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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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.121.18658.
For Sources of Funding and Disclosures, see page 1255.

*Hypertension* is available at www.ahajournals.org/journal/hyp

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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 $\chi^2$ 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.

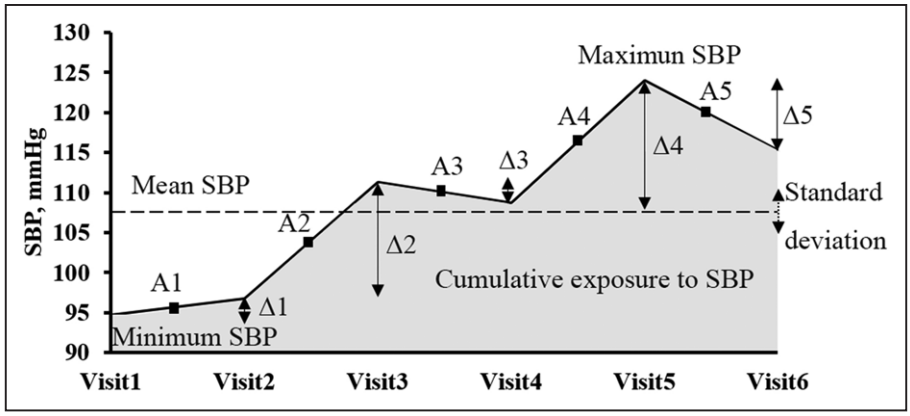


**Figure 1. The example of individual follow-up data of systolic blood pressure (SBP) across 6 visits ($Y_0$–$Y_{30}$).**
The absolute differences of BP between successive SBP measurements are shown as Δ1—Δ5. For example, Δ1 represents the difference in SBP between visit 1 and visit values. Average real 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

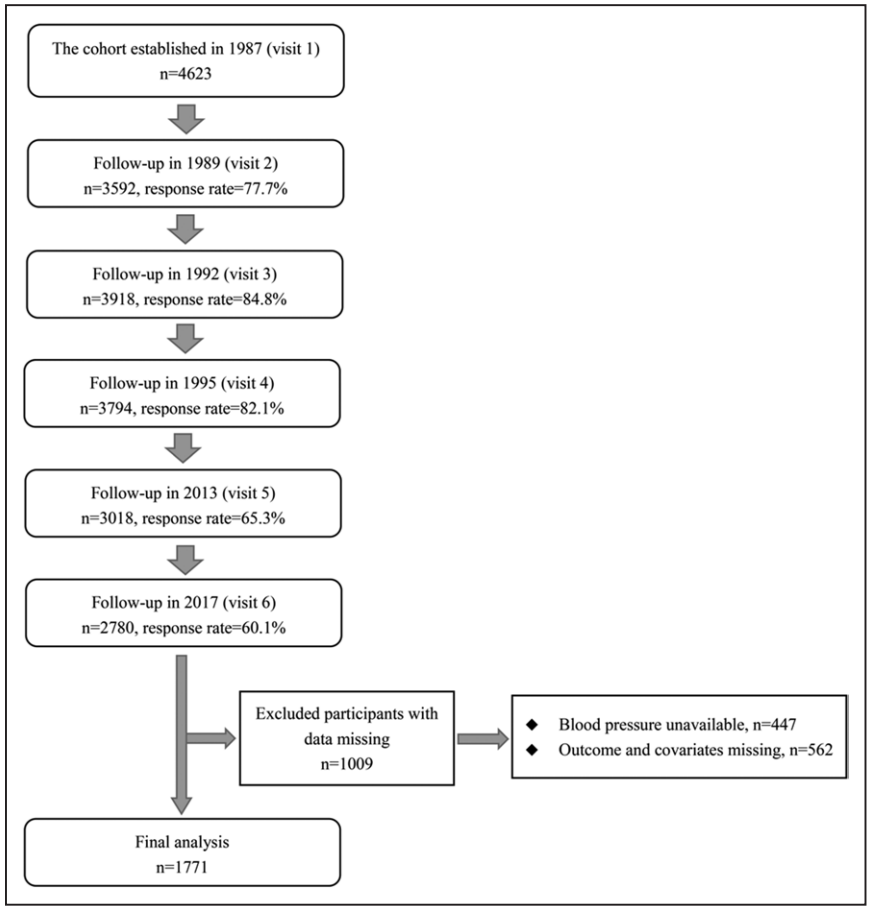


**Figure 2. Flow diagram showing the selection of the study population.**

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

**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 | $1.79\times10^{-6}$ ($9.0\times10^{-7}$–$3.25\times10^{-6}$) | $1.71\times10^{-6}$ ($9.22\times10^{-7}$–$3.05\times10^{-6}$) | $2.71\times10^{-6}$ ($1.49\times10^{-6}$–$4.95\times10^{-6}$) | <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 | $3.14\times10^{-4}$ ($2.02\times10^{-4}$–$4.66\times10^{-4}$) | $2.99\times10^{-4}$ ($1.93\times10^{-4}$–$4.42\times10^{-4}$) | $4.57\times10^{-4}$ ($2.69\times10^{-4}$–$6.77\times10^{-4}$) | <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 | $4.53\times10^{-6}$ ($2.45\times10^{-6}$–$8.22\times10^{-6}$) | $4.29\times10^{-6}$ ($2.34\times10^{-6}$–$7.54\times10^{-6}$) | $7.57\times10^{-6}$ ($4.18\times10^{-6}$–$1.45\times10^{-5}$) | <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 | $1.29\times10^{-2}$ ($9.63\times10^{-3}$–$1.74\times10^{-2}$) | $1.29\times10^{-2}$ ($9.55\times10^{-3}$–$1.74\times10^{-2}$) | $1.37\times10^{-2}$ ($1.07\times10^{-2}$–$1.85\times10^{-2}$) | 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.

## ARTICLE INFORMATION

Received November 2, 2021; accepted March 17, 2022.

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### Acknowledgments

We are grateful to the grassroots health staff in Hanzhong for providing administrative and technical support during the follow-up.

### Sources of Funding

This work was supported by the National Natural Science Foundation of China No. 81600327 (Y. Wang), No. 81870319, 82070437 (J.-J. Mu), No. 82070549 (H.-X. Li), Natural Science Basic Research Program of Shaanxi Province (2021JM-257, 2021JM-588), Institutional Foundation of the First Affiliated Hospital of Xi'an Jiaotong University No. 2019QN-06, 2021ZXY-14 (Y. Wang), British Heart Foundation (Centre of Research Excellence Award, RE/18/6/34217; C. Delles), the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University of China No. XJTU1AF-CRF-2019-004 (J.-J. Mu), XJTU1AF2021CRF-021 (Y. Wang) and XJTU1AFCRF-2017-021 (H.-X. Li), Research Incubation Fund of Xi'an People's Hospital No. FZ-61, Grants from the Major Chronic Noncommunicable Disease Prevention and Control Research Key Project of the Ministry of Science and Technology of China (2017YFC1307604 and 2016YFC1300104).

### Disclosures

None.

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