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ORIGINAL ARTICLE

Cumulative Exposure to Systolic Blood Pressure During Young Adulthood Through Midlife and the Urine Albumin-to-Creatinine Ratio at Midlife

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BACKGROUND
Higher blood pressure during young adulthood may increase cardiovascular and kidney disease risk later in life. This study examined the association of cumulative systolic blood pressure (SBP) exposure during young adulthood through midlife with urine albumin-to-creatinine ratios (ACR) measured during midlife.

METHODS
We used data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a biracial cohort recruited in 4 urban areas during years 1985–1986. Cumulative SBP was calculated as the average SBP between 2 exams multiplied by years between exams over 20 year years. ACR was measured 20 years after baseline when participants were age 43–50 years (midlife). A generalized additive model was used to examine the association of log ACR as a function of cumulative SBP with adjustment for covariates including SBP measured concurrently with ACR.

RESULTS
Cumulative SBP ranged from a low of 1,671 to a high of 3,260 mm Hg. Participants in the highest cumulative SBP quartile were more likely to be male (61.4% vs. 20.7%; $P < 0.001$), Black (61.5% vs. 25.6%; $P < 0.001$) and have elevated ACR (18.7% vs. 4.8%; $P < 0.001$) vs. lowest quartile. Spline regression curves of ACR vs. cumulative SBP demonstrated an inflection point in ACR with cumulative SBP levels >2,350 mm Hg with linear increases in ACR above this threshold. Adjusted geometric mean ACR values were significantly higher with cumulative SBP ≥2,500 vs. <2500 (9.18 [1.06] vs. 6.92 [1.02]; $P < 0.0001$).

CONCLUSION
Higher SBP during young adulthood through midlife is associated with higher ACR during midlife.

Keywords: albumin-to-creatinine ratios; blood pressure; chronic kidney disease; hypertension; microalbuminuria; midlife; race; risk factors; systolic blood pressure; urine albumin excretion; young adulthood; young adulthood.

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Increased urine albumin excretion is an important predictor of cardiovascular and kidney disease and all-cause mortality regardless of diabetes status.[1,2] Risk for both cardiovascular and kidney disease rises significantly with urine albumin-to-creatinine ratios (ACR) above 10 mg/g,[3,4] a level below clinical thresholds which define increased urine albumin excretion.[5] Cross-sectional studies have consistently demonstrated that elevated systolic blood pressure (SBP) is associated with increased urine albumin excretion.[6–9] The higher urine albumin excretion noted in the setting of elevated SBP has been hypothesized to reflect increased glomerular pressure, which depend on systemic blood pressure and autoregulation.[10] With the exception of malignant hypertension, risk for hypertensive end-organ damage from elevated SBP is, however, dependent on the cumulative exposure to elevated SBP[10,11] but SBP is not monitored among most adults before the age of 50 years. Thus, higher SBP levels during young adulthood may be an additional risk factor for future cardiovascular and kidney disease risk. This study examined the association of cumulative SBP exposure during young adulthood through midlife with the ACR measured later during midlife (after 20 years of follow-up), when participants were ages 43–50 years. The analysis focused on SBP and not diastolic blood pressure due to the known association between SBP, renal blood flow autoregulation, and risk of kidney injury.[12] We hypothesized that higher cumulative SBP exposure during young adulthood through midlife is associated with higher ACR during midlife in people without baseline diabetes. We also hypothesized that the association between cumulative SBP exposure and ACR at midlife is independent of SBP measured concurrently with the ACR.

METHODS

Study population

The source population was participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, a prospective cohort study sponsored by the National Heart, Lung, and Blood Institute designed to study early determinants of cardiovascular disease. Detailed methods for CARDIA have been published previously.[13] Briefly, CARDIA recruited 5,115 Black and White persons age 18–30 between 1985 and 1986 from 4 sites in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). All appropriate institutional review boards approved this study. After the first examination, subsequent visits occurred after 2, 5, 7, 10, 15, 20, and 25 years of follow-up. Urine albumin and creatinine was measured in spot urine samples collected during the year 20 and 25 visits (corresponding to years 2005–2006, and 2011–2012). This study examined the association between cumulative SBP exposure over 20 years during young adulthood and the ACR measured when a CARDIA participant was between the ages of 43–50 years old or midlife. The analysis was limited to CARDIA participants without diabetes at baseline.

At the initial CARDIA exam, participants' age ranged from 18–30 years. These small differences in baseline age may reflect marked differences in baseline cumulative SBP exposure given the known SBP trajectories with aging.[14] Thus, simple adjustment for baseline age may not account for potential differences in cumulative SBP prior to CARDIA enrolment. To minimize differences in baseline age and baseline cumulative SBP exposure, the cohort was divided into 2 subcohorts. The younger subcohort (baseline age 18–24 years) was followed from the year 5 exam until the year 25 exam. The older subcohort (baseline age 25–30 years) was followed from the baseline exam until the year 20 exam (Figure 1). These two subcohorts were then combined and analysed as one cohort. We included participants with SBP measurements at the CARDIA baseline exam, SBP measurements at study end and SBP measurement at one or more additional exams. Of the 5,115 CARDIA participants, we excluded 2,087 with missing blood pressure measurements at these time points. We also excluded 17 individuals with diabetes at the baseline exam, 7 individuals with missing information on diabetes status at the end of the follow-up period, and 105 individuals with missing information on ACR at the year 20 (older cohort) or year 25 (younger cohort) exam. An additional 50 participants were excluded due to missing information on covariates during the follow-up period. This left a total of 2,849 participants available for the primary analyses.

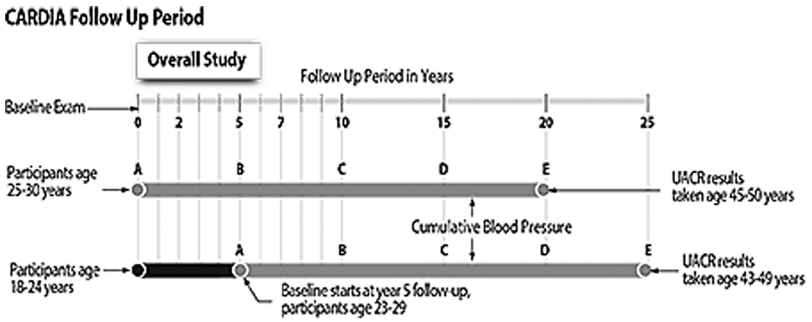


Figure 1. Description of the cohort. The cohort was divided into 2 subcohorts: a younger cohort with baseline age 18–24 years and an older cohort with baseline age 25–30 years. The older cohort was followed from the baseline exam until the year 20 exam (upper bar). The younger cohort was followed from the year 5 follow-up exam, when they were between the ages of 23–29 years, until the year 25 exam (bottom bar). These 2 subcohorts were created to minimize age differences that may reflect disparities in baseline cumulative systolic blood pressure. The letters A, B, C, D, and E designate the exams from each cohort used for computing cumulative blood pressure. These 2 subcohorts were created to minimize age differences that may reflect disparities in baseline cumulative systolic blood pressure.

Due to the large number of participants excluded from the main analysis due to missing data, we repeated analyses using inverse probability weighting.[15] We first excluded 33 adults with baseline diabetes and 295 with missing information on one of the baseline variables (mostly fasting glucose) leaving 4,787 in the prediction of inclusion analysis. Of the 4,787, 2,693 (95% of the original analytic sample) could be included in the weighted analysis.

Cumulative systolic blood pressure

Participants were asked to fast for at least 12 hours and not to smoke or engage in heavy physical activity for at least 2 hours prior to the exam. Venipuncture was performed after blood pressure was measured. At each exam, 3 blood pressure measurements were taken by centrally trained staff using a random zero sphygmanometer at each exam until the year 20 exam when concerns about mercury contained in the devices required a switch to the Omron HEM907XL sphygmomanometer (Omron Corporation, Kyota, Japan). Dual measurements on a subgroup of participants were used to calibrate blood pressure measurements and values calibrated to the sphygmomanometric measures were used for years 20 and 25 blood pressure measurements.[16] Blood pressure measurements were taken after 5 minutes of rest and were taken from the right arm with a minimum of 30 seconds between each reading. The mean of the last 2 measurements was calculated and used as the SBP measurement for that exam. Cumulative SBP was determined over a 20-year period. To ensure equal time between blood pressure measurements for the older and younger cohorts, SBP values at baseline and at years 5, 10, 15, and 20 were used for the older cohort and SBP values at years 5, 10, 15, 20, and 25 were used for the younger cohort (Figure 1). These SBP values at each time point were then averaged between consecutive visits and then multiplied by number of years between visits and summed to determine cumulative SBP.[17]

Urine Albumin-to-Creatinine Ratio

The ACR measured in a random urine specimen at midlife (after 20 years of follow-up when participants were ages 43–50 years) was the main outcome for the analyses. Albumin and creatinine were measured at the Northwest Lipid Research Laboratory in Seattle, Washington using a nephelometric procedure for albumin and the Jaffe method for creatinine. The ACR was adjusted for sex and race[18] and was analyzed as a continuous variable after log transformation. We also examined ACR categories: normal (<13 mg/g), high normal (≥13–24.9 mg/g), and increased (≥25 mg/g).[5]

Covariates

All data were collected using standardized protocols. Age, gender, and race were ascertained by self-report using standardized questionnaires. Blood and urine were collected at the study visit and stored at −70 °C until measurements were performed. Fasting glucose was measured using a standard laboratory technique. At each exam, diabetes was defined as fasting blood glucose ≥126 mg/dl and/or use of diabetes medications. Waist circumference was measured at the umbilicus and hip at the point of maximum extension of the buttocks to the nearest 0.5 cm in duplicate. Information on education, smoking status, and medication use was obtained *via* interviewers using standardized questionnaires.

Statistical methods

To examine the characteristics of the CARDIA participants across the spectrum of cumulative SBP, characteristics of participants were compared across cumulative SBP divided into quartiles. Values are shown as means (SD) for continuous variables, frequency (%) for categorical variables, and median (interquartile range) for variables with nonnormal distributions (ACR). Analysis of variance or chi-square test was used to compare continuous and dichotomous outcomes, respectively, across cumulative SBP quartiles. If the overall test was significant, then the 3 highest cumulative SBP quartiles were compared to the lowest cumulative SBP quartile. The level of statistical significance was set at $P < 0.01$ to account for multiple comparisons.

A generalized additive model (gam), implemented with the mgcv package in R.3.1.3 was then used to examine the association of log ACR at age 43–50 years as a function of cumulative SBP and of SBP measured concurrently with ACR (concurrent SBP) with simultaneous adjustment for age, race, sex, smoking status, waist circumference, and education, and blood pressure medication use, diabetes and smoking status at age 43–50 years. Another analysis was completed using the "segmented" function from the segmented package, also in R, to estimate the apparent breakpoint in the plot for log ACR versus cumulative SBP. This method assumes log ACR is a piecewise linear function of cumulative SBP with the slope of the regression line changing at an unknown cumulative SBP level. The Davies test, used to determine presence of a nonconstant regression parameter in the linear predictor of cumulative SBP,[19] was statistically significant indicating a nonlinear association between cumulative SBP exposure and ACR.

Given the known association between elevated SBP and ACR measured at a single time point, we examined the collinearity between cumulative SBP and SBP measured concurrently with ACR (concurrent SBP). As shown in Figure 2, concurrent SBP was highly correlated with cumulative SBP ($r = 0.72$; $P < 0.001$). To address the collinearity, we examined the cross-tabulation of adjusted least square means of log transformed ACR values by categories of cumulative SBP exposure (≥2,500 and <2,500 mm Hg). The cumulative SBP cut-point of 2,500 mm Hg was based on the maximal inflection of the adjusted spline regression curve of cumulative SBP vs. log transformed ACR (Figure 4a) at approximately this level (2,350 mm Hg) and because this cumulative SBP cut-point of 2,500 mm Hg is consistent with a time weighted average SBP of 125 mm Hg over 20 years. We also examined ACR by use of blood pressure lowering medication and categories of concurrent SBP (<120, 120–139, and ≥140 mm Hg) which were selected based on previous studies showing higher ACR with these concurrent SBP cut-points.[7] Models

then adjusted for age, race, sex, average waist circumference over the follow-up period, and education, diabetes and smoking status at midlife.[6]

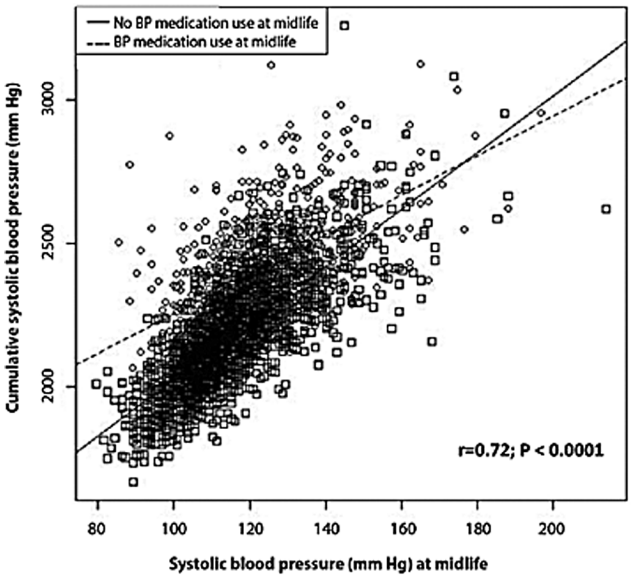


Figure 2. Scatterplot of cumulative systolic blood pressure over the 20-year follow-up period by systolic blood pressure measured at midlife (age 43–50 years). Cumulative systolic blood pressure exposure was calculated by averaging SBP values between consecutive visits and multiplied by number of years between visits and summed. Abbreviations: BP, blood pressure; SBP, systolic BP.

We then used general linear models with log transformed ACR as the dependent variable and fitted cumulative SBP exposure as a dichotomous variable (≥2,500 vs. <2,500 mm Hg) while adjusting for concurrent SBP as a continuous variable along with all other covariates. A general linear model was also fitted with concurrent SBP as categories: <120 mm Hg, 120–139 mm Hg, and ≥140 mm Hg and adjusted for cumulative SBP as a continuous variable along with all other covariates. The fully adjusted antilog of the arithmetic mean of log transformed ACR (geometric mean) was then compared by presence of cumulative SBP exposure ≥2,500 mm Hg or by concurrent SBP categories. We examined 2-way interactions between cumulative SBP and race, use of BP medication at age 43–50 years and concurrent SBP categories by fitting interaction terms in the fully adjusted general linear model with *P* value <0.1 considered statistically significant. Statistical analyses were completed using SAS v 9.4 (SAS Institute) and the statistical program R.

RESULTS

Table 1 shows the characteristics of the CARDIA participants at baseline by the cumulative SBP quartiles. Median cumulative SBP exposure in mm Hg (interquartile range) ranged from 1,996 (1,938–2,037) in the bottom quartile to 2,461 (2,399–2,565) in the highest quartile while mean baseline SBP ranged from 100 (7.0) mm Hg in the bottom quartile to 119 (10.4) mm Hg in the highest quartile. Use of blood pressure lowering medication at baseline was very low overall but ranged from 0.3% in the bottom cumulative SBP quartile to 2.5% in the highest cumulative SBP

Table 1. Study characteristics of CARDIA participants by quartiles of cumulative systolic blood pressure

Characteristic	Quartile 1 (*n* = 711)	Quartile 2 (*n* = 713)	Quartile 3 (*n* = 713)	Quartile 4 (*n* = 712)	Overall *P* value
Median cumulative systolic blood pressure in mm Hg over 20 years[a]	1,998 IQR 1,938–2,037	2,141 IQR 2,111–2,173	2,274 IQR 2,238–2,308	2,461 IQR 2,398–2,565	
Baseline age (years)[b]	27.3 (2.0)	27.2 (1.9)	27.1 (2.0)	27.3 (1.9)	0.3
Male (%)	21.0	41.5*	54.4*	61.8*	<0.001
Black (%)	25.3	38.7*	48.5*	61.4*	<0.001
Baseline waist circumference (cm)	73.5 (9.0)	77.6 (10.3)*	80.7 (10.7)*	85.4 (13.2)*	<0.001
Obesity at baseline (%)	5.9	10.3**	13.4*	27.3*	<0.001
Baseline fasting glucose (mg/dl)	80.7 (7.5)	81.7 (8.0)	82.5 (8.8)*	84.3 (7.8)*	<0.001
Baseline systolic blood pressure (mm Hg)	100 (7.0)	106 (7.1)*	111 (7.7)	119 (10.4)	<0.001
Baseline diastolic blood pressure (mm Hg)	63 (7.0)	67 (8.1)*	70 (8.6)*	75 (10.1)*	<0.001
Current smoker at baseline (%)	24.1	25.0	26.8	29.2	0.5
Antihypertensive medication use at baseline (%)	0.3	0.3	0.3	2.8*	<0.001
Years of education (%)	15.0 (2.3)	14.6 (2.3)	14.4 (2.3)	13.9 (2.3)*	<0.001
% Less than a high school education	3.6	4.8	5.3	8.9*	<0.001

Abbreviation: CARDIA, Coronary Artery Risk Development in Young Adults. *P < 0.001 vs. quartile 1; **P < 0.01 compared to quartile 1.

[a]Cumulative systolic blood pressure defined as the average blood pressure between 2 visits multiplied by the time between the 2 visits and then summed across all visits; cumulative systolic blood pressure values shown as median values and interquartile range (IQR).

[b]Baseline visit defined as the year 0 and year 5 exams for CARDIA participants ages 25–30 years and 18–24 years, respectively, at CARDIA enrolment (see Figure 1).

quartile. The ACR measured in a random urine specimen at midlife (after 20 years of follow-up when participants were ages 43–50 years) was the main outcome for the analyses. Increased ACR was present in 275 (9.7%) participants and high normal ACR was present in 259 (9.1%) of the participants. Frequency of increased ACR was over 3-fold higher (18.7% vs. 4.8%; $P < 0.0001$) in the highest quartile compared to the lowest cumulative SBP quartile (Figure 3).

Figure 4a shows the spline regression plot of cumulative SBP and ACR with adjustment for all covariates including concurrent SBP. The association between cumulative SBP and ACR appeared flat until a cumulative SBP of approximately 2,500 mm Hg, consistent with a time weighted average SBP of 125 mm Hg over 20 years. The maximum inflection point of cumulative SBP was estimated at 2,350 mm Hg (time weighted average SBP of 117.5 mm Hg) with the slope of log ACR before and after this breakpoint differing significantly (−0.03 per 100 mm Hg years and 0.13 per 100 mm Hg years, respectively, $P < 0.0001$). After cumulative SBP exceeded 2,350 mm Hg, ACR increased linearly with increasing cumulative SBP. Figure 4b shows the spline regression curve for concurrent SBP and log ACR with adjustment for all covariates including cumulative SBP as a continuous variable. The shape of the association between ACR and concurrent SBP appeared sigmoidal with a fairly linear increase in ACR values between concurrent SBP levels ranging from ~120 to 180 mm Hg. Confidence intervals around ACR values with concurrent SBP >180 mm Hg were very wide due to the limited number of participants with concurrent SBP in this range.

Table 2 shows that ACR generally differed across cumulative SBP categories within concurrent SBP categories and ACR differed across concurrent SBP categories within cumulative SBP categories. For example, among participants with concurrent SBP ≥140 mm Hg and no blood pressure medication use at study end, adjusted least square mean

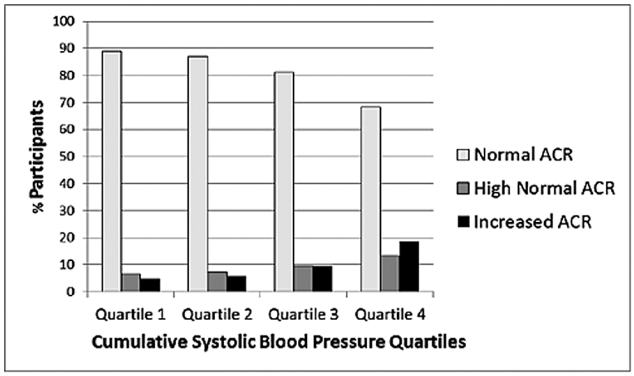
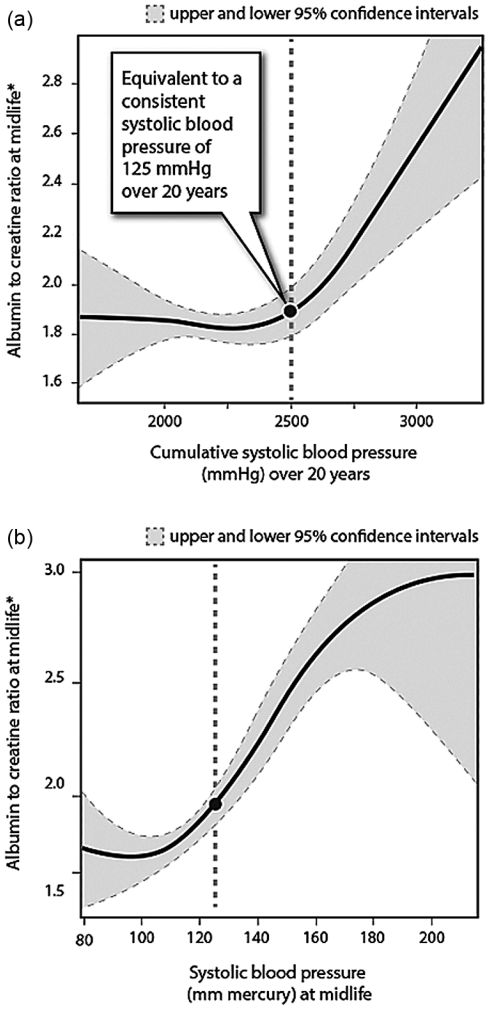


Figure 3. Frequency of urine-to-albumin-to creatinine (ACR) categories during midlife (age 43–50 years) by cumulative systolic blood pressure quartiles. ACR was adjusted for sex and race and categorized as normal (<13 mg/g), high normal (≥13–24.9 mg/g), and moderate to severely increased (≥25 mg/g). Cumulative systolic blood pressure over the 20-year follow-up period was calculated by averaging SBP values between consecutive visits and multiplied by number of years between visits and summed. Quartile 1: 1,937–2,037 mm Hg, Quartile 2: 2,111–2,173 mm Hg; Quartile 3: 2,238–2,309 mm Hg; and Quartile 4: 2,398–2,563 mm Hg.



Figures 4. Spline regression plot of log transformed albumin-to-creatinine ratios (ACR) measured during midlife by cumulative systolic blood pressure exposure over a 20 year period (**a**) and by systolic blood pressure measured concurrently with ACR (**b**). Adjusted for age, race, sex, smoking status, average waist circumference over the follow-up period, baseline education status, development of diabetes during the follow-up period, and smoking status, use of blood pressure lowering medications and systolic blood pressure at midlife. *Midlife defined as age 43–49 years for participants 18–24 years old at the initial CARDIA exam and age 45–50 years for participants 25–30 years at the initial CARDIA exam. Dotted lines indicate systolic blood pressure of 125 mm Hg (panel b) or cumulative systolic blood pressure exposure equivalent to a time weighted average systolic blood pressure of 125 mm Hg over 20 years (panel a). Abbreviation: CARDIA, Coronary Artery Risk Development in Young Adults.

ACR values were significantly higher in participants with cumulative SBP ≥2,500 mm Hg (time weighted average SBP ≥ 125 mm Hg) vs. those with cumulative SBP <2,500 mm Hg (16.23 [1.13] vs. 11.17 [1.11]; $P < 0.001$). Similar findings were noted among participants with blood pressure medication use at study end. Adjusted least square mean ACR values were also significantly higher among participants with concurrent SBP ≥140 vs. <120 mm Hg in participants with and without cumulative SBP ≥2,500 mm Hg or blood pressure medication use at study end (see Table 2). Sensitivity

Table 2. Adjusted geometric mean albumin-to-creatinine values (mg/g) by categories of cumulative systolic blood pressure, concurrent systolic blood pressure, and by use of blood pressure lowering medications at end of follow-up period

Cumulative systolic blood pressure < 2,500 mm Hg (time weighted average SBP < 125 mm Hg over 20 years)				Cumulative systolic blood pressure ≥ 2,500 mm Hg (time weighted average SBP ≥ 125 mm Hg over 20 years)			
Concurrent SBP	Group	Adjusted Geometric Mean ACR[a], original analysis	Adjusted Geometric Mean ACR[a], IPTW[b] analysis	Concurrent SBP	Group	Adjusted Geometric Mean ACR[a], original analysis	Adjusted Geometric Mean ACR[a], IPTW[b] analysis
No blood pressure medication at end of follow-up period							
<120 mm Hg	1	6.14 (1.02)	6.17 (1.02)	< 120 mmHg	4	7.81 (1.36)	10.57 (1.51)
120–139 mm Hg	2	7.90 (1.04)	7.81 (1.04)	120–139 mmHg	5	8.30 (1.13)	7.97 (1.13)
≥140 mm Hg	3	11.17 (1.11)*	11.05 (1.11)*	≥140 mmHg	6	16.23 (1.13)**	14.94 (1.14)**
Blood pressure medication use at end of follow-up period							
<120 mm Hg	7	6.55 (1.06)	6.64 (1.06)	< 120 mmHg	10	8.15 (1.16)	7.93 (1.15)
120–139 mm Hg	8	7.55 (1.08)	7.61 (1.08)	120–139 mmHg	11	10.19 (1.10)	10.20 (1.10)
≥140 mm Hg	9	14.18 (1.17)***	15.54 (1.17)***	≥140 mmHg	12	20.03 (1.12)****	19.32 (1.11)****

Values are shown as geometric means (SE) for original analysis and for sensitivity analysis using inverse probability treatment weighted (IPTW) analysis. *P < 0.001 compared to group 1; **P < 0.001 compared to group 1, 2; ***P < 0.001 compared to groups 7, 8; ****P < 0.001 compare to groups 7, 8, 10, 11.

[a]ACR, albumin-to-creatinine ratios (mg/g); values shown are geometric means adjusted for cumulative systolic blood pressure categories, concurrent systolic blood pressure categories and blood pressure medication use at end of follow-up period, age, race, sex, average waist circumference, education and smoking status, and development of diabetes during the follow-up period.

[b]Inverse probability treatment weighted (IPTW) analysis.

analyses using inverse probability weighting showed very similar findings (Table 2).

Geometric mean ACR values adjusted for all covariates including concurrent SBP were significantly higher in participants with cumulative SBP exposure ≥2,500 vs. <2,500 mm Hg (9.18 [SE 1.06] vs. 6.92 [SE 1.02]; P < 0.0001). Adjusted geometric mean ACR values were also significantly higher (P < 0.001) among participants with concurrent SBP ≥140 mm Hg (13.34 [SE 1.07]) and with concurrent SBP 120–139 mm Hg (7.74 [SE 1.03]) compared to participants with concurrent SBP <120 mm Hg (6.40 [SE 1.02]). Interaction terms between cumulative SBP and race, blood pressure medication use, and concurrent SBP categories did not reach statistical significance (all interaction term P values >0.2).

DISCUSSION

The findings from this study show that higher exposure to cumulative SBP during young adulthood through midlife is associated with higher ACR levels during midlife. In addition, we found that higher SBP measured concurrently with ACR is associated with higher ACR levels consistent with previous studies.[6–9] After adjustment for all covariates including concurrent SBP and use of blood pressure lowering medications, ACR values remained significantly higher among adults with cumulative SBP exposure ≥2,500 mm Hg, a level consistent with a time weighted average SBP value ≥125 mm Hg over a 20-year period. It should be noted that cumulative SBP does not equate with average SBP because calculation of mean blood pressure values over time do not account for the amount of time an individual is exposed to a given SBP level.

Few studies have examined associations between cumulative SBP exposure and ACR, a marker of both cardiovascular and kidney disease risk.[1,3,4,20] In the Multi-Ethnic Study of Atherosclerosis, a cohort of adults aged 45–84 years at baseline without clinical cardiovascular disease, every 100 mm Hg increment in cumulative SBP exposure over a median follow-up of 9.4 years was associated with 23% higher odds of ACR progression.[21] The role of elevated SBP for chronic kidney disease incidence has been difficult to quantify given that elevated SBP accelerates progression of most kidney diseases.[10] However, the persistent presence of increased urine albumin excretion now defines presence of kidney disease, regardless of glomerular filtration rate.[5] In addition, levels of ACR below thresholds that define moderately increased urine albumin excretion are significantly associated with subclinical measures of cardiovascular disease[22,23] and have been linked with increased cardiovascular disease risk,[1,24] stroke,[25] and poor cognitive function.[26,27] The associations between end-organ damage and higher levels of ACR may be linked through higher cumulative SBP exposure. Over 2 decades ago, Wilson *et al.* demonstrated a significant and positive association between cumulative SBP measured over a 34-year follow-up period and presence of carotid artery stenosis at the end of the follow-up period among 1,090 Framingham Heart Study participants.[28] Higher SBP levels during young

adulthood have also been linked with increased risk of coronary artery calcification,[29] left ventricular systolic, and diastolic dysfunction during midlife.[30]

The strengths of this study include the long follow-up period during young adulthood and the weaknesses of the study include the use of the ACR measured at one time point. However, our findings are supported by previous studies demonstrating an association between higher cumulative SBP exposure and progression of ACR measured in spot urine specimens.[21,31] The large number of CARDIA participants with missing SBP data is a limitation. However, we repeated analyses using inverse probability weighting and found very similar findings. Our analyses also examined the separate effects of 2 correlated variables, cumulative SBP exposure, and concurrent SBP on ACR measured during midlife. We showed monotonic increases in adjusted geometric mean ACR across cumulative SBP categories within concurrent SBP categories, and *vice versa*.

In conclusion, higher levels of cumulative SBP exposure during young adulthood through midlife and concurrent SBP are associated with higher ACR levels at midlife. Future studies should examine the association between cumulative SBP during young adulthood through midlife and cardiovascular outcomes and kidney function decline.

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DISCLOSURE

The authors declared no conflict of interest.

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