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ORIGINAL ARTICLE

Longitudinal Blood Pressure Changes and Kidney Function Decline in Persons Without Chronic Kidney Disease: Findings From the MESA Study

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BACKGROUND
While changes in blood pressure (BP) are independently associated with cardiovascular events, less is known about the association between changes in BP and subsequent changes in renal function in adults with an estimated glomerular filtration rate (eGFR) of >60 ml/min/1.73 m^2.

METHODS
The present study included 3,920 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) study who had ≥2 BP measurements during the first 5 years of MESA and had eGFR measurements at both year 5 and 10. Change in BP was estimated as the annualized slope of BP between year 0 and 5 based on linear mixed models (mean number of measurements = 4.0). Participants were then grouped into 1 of 3 categories based on the distribution of systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) change (top 20%, middle 21–79%, bottom 20%). We calculated eGFR from cystatin C (ml/min/1.73 m^2), estimated annual change in eGFR (ml/min/1.73 m^2/year), and defined rapid kidney function decline as a >30% decrease in eGFR from year 5 to 10. We used multivariable logistic regression adjusting for year 0 demographic and clinical characteristics, including eGFR and BP, to determine associations of BP change with rapid kidney function decline.

RESULTS
Median age was 59 [interquartile range (IQR): 52, 67] and median eGFR at year 0 was 95.5 (IQR: 81.7, 105.9) ml/min/1.73 m^2. Median SBP at year 0 was 111, 121, and 147 mm Hg for increasing, stable, and decreasing SBP change, respectively. Increasing SBP and widening PP change were each associated with higher odds of rapid kidney function decline compared with stable SBP and PP groups, respectively [odds ratio, OR 1.7 (95% confidence interval, CI 1.3, 2.4) for SBP; OR 1.4 (95% CI 1.1, 1.9) for PP]. Decreasing SBP was associated with rapid kidney function decline after adjusting for all covariates except for year 0 BP [OR 1.4 (95% CI 1.0, 1.8)], but this association was no longer statistically significant after adjustment for year 0 BP. There were no significant associations between DBP change and rapid decline in the fully adjusted models. Similar findings were seen with annual change in eGFR.

CONCLUSIONS
Increasing SBP and widening PP over time were associated with greater risk for accelerated kidney function decline even at BP levels below established hypertension thresholds.

Keywords: blood pressure; blood pressure change; blood pressure goals; hypertension; rapid kidney function decline.

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Hypertension is a well-established risk factor for progression from chronic kidney disease (CKD) to end-stage renal disease.[1,2] Ideal blood pressure (BP) goals in adults are an area of considerable controversy.[3] Recently, clinical trials have shown clinical benefit for more aggressive BP lowering in select patient populations.[4–6] However, lowering BP through treatment with antihypertensive agents has not shown to be renal-protective in patients without established CKD, and aggressive BP reduction is associated with increased risk of accelerated renal function decline in patients with preserved estimated glomerular filtration rate (eGFR).[4,7]

BP is dynamic and there is growing interest in the clinical importance in BP change over time. Changes in BP have been independently associated with cardiovascular outcomes.[8,9] An area of uncertainty is the association of BP change with subsequent changes in renal function in patients with preserved eGFR. Among patients with established CKD, time-updated measurements of elevated BP are more strongly correlated with the development of end-stage renal disease and disease progression compared with isolated, single measurements of elevated BP.[10] In one population-based, retrospective study of elderly persons, decreasing systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) over time were associated with worsening renal function.[11] To our knowledge, no studies to date have examined the role of BP change over time on later renal function in a mixed-age,

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multiethnic, cohort of adults with preserved eGFR. This question has clinical relevance in helping understand pathways to renal dysfunction.

We designed this study to evaluate the independent association of BP change with renal function decline. We hypothesized that BP change would be associated with later renal function decline independent of year 0 BP and eGFR. Specifically, our hypothesis was that participants with increasing SBP, decreasing DBP, and widening PP would have increased risk of renal function decline throughout a range of year 0 BP.

METHODS

Subjects

We included data from participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a large prospective cohort study designed to identify correlates of subclinical cardiovascular disease and its progression in a multiethnic population. Study design, recruitment, and data procurement have been described previously.[12] Briefly, 6,814 men and women between the ages of 45 and 84 years were enrolled between July 2000 and August 2002 at 6 study sites across the United States. Subjects were excluded if they had a history of known cardiovascular disease or weighed >300 lbs. All study participants provided consent and the study design was approved by the institutional review boards at each study site. Participants had 4 visits in addition to year 0 exam. These occurred at approximately 1.5, 3, 5, and 10 years following study enrollment.

A priori, we divided the cohort data into 2 consecutive 5-year periods: the first period (correlating to year 0 through year 5) was used to determine BP change and the second period (years 5 through year 10) was used to determine subsequent kidney function change. Study participants were restricted to those with preserved kidney function, defined as having an eGFR of >60 ml/min/1.73 m^2 at year 0, those who had at least 2 BP measurements between year 0 and year 5, and cystatin C from blood measurements at both year 5 and year 10, and those for whom we knew about use of antihypertension medications. Of the original MESA cohort, 2,894 participants were excluded in total. Participants were excluded if they had less than 2 BP measurements between years 0 and 5 (429 participants), did not have cystatin C measurements at both years 5 and 10 (2,227 participants), had no information on use of antihypertension medications (2 participants), or had a year 0 eGFR that was equal to or less than 60 ml/min/1.73 m^2 or unknown (236 participants). This left 3,920 participants in our analysis.

Outcomes

eGFR was estimated using cystatin C, measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring) and corrected for assay drift.[13] eGFR was calculated using the cystatin C CKD Epi equation.[14]

The primary outcome was rapid kidney function decline, defined as ≥30% decrease in eGFR between year 5 and year 10. This outcome has been associated with adverse cardiovascular events, development of end-stage renal disease, and has been recommended as a surrogate outcome in trials.[15] A second outcome, annualized change in eGFR from year 5 to year 10 was calculated and reported as ml/min/1.73 m^2/year.[16]

Primary predictor

The primary independent variables of interest were annualized change in SBP, DBP, and PP between year 0 and year 5. BP measurements were obtained using the Dinamap automated BP device (Dinamap Monitor Pro 100). At each study exam, 3 sequential measures of SBP and DBP were obtained and the average of the second and third measurements recorded.[17] PP was calculated as the difference between these SBP and DBP measures. To determine discrete categories of BP change, we used a data-driven approach. Specifically, we calculated change per year in each BP parameter for each individual participant using the slope from a linear mixed model with all measurements of that BP parameter obtained between the year 0 and year 5 examinations (mean number of measurements = 4.0 for all parameters). Based on the distribution of change in each BP parameter, we categorized BP change into 3 groups: the bottom 20% (i.e., largest decreases), middle 21–79% (defined as stable), and top 20% (i.e., largest increases) (Figure 1). Given that for SBP, the vast majority of the participants in the top 20% change group had increasing SBP, this group was described as "SBP increasing", while the reference group of the 21st–79th percentile was labeled "SBP stable", and the bottom 20% group "SBP decreasing".

Covariates

Information on age, gender, race, ethnicity, marital status, socioeconomic factors (income, education, occupational status), smoking history, and self-reported general health were obtained from a questionnaire administered at year 0. Height and weight were measured at year 0 with participants wearing light clothing without shoes. Body mass index was calculated as weight in kilograms divided by height in meters squared. Diabetes was defined as either a fasting glucose ≥126 mg/dl or use of oral hypoglycemic medication or insulin at year 0. eGFR and BP at year 0 were also included as covariates.

Any antihypertension medication use from year 0 to year 5 was included to evaluate effect modification. Participants were asked to bring all medications to each examination, and medication use was assessed by medication inventory.

Statistical analysis

We described characteristics of the study sample across the 3 SBP change groups. We tested for differences across groups using chi-square tests for categorical variables and nonparametric Kruskal–Wallis tests for continuous variables. We also compared characteristics of MESA participants included in our analysis to those participants who had a preserved eGFR at year 0 but were excluded.

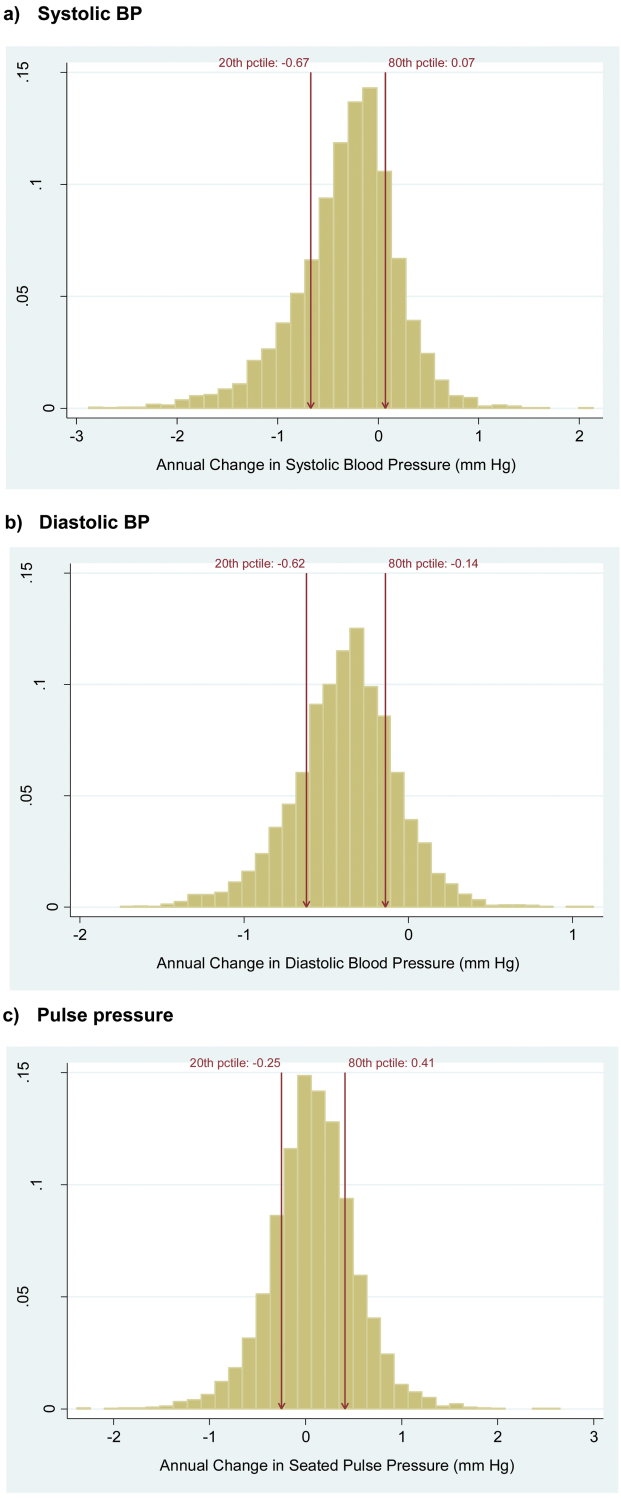

Figure 1. Distribution of SBP, DBP, and PP by highest and lowest 20%. (**a**) Systolic BP. (**b**) Diastolic BP. (**c**) Pulse pressure. Abbreviations: BP, blood pressure; DBP, diastolic BP; PP, pulse pressure; SBP, systolic BP.

For the primary analysis of rapid kidney function decline, we first cross-tabulated the percentage of participants with rapid kidney function decline within each SBP change group and across clinically relevant year 0 BP levels. We used multivariable logistic regression to calculate separate odds ratios (ORs) and 95% confidence intervals (CIs) for kidney function decline for the top and bottom 20% group compared to the middle 21st–79th percentile group (the referent). Covariates were added in 3 separate multivariable models in a stepwise manner. Model 1 adjusted for age only. Model 2 adjusted for age, gender, race/ethnicity, marital status, income, education, occupational status, smoking status, general health, body mass index, diabetes status, and year 0 eGFR. Model 3 included all the covariates in model 2 with the addition of year 0 BP. Covariates were selected *a priori* for inclusion in the models if they were known confounders or known to influence renal function from previous literature review.

For the secondary outcome, annualized change in eGFR, linear regression was used to estimate mean change per year in eGFR (ml/min/1.73 m^2) and 95% CIs based on robust standard errors for the top and bottom 20% group for each BP parameter compared to the middle 21st–79th percentile group. Covariate adjustment followed the same stepwise approach in the secondary analysis as in the primary analysis.

Since we were also interested in the potential importance of antihypertension medication, we stratified our analyses *a priori* by use of one or more antihypertension medications vs. never use of antihypertension medications at any point between years 0 and 5, adjusting for similar covariates in the primary analysis. We tested for interaction between use of antihypertension medications and renal function using the Global Wald test method.

Sensitivity analysis

Because the majority of individuals in the top 20% change in DBP group had a net annual "decrease" in DBP, a *post-hoc* sensitivity analysis of the association between change in DBP and rapid kidney function decline was performed using alternative categories of DBP change. Cut-points of <−0.75 mm Hg, ≥−0.75 mm Hg to ≤0 mm Hg, and >0 mm Hg were chosen to reflect those with decreasing, stable, and increasing DBP, respectively.

Sensitivity analyses were also performed using groups of percentage change in each BP parameter from year 0 to year 5 rather than groups of absolute annual change. Percentage change was categorized into the bottom 10% (i.e., including largest decreases), the middle 11–89%, and the top 10% (i.e., including largest increases).

Because albuminuria has been associated with rapid decline in eGFR as well as BP, we also conducted exploratory analyses investigating whether the presence of albuminuria [albumin-to-creatinine ratio (ACR) ≥ 30] accounted for our findings.[18–20] ACR was available for study participants at year 0 and 4. We first added ACR at year 4 into the fully adjusted model to investigate whether the association between BP change and subsequent rapid decline in kidney function was mediated by albuminuria. We also examined whether the presence of albuminuria was a significant effect modifier on the observed associations by testing for interaction. Finally, we repeated our main analyses after excluding 251 persons with albuminuria at baseline.

In order to account for differences in characteristics of persons included in our analysis compared to all MESA participants with preserved eGFR at year 0, we performed a sensitivity analysis incorporating inverse probability weights of inclusion to our models. The inverse probability weights were estimated for all MESA participants with preserved eGFR at year 0 by fitting logistic regression models of an indicator of sample inclusion regressed on all covariates from the fully adjusted model of eGFR rapid decline for each predictor of interest.

RESULTS

Patient characteristics

The demographic and clinical characteristics of the study cohort for SBP are described in Table 1. Persons with stable SBP change had a median SBP of 119 mm Hg at year 0 and a median SBP of 117 mm Hg at year 5. Persons with decreasing SBP change had a median year 0 SBP of 144 mm Hg, which fell to a median SBP of 118 mm Hg at year 5. Persons with increasing SBP change had a median SBP of 110 mm Hg at year 0, which rose to a median SBP of 131 mm Hg at year 5.

Compared to the stable and increasing SBP groups, the SBP decreasing group was older, more likely to be Black, have a diagnosis of diabetes or hypertension, take an antihypertension medication, be widowed/divorced/separated, have a higher body mass index, have a lower family income, educational status, and self-reported health. These participants also had a lower eGFR at year 0 compared to those in the stable and increasing groups.

Distribution of change in BP parameters

The distributions of BP change per year for SBP, DBP, and PP are illustrated in Figure 1. The median SBP change for all participants was −0.25 (interquartile range [IQR]: −0.58, 0.00) mm Hg/year. For DBP, the median change was −0.37 (IQR: −0.57, −0.19) mm Hg/year for all participants. For PP, the median change was −0.08 (IQR: −0.18, 0.35) mm Hg/year for all participants. The median intragroup change in SBP was +0.25, −0.25, −0.97 mm Hg/year for the SBP increasing, stable, and decreasing groups, respectively.

For DBP, the median intragroup change in BP was −0.01, −0.37, and −0.78 mm Hg for the highest 20%, middle 21st–79th%, and bottom 20% group, respectively. For PP, the median change in BP was +0.62, +0.08, and −0.45 mm Hg for the highest 20%, middle 21st–79th%, and bottom 20% group, respectively.

Association of BP change with rapid kidney function decline

The category of persons with the lowest year 0 SBP and stable SBP change had the smallest proportion of participants with rapid decline (Table 2). Higher year 0 SBP groups had larger proportions of participants with rapid decline. There was a higher percentage of participants with rapid decline in the SBP increasing groups and the SBP decreasing groups compared to the SBP stable group across all year 0 SBP categories.

In the multivariate analysis (Table 3), persons whose SBP was increasing had 52% higher odds (95% CI 1.1, 2.1) of rapid kidney function decline when adjusting for covariates and year 0 eGFR, compared to the SBP stable group (model 2). This association was slightly strengthened when year 0 SBP was added to the model (model 3). Persons with decreasing SBP had higher odds of rapid kidney function decline compared to the SBP stable group in models 1 and 2. However, the association disappeared after adding year 0 SBP in model 3.

Compared with stable PP, widening PP was associated with 35% higher odds (CI 1.0, 1.8) of rapid kidney function decline in model 2. Adjustment for year 0 BP strengthened the association slightly in model 3. The association of the PP-narrowing group with rapid kidney function decline when adjusted only for age (model 1) was attenuated when additional covariates were added (models 2 and 3).

There was no statistically significant association between the DBP change groups and rapid kidney function decline in fully adjusted models.

Association of BP change with annual change in kidney function

Table 4 illustrates the association between BP change groups and annual change in eGFR. Similar to our findings above, the SBP increasing group had a statistically significantly greater rate of eGFR decline compared to the SBP stable group in all models. PP widening was also associated with a more rapid rate of eGFR decline in all models.

Figure 2 depicts associations between BP change groups and rapid renal function decline by antihypertension medication using model 3. There were no statistically significant interactions between BP change group and antihypertension medication for any BP parameter (*P* values 0.36 for SBP, 0.10 for DBP, and 0.21 for PP).

Sensitivity analyses

Results examining odds of rapid kidney function decline and annual change in eGFR were similar when looking at alternative percentage cut-offs for change in SBP. For example, compared to participants in the middle 80% group, those with the top 10% increase in SBP had a 39% increased odds of rapid kidney function decline (CI 1.0, 1.9) in model 3.

When comparing the 345 participants who had an increase in DBP (>0 mm Hg increase in DBP) during the study period to those who had more stable DBP (≥−0.75 mm Hg and ≤0 mm Hg change in DBP, $n = 3{,}092$), there was 58% increased odds of rapid kidney function decline (CI 1.1, 2.3) in model 3.

There was no evidence of confounding with the addition of albuminuria into our models. Associations of increases in SBP and PP with rapid decline in eGFR remained virtually unchanged after adding albuminuria to model 3 [ORs: 1.7 (95% CI 1.2, 2.4) and 1.4 (95% CI 1.1, 2.0), respectively]. We found no significant differences by albuminuria status

Table 1. Participant characteristics by SBP change group at year 0

	SBP change						
	SBP decreasing		SBP stable		SBP increasing		*P* value
N	784		2,352		784		
Age, median (IQR)	64 (56–70)		58 (51–65)		58 (52–66)		<0.01
	(*n*, % total)		(*n*, % total)		(*n*, % total)		
Male	379	(48)	1,168	(50)	339	(43)	<0.01
Race/ethnicity							<0.01
White	295	(38)	961	(41)	333	(43)	
Chinese-American	80	(10)	276	(12)	108	(14)	
Black	247	(32)	582	(25)	167	(21)	
Hispanic	162	(21)	533	(23)	176	(22)	
Marital status							0.02
Married/living as married	491	(63)	1,528	(65)	518	(66)	
Widowed/divorced/separated	234	(30)	584	(25)	191	(24)	
Never married	54	(7)	222	(9)	67	(9)	
Gross family income							<0.01
<$75,000	579	(74)	1,668	(71)	538	(69)	
≥$75,000	179	(23)	633	(27)	227	(29)	
Education							<0.01
<High school	289	(37)	680	(29)	235	(30)	
High school only	232	(30)	682	(29)	217	(28)	
Associate degree or higher	263	(34)	986	(42)	331	(42)	
Current occupation							<0.01
Employed/homemaker	436	(56)	1,617	(69)	567	(73)	
Unemployed	19	(2)	48	(2)	8	(1)	
Retired	328	(42)	683	(29)	208	(27)	
Cigarette smoking status							0.06
Never	378	(48)	1,215	(52)	416	(53)	
Former	322	(41)	859	(37)	266	(34)	
Current	84	(11)	274	(12)	101	(13)	
General health (self-report)							<0.01
Poor or fair	77	(10)	163	(7)	41	(5)	
Good	340	(43)	859	(37)	312	(40)	
Very good or excellent	361	(46)	1,311	(56)	427	(55)	
Body mass index (WHO categories)							<0.01
BMI <25.0 (normal weight)	167	(21)	711	(30)	278	(36)	
BMI 25.0–29.9 (overweight)	323	(41)	961	(41)	282	(36)	
BMI 30+ (obese)	294	(38)	680	(29)	224	(29)	
Diabetes	110	(14)	199	(9)	68	(9)	<0.01
Hypertension	613	(78)	713	(30)	197	(25)	<0.01
Hypertension medication (any at baseline)	402	(51)	641	(27)	205	(26)	<0.01
			/----------Median (IQR)----------/				
Albumin/creatinine (mg/g)	7	(4–15)	5	(3–8)	5	(3–7)	<0.01
Year 0 SBP (mm Hg)	144	(135–157)	119	(110–131)	110	(102–120)	<0.01
Year 0 eGFR (ml/min/1.73 m^2)	92	(78–103)	96	(83–107)	96	(83–106)	<0.01
5-Year SBP (mm Hg)	118	(109–131)	117	(107–132)	131	(116–144)	<0.01
5-Year eGFR (ml/min/1.73 m^2)	81	(69–96)	90	(77–100)	90	(78–100)	<0.01
Year 0 heart rate (BPM)	62	(56–69)	62	(56–68)	61	(56–68)	0.13

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SBP, systolic blood pressure; WHO, World Health Organization.

[a]Values may not add up to 100% due to missing values.

Table 2. Rapid eGFR decline by SBP change group and year 0 SBP category

Year 0 SBP (mm Hg)		SBP decreasing	SBP stable	SBP increasing
<120	*N*	29	1,258	591
	% (*n*) with rapid eGFR decline	6.9 (2)	4.8 (61)	8.0 (47)
120–139	*N*	269	805	157
	% (*n*) with rapid eGFR decline	10.0 (27)	7.1 (57)	13.4 (21)
140+	*N*	486	289	36
	% (*n*) with rapid eGFR decline	13.4 (65)	12.5 (36)	13.9 (5)

Abbreviations: eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

Table 3. Association of BP change groups with rapid decline in eGFR

		Age-adjusted only		Adjusted[a]		Adjusted ± BP[b]	
	N (%) with rapid decline	OR	[95% CI]	OR	[95% CI]	OR	[95% CI]
Rapid decline in eGFR							
SBP decreasing (*n* = 784)	94 (12.0)	1.72*	[1.3,2.3]	1.37*	[1.0,1.8]	1.03	[0.7,1.5]
SBP stable (*n* = 2,352)	154 (6.5)	Ref	–	Ref	–	Ref	–
SBP increasing (*n* = 784)	73 (9.3)	1.47*	[1.1,2.0]	1.52*	[1.1,2.1]	1.73*	[1.3,2.4]
DBP bottom 20% (*n* = 784)	79 (10.1)	1.34*	[1.0,1.8]	1.19	[0.9,1.6]	1.25	[0.9,1.7]
DBP 21–79% (*n* = 2,352)	173 (7.4)	Ref	–	Ref	–	Ref	–
DBP top 20% (*n* = 784)	69 (8.8)	1.27	[0.9,1.7]	1.33	[1.0,1.8]	1.29	[0.9,1.8]
PP narrowing (*n* = 784)	82 (10.5)	1.43*	[1.1,1.9]	1.32	[1.0,1.8]	1.03	[0.7,1.4]
PP stable (*n* = 2,352)	162 (6.9)	Ref	–	Ref	–	Ref	–
PP widening (*n* = 784)	77 (9.8)	1.33	[1.0,1.8]	1.35	[1.0,1.8]	1.42*	[1.1,1.9]
Observations	3,920	3,920		3,772		3,772	

*$P \leq 0.05$. Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic BP; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; PP, pulse pressure; SBP, systolic BP.

[a]Adjusted for age, gender, race/ethnicity, marital status, income, education, occupational status, smoking status, general health, BMI, diabetes, and year 0 eGFR.

[b]Adjusted analysis + year 0 BP (effects of SBP change adjusted for year 0 SBP; DBP change adjusted for year 0 DBP; PP change adjusted for year 0 PP and SBP).

(*P* for interaction >0.05 for all). Finally, we repeated our main analyses after excluding 251 persons with ACR ≥30 mg/g at baseline, and results were not materially different. For example, compared to SBP stable, SBP increasing was associated with rapid decline [OR: 1.6 (95% CI 1.2, 2.3), and SBP decreasing was not significantly associated with rapid decline [OR: 1.0 (95% CI 0.6 to 1.4)] after full adjustment, including baseline BP.

Among MESA participants with a preserved eGFR at year 0, those included in this study were more likely to be younger, White, and to have socioeconomic advantages compared to those who were excluded. Included individuals also had a higher median year 0 eGFR and a lower median year 0 SBP and PP compared to individuals that were not included (Supplementary Table 1). After applying the inverse probability weights, there were no differences in baseline characteristics among MESA participants with a preserved eGFR at year 0 by sample inclusion/exclusion status (*P* values > 0.70). In addition, weighed multivariable logistic regression analyses for the outcome rapid decline were not materially different from main analyses. For example, compared with stable SBP, persons with SBP increasing had 50% higher odds of rapid renal function decline [ORs: 1.50 (95%CI 1.1, 2.1)] when adjusting for covariates and year 0 eGFR and 75% higher odds [ORs: 1.75 (95%CI 1.3, 2.1)] of rapid renal function decline after additional adjustment for year 0 SBP.

DISCUSSION

We investigated the association between 5-year BP change and subsequent renal function decline in a large, ethnically diverse cohort with preserved renal function. We found that participants with stable SBP had the slowest rates of eGFR decline. Those participants with the largest increases in SBP over 5 years had the highest likelihood of developing rapid kidney function decline later in life, across a wide range of starting SBP levels including levels not considered clinically abnormal. Decreasing SBP was also associated with higher likelihood of rapid kidney function decline compared with stable SBP, even after adjusting for demographics

Table 4. Association of BP change groups with annual change in eGFR

		Age-adjusted		Adjusted*a*		Adjusted ± BP*b*	
	Mean change [SD] ml/min/year	β	[95% CI]	β	[95% CI]	β	[95% CI]
Annual change in eGFR							
SBP decreasing	−2.44 [2.6]	−0.37*	[−0.6, −0.2]	−0.23*	[−0.4, −0.0]	−0.02	[−0.3, 0.2]
SBP stable	−2.02 [2.5]	Ref	Ref	Ref	Ref	Ref	Ref
SBP increasing	−2.37 [2.7]	−0.36*	[−0.6, −0.1]	−0.37*	[−0.6, −0.1]	−0.45*	[−0.7, −0.2]
DBP bottom 20%	−2.35 [2.5]	−0.24*	[−0.4, −0.0]	−0.15	[−0.4, 0.1]	−0.15	[−0.4, 0.1]
DBP 21–79%	−2.09 [2.6]	Ref	Ref	Ref	Ref	Ref	Ref
DBP top 20%	−2.25 [2.7]	−0.18	[−0.4, 0.0]	−0.22*	[−0.4, −0.0]	−0.21	[−0.4, 0.0]
PP narrowing	−2.26 [2.6]	−0.17	[−0.4, 0.0]	−0.11	[−0.3, 0.1]	0.06	[−0.2, 0.3]
PP stable	−2.05 [2.6]	Ref	Ref	Ref	Ref	Ref	Ref
PP widening	−2.44 [2.6]	−0.34*	[−0.6, −0.1]	−0.31*	[−0.5, −0.1]	−0.34*	[−0.6, −0.1]
Observations		3,920		3,772		3,772	

*$P \leq 0.05$. Abbreviations: BP, blood pressure; DBP, diastolic BP; CI, confidence interval; eGFR, estimated glomerular filtration rate; PP, pulse pressure; SBP, systolic BP.

[a]Adjusted for age, gender, race/ethnicity, marital status, income, education, occupational status, smoking status, general health, BMI, diabetes, and year 0 eGFR.

[b]Adjusted analysis + year 0 BP (effects of SBP change adjusted for year 0 SBP; DBP change adjusted for year 0 DBP; PP change adjusted for year 0 PP and SBP).

and comorbidities, but this association was explained by high starting SBP. Findings for DBP were sensitive to which cut-points were used and DBP change was not significantly associated with rapid kidney function decline using our prespecified cut-offs.

The relationship between BP change over time and renal function decline in healthy populations has been sparsely studied. One population-based, retrospective cohort from Flanders, Belgium, found that decreasing SBP and PP were associated with worsening renal function in patients older than 60 years old, independent of baseline BP.[11] Our findings may differ because our cohort had preserved eGFR at year 0, included both elderly and middle-aged participants, and included a more ethnically mixed population of participants.[17] The importance of repeated BP measures over time on renal function was also highlighted by a prospective cohort study by Anderson *et al.*[10] Among over 3,700 participants with established CKD, time-updated SBP measurements above 130 mm Hg over a median of 5.7 years were found to be more strongly associated with increased risk of progression to end-stage renal disease compared to a starting SBP measurement above 130 mm Hg. Our results corroborate these findings in a population with preserved eGFR.

In the setting of randomized controlled trials, aggressive BP goals have resulted in faster rates of renal function decline.[4,7,21] Our results associate decreasing SBP with increased odds of rapid kidney function decline, but the association is completely attenuated after accounting for year 0 SBP. Notably, the mean year 0 SBP was 144 mm Hg in the decreasing group, which may indicate a history of exposure to hypertension. This finding highlights the importance of history of BP in determining risk of renal dysfunction. Several studies have examined the association between cumulative exposure to elevated BP and cardiovascular outcomes. For example, among participants in MESA with SBP <120 mm Hg, those on BP medications had more than 2-fold odds of developing cardiovascular disease compared to participants who did not take any BP medications.[9] In the Atherosclerosis Risk in Communities (ARIC) study cohort which included nearly 16,000 45- to 64-year old, community-dwelling adults randomly chosen across 4 study sites in the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN), higher cumulative SBP load was associated with increased odds of cardiovascular disease mortality, independent of one-time BP measurements.[8]

Interestingly, in the SBP increasing group, where we found the highest odds of rapid renal function decline, median year 0 BP was 110 mm Hg and increased to a median of 131 mm Hg at year 5, values well below current JNC8 guidelines for treatment of hypertension. This finding suggests that increasing SBP change compared with stable SBP may have a deleterious effect on renal function well before the onset of clinically significant hypertension. This process may occur through hypertensive nephrosclerosis *via* alterations in kidney hemodynamics and changes in autoregulatory mechanisms in the renal vasculature.[22] The development of nephrosclerotic changes may occur in certain patient populations, specifically African Americans, more frequently than other ethnic groups.[23]

Strengths of this study include its large size, multiethnic participants, population with preserved eGFR at year 0, prospective design, and use of cystatin C to calculate eGFR. Limitations include the fact that BP and eGFR change were only obtained during study visits and therefore we may have missed some clinically significant fluctuations in these 2 measurements between these time points. Also, participants with lower year 0 BPs tended to increase BP

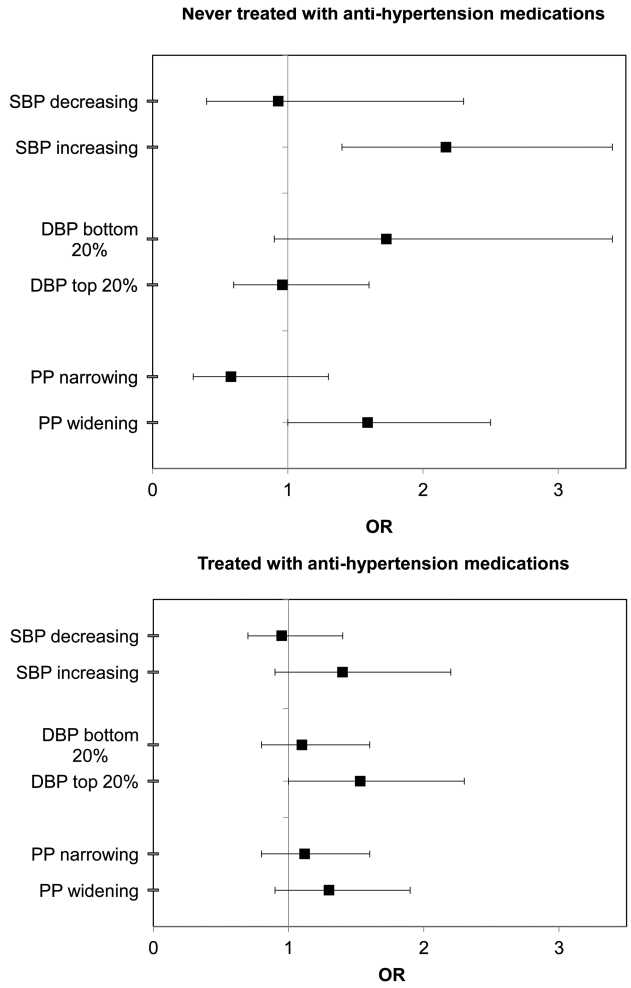

Figure 2. (**a** and **b**): Association of BP change with rapid kidney function decline among those never treated and treated with antihypertension medications (fully adjusted model 3, stable BP group is referent for all 3 BP categories). Abbreviations: BP, blood pressure; DBP, diastolic BP; OR, odds ratio; PP, pulse pressure; SBP, systolic BP.

over the 5-year period, while those with higher year 0 BP tended to decrease BP. This trend could represent regression to the mean and highlight the inherent measurement uncertainties of ascertaining BP. However, regression to the mean would be expected to bias toward the null and significant results were found in this study. Our study also was not powered to make conclusions about the effect of antihypertension medications on renal outcomes, and we did not have information on the number or types of antihypertension agents used. We also did not have information on changes in medication use during the study period. Additionally, some participants who did not have renal function data between year 5 and 10 were not included in the analysis because they died during this time period. As such, our findings may be biased by only including survivors. Data on ACR were only available mid-point in the BP change determination phase, as opposed to other covariates that were included in our analysis at year 0. Finally, our findings that increases in SBP are associated with increased odds of rapid kidney function decline compared to more stable SBP could in part reflect increased cumulative exposure to higher levels of BP among persons with increasing SBP.[24] However, this association was observed even among persons with SBP levels at year 0 not considered to be elevated (<120 mm Hg).

To our knowledge, this is one of the first prospective cohort studies examining the relationship between BP change and its association with subsequent renal function in a population with preserved eGFR. Our findings support the hypothesis that BP change is an important factor determining subsequent renal function. When thinking about potential renal dysfunction, clinicians should consider taking into account change in BP even if they have not yet met established thresholds for treatment of hypertension among patients with preserved eGFR.

SUPPLEMENTARY DATA

Supplementary data are available at *American Journal of Hypertension* online.

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DISCLOSURE

Dr Shlipak is a Scientific Advisor for Cricket Health and Tai Diagnostics. Dr Peralta is a consultant for Cricket Health Inc. and Vital Labs Inc. Other authors declared no conflict of interest.

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