinese adults: an interventional trial. *Sci Rep.* 2018;8:1434. doi: 10.1038/s41598-018-20048-2
29. Wang Y, Chen C, Yan Y, Yuan Y, Wang KK, Chu C, Hu JW, Ma Q, Liao YY, Fu BW, et al. Association of uric acid in serum and urine with subclinical renal damage: Hanzhong Adolescent Hypertension Study. *PLoS One.* 2019;14:e0224680. doi: 10.1371/journal.pone.0224680
30. Wang Y, Yuan Y, Gao WH, Yan Y, Wang KK, Qu PF, Hu JW, Chu C, Wang LJ, Gao K, et al. Predictors for progressions of brachial-ankle pulse wave velocity and carotid intima-media thickness over a 12-year follow-up: Hanzhong Adolescent Hypertension Study. *J Hypertens.* 2019;37:1167–1175. doi: 10.1097/HJH.0000000000002020
31. Nwabuo CC, Yano Y, Moreira HT, Appiah D, Vasconcellos HD, Aghaji QN, Viera A, Rana JS, Shah RV, Murthy VL, et al. Association between visit-to-visit blood pressure variability in early adulthood and myocardial structure and function in later life. *JAMA Cardiol.* 2020;5:795–801. doi: 10.1001/jamacardio.2020.0799
32. Yano Y, Ning H, Allen N, Reis JP, Launer LJ, Liu K, Yaffe K, Greenland P, Lloyd-Jones DM. Long-term blood pressure variability throughout young adulthood and cognitive function in midlife: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Hypertension.* 2014;64:983–988. doi: 10.1161/HYPERTENSIONAHA.114.03978
33. Hastie CE, Jeemon P, Coleman H, McCallum L, Patel R, Dawson J, Sloan W, Meredith P, Jones GC, Muir S, et al. Long-term and ultra long-term blood pressure variability during follow-up and mortality in 14,522 patients with hypertension. *Hypertension.* 2013;62:698–705. doi: 10.1161/HYPERTENSIONAHA.113.01343
34. Wang Y, Du MF, Gao WH, Fu BW, Ma Q, Yan Y, Yuan Y, Chu C, Chen C, Liao YY, et al. Risk factors for subclinical renal damage and its progression: Hanzhong Adolescent Hypertension Study. *Eur J Clin Nutr.* 2021;75:531–538. doi: 10.1038/s41430-020-00752-x
35. Wang Y, Zhang XY, Gao WH, Du MF, Chu C, Wang D, Chen C, Yuan Y, Ma Q, Liao YY, et al. Association of uric acid in serum and urine with arterial stiffness: hanzhong adolescent hypertension study. *Dis Markers.* 2020;2020:1638515. doi: 10.1155/2020/1638515
36. Wang Y, Jia H, Gao WH, Zou T, Yao S, Du MF, Zhang XY, Chu C, Liao YY, Chen C, et al. Associations of plasma PAPP-A2 and genetic variations with salt sensitivity, blood pressure changes and hypertension incidence in Chinese adults. *J Hypertens.* 2021;39:1817–1825. doi: 10.1097/HJH.0000000000002846
37. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* 2020;76(3 Suppl 1):S1–S107. doi: 10.1053/j.ajkd.2020.05.006
38. Wang JG, Bu PL, Chen LY, Chen X, Chen YY, Cheng WL, Chu SL, Cui ZQ, Dai QY, Feng YQ, et al. 2019 Chinese Hypertension League guidelines on home blood pressure monitoring. *J Clin Hypertens (Greenwich).* 2020;22:378–383. doi: 10.1111/jch.13779
39. Weng J, Ji L, Jia W, Lu J, Zhou Z, Zou D, Zhu D, Chen L, Chen L, Guo L, et al; Chinese Diabetes Society. Standards of care for type 2 diabetes in China. *Diabetes Metab Res Rev.* 2016;32:442–458. doi: 10.1002/dmrr.2827
40. Pan J, Ren Z, Li W, Wei Z, Rao H, Ren H, Zhang Z, Song W, He Y, Li C, et al. Prevalence of hyperlipidemia in Shanxi Province, China and application of Bayesian networks to analyse its related factors. *Sci Rep.* 2018;8:3750. doi: 10.1038/s41598-018-22167-2
41. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int.* 2020;98:S1–1S115. doi: 10.1016/j.kint.2020.06.019
42. Mancia G, Schumacher H, Böhm M, Mann JFE, Redon J, Facchetti R, Schmieder RE, Lonn EM, Teo KK, Yusuf S. Visit-to-visit blood pressure variability and renal outcomes: results from ONTARGET and TRANSCEND trials. *J Hypertens.* 2020;38:2050–2058. doi: 10.1097/HJH.0000000000002567
43. Suzuki D, Hoshide S, Kario K. Associations between day-by-day home blood pressure variability and renal function and albuminuria in patients with and without diabetes. *Am J Hypertens.* 2020;33:860–868. doi: 10.1093/ajh/hpaa091
44. Ushigome E, Fukui M, Hamaguchi M, Senmaru T, Sakabe K, Tanaka M, Yamazaki M, Hasegawa G, Nakamura N. The coefficient variation of home blood pressure is a novel factor associated with macroalbuminuria in type 2 diabetes mellitus. *Hypertens Res.* 2011;34:1271–1275. doi: 10.1038/hr.2011.128
45. Matsumoto S, Ushigome E, Matsushita K, Fukuda T, Mitsuhashi K, Majima S, Hasegawa G, Nakamura N, Ushigome H, Yamazaki M, et al. Home blood pressure variability from the stored memory is correlated with albuminuria, but from the logbook is not. *Am J Hypertens.* 2017;30:993–998. doi: 10.1093/ajh/hpx095
46. Noshad S, Mousavizadeh M, Mozafari M, Nakhjavani M, Esteghamati A. Visit-to-visit blood pressure variability is related to albuminuria variability and progression in patients with type 2 diabetes. *J Hum Hypertens.* 2014;28:37–43. doi: 10.1038/jhh.2013.36
47. Cheng CH. Albuminuria in childhood is a risk factor for chronic kidney disease and end-stage renal disease. *Pediatr Neonatol.* 2016;57:263–264. doi: 10.1016/j.pedneo.2015.05.005
48. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallé JP, Young J, Rashkow A, Joyce C, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001;286:421–426. doi: 10.1001/jama.286.4.421
49. Silacci P, Desgeorges A, Mazzolai L, Chambaz C, Hayoz D. Flow pulsatility is a critical determinant of oxidative stress in endothelial cells. *Hypertension.* 2001;38:1162–1166. doi: 10.1161/hy1101.095993
50. Chappell DC, Varner SE, Nerem RM, Medford RM, Alexander RW. Oscillatory shear stress stimulates adhesion molecule expression in cultured human endothelium. *Circ Res.* 1998;82:532–539. doi: 10.1161/01.res.82.5.532
51. Miao CY, Xie HH, Zhan LS, Su DF. Blood pressure variability is more important than blood pressure level in determination of end-organ damage in rats. *J Hypertens.* 2006;24:1125–1135. doi: 10.1097/01.hjh.0000226203.57818.88
52. Aoki Y, Kai H, Kajimoto H, Kudo H, Takayama N, Yasuoka S, Anegawa T, Iwamoto Y, Uchiwa H, Fukuda K, et al. Large blood pressure variability aggravates arteriolosclerosis and cortical sclerotic changes in the kidney in hypertensive rats. *Circ J.* 2014;78:2284–2291. doi: 10.1253/circj.cj-14-0027
53. Faramawi MF, Delongchamp R, Said Q, Jadhav S, Abouelenien S. Metabolic syndrome is associated with visit-to-visit systolic blood pressure variability in the US adults. *Hypertens Res.* 2014;37:875–879. doi: 10.1038/hr.2014.89