Blood Pressure Components and Decline in Kidney Function in Community-Living Older Adults: The Cardiovascular Health Study

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BACKGROUND
Although hypertension contributes to kidney dysfunction in the general population, the contributions of elevated systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) to kidney function decline in community-dwelling older adults are unknown.

METHODS
We used linear and logistic regression to examine the separate and combined associations of SBP, DBP, and PP at baseline with kidney function decline among 4,365 older adults in the Cardiovascular Health Study. We used cystatin C to estimate glomerular filtration rate on 3 occasions over 7 years of follow-up. We defined rapid decline ≥ 3 ml/min/year.

RESULTS
Average age was 72.2 and mean (standard deviation) SBP, DBP, and PP were 135 (21), 71 (11), and 65 (18) mm Hg, respectively. SBP and PP, rather than DBP, were most significantly associated with kidney function decline. In adjusted linear models, each 10-mm Hg increment in SBP and PP was associated with 0.13 ml/min/year (–0.19, –0.08, $P < 0.001$) and 0.15-ml/min/year faster decline (–0.21, –0.09, $P < 0.001$), respectively. Each 10-mm Hg increment in DBP was associated with a nonsignificant 0.10-ml/min/year faster decline (95% confidence interval, –0.20, 0.01). In adjusted logistic models, SBP had the strongest associations with rapid decline, with 14% increased hazard of rapid decline (95% confidence interval, 10% to 17%, $P < 0.01$) per 10 mm Hg. In models combining BP components, only SBP consistently had independent associations with rapid decline.

CONCLUSIONS
Our findings suggest that elevated BP, particularly SBP, contributes to declining kidney function in older adults.

Keywords: blood pressure; cystatin C; diastolic blood pressure; elderly; hypertension; kidney function; systolic blood pressure.

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Chronic kidney disease is very common in the US population, and it is present in >30% of adults over age 65.[1] High blood pressure (BP) is a well-established risk factor for chronic kidney disease and end stage renal disease in youth and middle age.[2,3] Elevated pressure in the renal vasculature and consequent elevated intraglomerular pressure lead to failure of autoregulation and endothelial dysfunction and eventually to progressive glomerular and interstitial fibrosis.

In contrast, data on the association of high BP with kidney function decline in the elderly, in whom hypertension is highly prevalent,[4] are less clear.[5,6] In particular, neither randomized trial data nor genome-wide association study data provide clear supporting data for associations between lower BP and reduced risk for kidney function decline. For example, in the placebo arm of the Systolic Hypertension in the Elderly Program, elevated systolic pressure was associated with kidney

function decline. Because this arm only included individuals with systolic hypertension, it cannot be easily generalized to a community-dwelling older population.[7] The Hypertension in the Very Elderly Trial has not reported kidney function outcomes. In the large International Consortium for Blood Pressure Genome-Wide Association studies, which provide analysis of associations between BP variants and cardiovascular disease, no association was seen between these variants and chronic kidney disease.[8]

In addition, the relative associations of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) with kidney function decline in the elderly are uncertain. This is of particular clinical importance because hypertension in the elderly is primarily characterized by high SBP and normal to low DBP (isolated systolic hypertension [ISH]).[9] In the Cardiovascular Health Study, SBP was the best predictor of cardiovascular events, not PP or DBP.[10] In the Framingham Heart Study, however, the association of each BP component with cardiovascular risk varied by age; contrary to associations in young and middle age, PP was the strongest predictor of coronary heart disease in the elderly and DBP was negatively associated with risk.[11] The associations of each BP component with kidney function decline are not well known.

Recently, the American Heart Association consensus statement on treatment of hypertension in older adults highlighted this large knowledge gap.[12] Therefore, we designed this study to examine the associations of SBP, DBP, and PP with kidney function decline using data from the Cardiovascular Health Study.

METHODS

Study population

The Cardiovascular Health Study recruited individuals aged ≤ 65 years from Medicare eligibility lists in 4 US communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania).[13] The study recruited an initial cohort of 5,201 primarily white individuals in 1989–1990 (baseline). Subsequently, in 1992–1993 (study year 3), an additional 687 African American participants were recruited. Blood samples that were collected in 1989–1990, 1992–1993, and 1996–1997 (baseline, year 3, and year 7) were assayed for kidney function. We included all individuals with baseline measures of BP and at least 2 available measures of kidney function. In total, 4,365 of the 5,888 participants in the Cardiovascular Health Study met criteria for inclusion in this analysis.

All participants provided written informed consent. The institutional review boards of the University of Washington and the affiliated clinical centers approved the study.

Predictor variables: Systolic, diastolic, and pulse pressures

BP was assessed at the initial clinic visit. Participants were asked to fast for at least 12 hours and to refrain from smoking for 30 minutes before the clinic visit. Trained study personnel obtained 3-seated BP readings with a random zero sphygmomanometer; the average of the last 2 readings was recorded. Patients were also asked about a history of hypertension, and the use of antihypertensive medications was noted using a medication inventory interview.[14] PP was calculated as the difference between the average SBPs and DBPs.

Outcome variables: Change in estimated glomerular filtration rate using cystatin C

Cystatin C levels were measured from frozen samples using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade Behring [now Siemens Healthcare Diagnostics Inc], Deerfield, IL) with a nephelometer (BNII, Siemens Healthcare Diagnostics Inc). Previous work has shown this assay to be stable through several freeze–thaw cycles.[15] Intraassay coefficients of variation ranged from 2.0% to 2.8%, and inter coefficients of variation ranged from 2.3% to 3.1%.

To calculate change in kidney function over time, we first used estimating equations to transform each cystatin C measurement into a glomerular filtration rate (GFR) estimate. This transformation was derived from a pooling of cohorts that used iothalamate clearance as the criterion standard; we used the equation $eGFR_{cys} = 76.7 \times cystatin\ C^{-1.19}$.[16] Rates of change were calculated using the 2 or 3 available $eGFR_{cys}$ measurements by calculating a least-squares regression slope. As in previous work, we defined an annual loss of 3 ml/min/1.73 m² as rapid decline; this change is known to be associated with clinically deleterious outcomes.[17,18]

Covariates

We examined a number of covariates that might plausibly confound the associations between systolic, diastolic, and pulse pressures and kidney function changes. We included demographic variables (age, gender, race); cardiovascular risk factors including body mass index, smoking, diabetes (use of insulin or an oral hypoglycemic agent or a fasting blood sugar >7 mmol/L [126 mg/dl]), low-density lipoprotein and high-density lipoprotein; and prevalent cardiovascular disease (transient ischemic attack, stroke, coronary artery disease, myocardial infarction, or heart failure). Demographic variables that were not different across groups (income, education) were not included as covariates.

Analytical methods

We first examined the distribution of baseline characteristics according to categories of SBP (by 10-mm Hg increments) using analysis of variance or χ^2 where appropriate. We modeled SBP and DBP as continuous variables in graphical form, using generalized additive models. After confirming linear relationships with kidney function decline, we categorized BP values in 10-mm Hg increments.

We proceeded to examine the associations of systolic, diastolic, and pulse pressures separately with change in kidney

function. For these analyses, we used a series of nested linear models. Initially we examined unadjusted associations, then we used models adjusted for demographic factors and risk factors for cardiovascular disease.

We then used logistic regression to evaluate associations between each BP component and rapid decline in kidney function as a dichotomized outcome as above, using the lowest category of BP as the referent. Finally, we evaluated potential joint effects of the 3 BP components by adding them in pair-wise combinations to a model of rapid decline in $eGFR_{cys}$.

Due to the high prevalence of ISH in the elderly, we also performed a separate analysis to examine the association of each BP component with kidney function decline among persons with SBP ≥ 140 mm Hg and DBP < 90 mm Hg. In a secondary a priori analysis, we stratified by use of antihypertensive medications in both the entire cohort and in those with ISH to determine whether associations between BP components and kidney function decline would differ among users and nonusers of antihypertensive medications. We assessed P values for interaction between BP components and medications with kidney function decline. We performed sensitivity analyses using only those with 3 measures of kidney function (58% of cohort) and using generalized estimating equations instead of linear models. We also assessed whether results were robust using combined cystatin C and creatinine-based GFR estimating equations.

Analyses were performed using S-Plus (release 8.0; Insightful Inc, Seattle, Washington) and SPSS statistical software (release 16.0.2; SPSS Inc, Chicago, IL).

RESULTS

Of the original 5,888 individuals recruited for the Cardiovascular Health Study, 1,523 did not have repeated measures of cystatin C and thus were excluded from this study. These individuals were older and had more comorbidities than those who had repeated measures of cystatin C, as reported previously.[18] Of the 4,365 participants included in this study, mean (standard deviation) systolic, diastolic, and pulse pressures were 135 (21), 71 (11), and 65 (18) mm Hg, respectively; 1,994 (46%) reported antihypertensive use. In general, those with higher SBP were older, had higher BMI and wider PP, and were more likely to have diabetes, subclinical and prevalent cardiovascular disease (Table 1). Isolated systolic hypertension was present in 1,499, representing 34% of the cohort but 61% of those with hypertension at the study visit. Median (interquartile range) annual decline in $eGFR_{cys}$ was −1.58 [−3.00, −0.33]. Rapid decline in $eGFR_{cys}$ was seen in 1,075 (25%) of the cohort overall, with increasing rates among those with higher SBP (Figure 1).

Among the entire cohort, we found that higher SBP was associated with faster kidney function decline. In multivariate linear models, for each 10-mm Hg increment in SBP, there was a 0.13-ml/min/year faster decline in $eGFR_{cys}$ (95% confidence interval, 0.08, 0.19, $P < 0.001$); higher PP was also associated with faster decline, whereas the association of DBP with decline was not significant (Table 2).

Distribution of antihypertensive medication classes between those with or without rapid decline in kidney function were not significantly different. We stratified by

Table 1. Participant characteristics at baseline by systolic blood pressure categories

Characteristic	Systolic blood pressure (mm Hg)					
	< 120	120–129	130–139	140–149	150–159	≥ 160
N	1,022	835	828	677	442	561
Age, years	71 (5)	72 (5)	72 (5)	73 (5)	73 (5)	74 (5)
Male	409 (40%)	364 (44%)	357 (43%)	260 (38%)	159 (36%)	219 (39%)
African American	86 (8%)	103 (12%)	107 (13%)	91 (13%)	86 (20%)	109 (19%)
Diabetes	93 (9%)	103 (12%)	131 (16%)	114 (17%)	73 (17%)	102 (18%)
Former smoker	45 (45%)	357 (43%)	354 (43%)	276 (41%)	184 (42%)	238 (43%)
Current smoker	143 (14%)	99 (12%)	83 (10%)	53 (8%)	38 (9%)	49 (9%)
Body mass index, kg/m^2	25.8 (4.2)	26.5 (4.6)	27.2 (4.5)	27.3 (4.6)	27.1 (4.7)	26.9 (4.8)
Diastolic blood pressure, mm Hg	63 (8)	68 (9)	71 (10)	74 (10)	77 (10)	80 (12)
Pulse pressure, mm Hg	47 (9)	57 (9)	63 (10)	71 (10)	77 (10)	94 (16)
Low-density lipoprotein, mg/dl	129 (36)	130 (34)	130 (35)	131 (34)	128 (35)	132 (35)
High-density lipoprotein, mg/dl	55 (16)	54 (16)	54 (15)	54 (15)	56 (17)	55 (15)
Triglycerides, mg/dl	113 [88, 153]	122 [92,1.64]	124 [96,169]	130 [94,178]	122 [89,163]	120 [94,166]
Hemoglobin, g/dl	14.0 (1.3)	14.1 (1.4)	14.0 (1.3)	14.0 (1.3)	13.9 (1.2)	14.0 (1.7)
Prevalent cardiovascular disease	218 (21%)	202 (24%)	183 (22%)	139 (21%)	92 (21%)	144 (26%)
Prevalent heart failure	29 (3%)	29 (4%)	30 (4%)	13 (2%)	13 (3%)	22 (4%)
$eGFR_{cys}$, ml/min/1.73 m^2	82 (43)	79 (18)	79 (17)	78 (18)	79 (18)	77 (20)
Taking blood pressure medications	362 (35%)	347 (42%)	387 (47%)	330 (49%)	216 (49%)	352 (63%)

use of antihypertensive medications as specified a priori; however, the *P* values for interaction were not statistically significant for the associations of SBP, DBP, or PP with kidney function decline. In addition, the association between DBP and kidney decline appeared qualitatively different between treated vs. untreated persons. Among those not using antihypertensive medications, higher DBP was associated with faster kidney function decline, whereas there was no association among treated persons (Table 2).
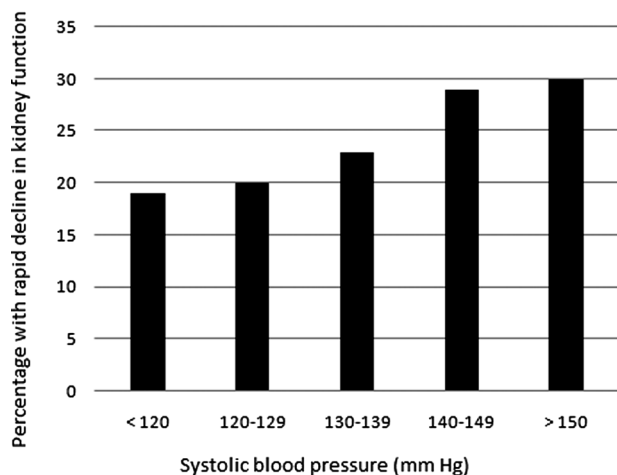
Figure 1. Rates of rapid decline of kidney function across systolic blood pressure categories.

We then considered the association of clinically significant categories of systolic, diastolic, and pulse pressures with rapid decline in kidney function. Higher SBP categories were associated with faster rates of kidney function decline. Compared with persons with SBP < 120, persons with SBP 130 had only a 27% higher odds of rapid decline, while persons with SBP ≥ 140 had almost 2-fold higher odds of rapid decline in kidney function; similar associations were seen for PP, with approximately 2-fold risk seen with PP > 80 mm Hg. The odds of rapid decline associated with elevated DBP were less pronounced, with a 50% increased risk in those with DBP > 90 mm Hg (Figure 2).

When we studied the association of each BP component with kidney function decline among persons with ISH, we found that SBP was associated with kidney function decline only among those not taking antihypertensive medications (Table 3). In contrast, the association of SBP and kidney function decline was not significant among participants with treated ISH (*P* value for interaction, 0.079).

When we added BP components sequentially to a model of rapid change in eGFR$_{cys}$, we found that SBP attenuated the associations between either DBP or PP and rapid decline (Table 4), suggesting that findings with PP were driven mainly by SBP.

In sensitivity analyses, results were robust in those with 3 vs. 2 measures of kidney function and were similar using the generalized estimating equation modeling technique. Use of combined cystatin C– and creatinine-based eGFR estimates did not substantially alter the results of the analysis.

Table 2. Blood pressure as a predictor of change in eGFR$_{cys}$ in ml/min/1.73 m^2/year (linear regression)

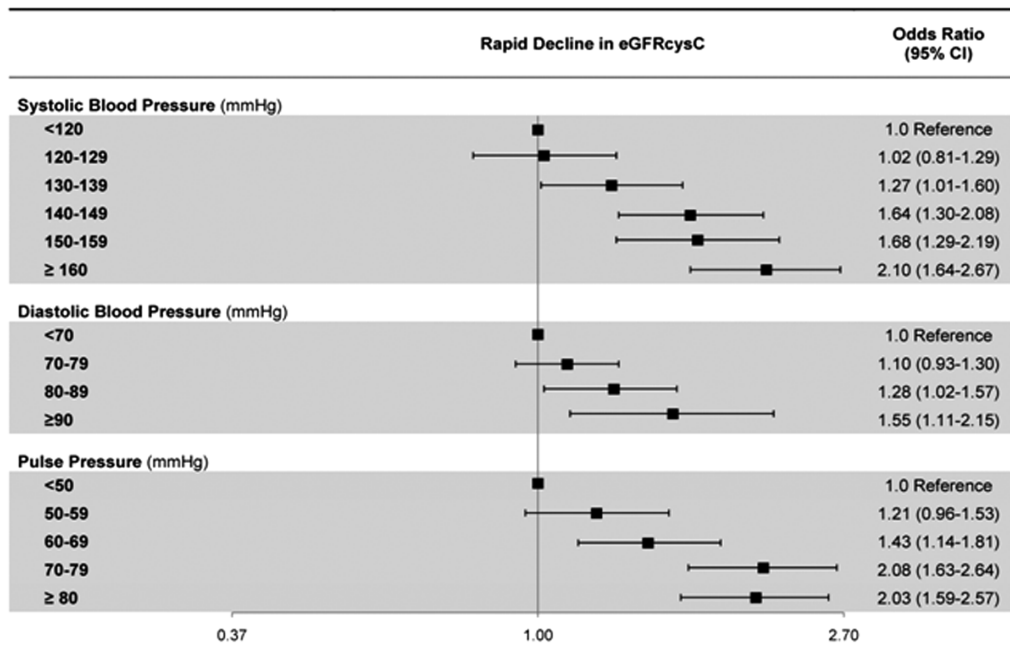| Continuous blood pressure measures	ΔeGFR$_{cys}$					
	Full cohort		Stratified by hypertensive medication use at baseline			
			No (n = 2,371)		Yes (n = 1,994)	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Systolic blood pressure (per 10 mm Hg)†						
Unadjusted	–0.15 (–0.20, –0.10)	<0.001	–0.17 (–0.25, –0.08)	<0.001	–0.15 (–0.20, –0.09)	<0.001
Demo adjusted[a]	–0.14 (–0.19, –0.09)	<0.001	–0.16 (–0.24, –0.07)	0.001	–0.13 (–0.19, –0.08)	<0.001
Fully adjusted[b]	–0.13 (–0.19, –0.08)	<0.001	–0.13 (–0.22, –0.04)	0.004	–0.13 (–0.19, –0.08)	<0.001
Diastolic blood pressure (per 10 mm Hg)‡						
Unadjusted	–0.09 (–0.19, 0.01)	0.080	–0.16 (–0.32, –0.004)	0.045	–0.01 (–0.12, 0.10)	0.865
Demo adjusted[a]	–0.10 (–0.20, 0.03)	0.056	–0.18 (–0.34, –0.017)	0.031	–0.01 (–0.12, 0.10)	0.801
Fully adjusted[b]	–0.10 (–0.20, 0.01)	0.051	–0.17 (–0.33, 0.001)	0.051	–0.03 (–0.14, 0.08)	0.631
Pulse pressure (per 10 mm Hg)§						
Unadjusted	–0.17 (–0.23, –0.11)	<0.001	–0.16 (–0.26, –0.06)	0.002	–0.19 (–0.25, –0.13)	<0.001
Demo adjusted[a]	–0.16 (–0.22, –0.10)	<0.001	–0.15 (–0.25, –0.04)	0.007	–0.18 (–0.25, –0.12)	<0.001
Fully adjusted[b]	–0.15 (–0.21, –0.09)	<0.001	–0.12 (–0.23, –0.01)	0.029	–0.18 (–0.24, –0.11)	<0.001

Abbreviation: CI, confidence interval.
[a]Adjusted for age, gender, race.
[b]Adjusted for age, gender, race, body mass index, smoking, diabetes mellitus, prevalent cardiovascular disease, low-density lipoprotein, and high-density lipoprotein .
†*P* value for interaction between systolic blood pressure and hypertensive medications = 0.802.
‡*P* value for interaction between diastolic blood pressure and hypertensive medications = 0.191.
§*P* value for interaction between pulse pressure and hypertensive medications = 0.419.

Figure 2. Adjusted association of blood pressure categories with rapid decline in eGFR$_{cys}$.

Table 3. Blood pressure as a predictor of change in eGFR$_{cys}$ in participants with isolated systolic hypertension (linear regression)

	ΔeGFR$_{cys}$					
	Isolated systolic hypertension (SBP ≥ 140 and DBP < 90) N = 1,499		Stratified by hypertensive medication use at baseline			
			No (n = 711)		Yes (n = 788)	
Continuous BP measures	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
SBP (per 10 mm Hg)						
Unadjusted	0.06 (0.16, 0.04)	0.231	0.17 (0.32, 0.03)	0.019	0.01 (0.13, 0.14)	0.990
Demo adjusted[a]	0.04 (0.14, 0.06)	0.416	0.16 (0.31, 0.01)	0.032	0.03 (0.11, 0.16)	0.721
Fully adjusted[b]	0.04 (0.14, 0.06)	0.457	0.15 (0.29, 0.01)	0.049	0.03 (0.10, 0.17)	0.639
DBP (per 10 mm Hg)						
Unadjusted	0.02 (0.12, 0.16)	0.788	0.10 (0.30, 0.10)	0.321	0.12 (0.09, 0.33)	0.248
Demo adjusted[a]	0.001 (0.15, 0.15)	0.996	0.14 (0.34, 0.07)	0.189	0.11 (0.10, 0.33)	0.300
Fully adjusted[b]	0.04 (0.19, 0.11)	0.567	0.19 (0.39, 0.01)	0.066	0.08 (0.14, 0.29)	0.475
PP (per 10 mm Hg)						
Unadjusted	0.06 (0.15, 0.03)	0.210	0.09 (0.22, 0.04)	0.160	0.04 (0.17, 0.08)	0.494
Demo adjusted[a]	0.04 (0.13, 0.06)	0.447	0.07 (0.21, 0.06)	0.287	0.02 (0.15, 0.11)	0.770
Fully adjusted[b]	0.02 (0.11, 0.08)	0.737	0.04 (0.17, 0.09)	0.556	0.001 (0.13, 0.13)	0.990

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; ISH, isolated systolic hypertension; PP, pulse pressure; SBP, systolic blood pressure.

P value for interaction between SBP and hypertensive medications = 0.079. P value for interaction between DBP and hypertensive medications = 0.112. P value for interaction between PP and hypertensive medications = 0.608. ISH is defined as systolic blood pressure ≥ 140 and diastolic blood pressure < 90.

[a]Adjusted for age, gender, and race.

[b]Adjusted for age, gender, race, body mass index, smoking, diabetes mellitus, prevalent cardiovascular disease, low-density lipoprotein, and high-density lipoprotein.

Table 4. Comparison of BP measures with risk of rapid decline (decline in eGFR$_{cys}$ > 3 ml/min/1.73 m^2)

Model (adjusted [a])	Δ eGFR$_{cys}$ > 3		
	SBP [b]	DBP [b]	PP [b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
SBP	1.14 (1.10, 1.17)	--	--
DBP	--	1.09 (1.02, 1.17)	--
PP	--	--	1.15 (1.11, 1.20)
SBP + DBP	1.15 (1.11, 1.20)	0.94 (0.87, 1.02)	--
SBP + PP	1.09 (1.02, 1.16)	--	1.06 (0.98, 1.15)
DBP + PP	--	1.09 (1.02, 1.16)	1.15 (1.11, 1.20)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure.
[a]Adjusted for age, gender, race, hypertension medications, body mass index, smoking, diabetes mellitus, prevalent cardiovascular disease, low-density lipoprotein, and high-density lipoprotein.
[b]Continuous per 10 mm Hg

DISCUSSION

We found that in this large cohort of community-dwelling elderly individuals, each component of BP was associated with kidney function decline, with SBP having the strongest association. Our findings were parallel to those observed by Psaty and colleagues in examining BP components and cardiovascular outcomes in the same cohort[10]; in both investigations SBP had stronger independent associations with the outcomes of interest in comparison with PP or DBP.

Our data provide additional support for the association of systolic hypertension with kidney function decline, even in an older population. We observed a statistically significant risk of rapid kidney function decline associated with SBP levels > 130 mm Hg, values below those recommended as treatment targets for the general hypertensive population.

A number of studies have suggested increased risk of other outcomes, such as stroke and cardiovascular and all-cause mortality, at low DBP levels in older adults.[19–21] In those with ISH in the Systolic Hypertension in the Elderly Program Study, DBP was not significantly associated with declining kidney function.[22] We demonstrated an absence of significant associations between DBP and declining kidney function, both in the overall cohort and in those with ISH. This finding may add to the overall idea that it is systolic, rather than diastolic, hypertension that is of most importance in older adults, whereas in prior studies in younger populations, both diastolic and systolic hypertension were associated with progression to end-stage kidney failure.[3]

Of interest is the subgroup finding that those with treated ISH did not have the same association between SBP and decline as did those not taking antihypertensive agents. There are several potential explanations for this observation, including confounding by indication or by unmeasured comorbidities. It is possible that those not treated could potentially benefit from treatment in terms of preservation of kidney function; however, this cannot be inferred from our observational data.

Our finding that PP is associated with kidney function decline suggests that arterial stiffness is an important component when considering the associations of BP and kidney function decline in the elderly. In this cohort, as in other older cohorts, PP is mainly driven by elevations in SBP rather than decreases in DBP, explaining the attenuation of the association between PP and kidney function decline after adjusting for SBP. This phenomenon is likely explained by increased arterial stiffness associated with aging; in this age group, elevations in SBP are indicative of arterial stiffness.

In our study, overall findings were similar for SBP regardless of whether BP medication was in use to achieve any given BP level. This is in contrast to associations between BP components and cardiovascular outcomes, which were attenuated in those taking antihypertensive medications.[14] Antihypertensive medications may have pleiotropic effects unrelated to BP control on cardiovascular outcomes,[23] whereas in the case of kidney function, their effect may occur mainly through achieved BP control. Of note, the prevalence of angiotensin-converting-enzyme inhibitor use in this study was low at baseline (less than 7%), and we did not have power to detect an interaction of angiotensin-converting-enzyme inhibitors and BP with kidney function decline. We did detect somewhat diminished associations between diastolic hypertension and kidney function decline in those who reported the use of antihypertensive agents. Although our overall findings are that DBP does not have independent associations with kidney function decline, this could suggest some additional effect of medication use on kidney function decline in those with diastolic hypertension and can be explored in further studies.

The strengths of this study include the large sample, detailed measures of important potential confounders, repeated measures of kidney function, and long follow-up time. Whereas most of the available clinical trial data are from studies that excluded participants with comorbid diseases, this cohort study included a broad sample of older adults with multiple comorbid conditions and thus is more generalizable to older adults.

This study also has several limitations. The subset of participants we could study were able to return for at least 1 follow-up visit and thus are healthier than the original community-based sample. Since the data were collected in an

observational cohort setting, use of antihypertensive medications was at the discretion of the participant and his or her physician, and thus we cannot infer a causal relationship between BP treatment and outcomes. Interestingly, interaction terms for treated vs. untreated BP were nonsignificant, suggesting that achieved SBP level rather than medication use itself was most important in driving kidney function outcomes in this cohort. We do not have information on proteinuria, which is known to have significant effects on risk of progressive kidney disease, nor do we have measured GFR by direct clearance. We did not observe an increased risk of kidney function decline in those with SBP < 120 mm Hg or DBP < 70 mm Hg, but our confidence limits do not allow us to exclude a J-shaped association at the extremes of low SBP or DBP.

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DISCLOSURE

The authors declared no conflict of interest.

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