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Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders

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ABSTRACT

Background. Previous studies in HIV-infected individuals have demonstrated serum albumin to be strongly associated with kidney function decline, independent of urine albumin and inflammatory markers. Lower serum albumin concentrations may be an under-appreciated risk factor for kidney function decline in elders.

Methods. We performed a cohort analysis in the Health Aging and Body Composition Study, a cohort of well-functioning, biracial, community-dwelling elders between the age of 70 and 79 years. We examined the associations of serum albumin concentration with longitudinal kidney function decline by estimated glomerular filtration rate (eGFR). Outcomes included linear eGFR decline, rapid kidney function decline defined as >30% decrease in eGFR, defined as a final eGFR <60 mL/min/1.73 m^2 in those with an eGFR >60 mL/min/1.73 m^2 at baseline. Cystatin C-based eGFR was calculated at baseline, Year 3 and Year 10.

Results. Mean age was 74 years, and mean eGFR was 73 mL/min/1.73 m^2 at baseline. The mean rate of eGFR change was 1.81 mL/min/1.73 m^2 per year. After multivariate adjustment, lower serum albumin concentrations were strongly and independently associated with kidney function decline (−0.11 mL/min/1.73 m^2 per year for each standard deviation decrease serum albumin; −0.01 to − 0.20) with no attenuation after adjustment for urine albumin and inflammatory markers (−0.12, −0.03 to − 0.22). When divided into quartiles, serum albumin levels ≤3.80 g/dL were associated with increased odds of rapid kidney function decline (odds ratio 1.59; 1.12–2.26) and increased risk of incident chronic kidney disease (incident rate ratio 1.29; 1.03–1.62) relative to levels >4.21g/dL. Urine albumin to creatinine ratio (ACR) was also significantly and independently associated with kidney function decline (−0.08 mL/min/1.73 m^2 per year for urine ACR >30 mg/g; −0.82 to − 0.13).

Conclusions. Lower serum albumin levels are strongly and independently associated with kidney function decline in elders, independent of clinical risk factors, urine albumin and measured inflammatory markers.

Keywords: albumin, CKD, ESRD, age, inflammation

INTRODUCTION

Reduced kidney function in the elderly population is strongly and independently associated with cardiovascular disease, heart failure and mortality [1, 2]. The underlying risk factors for the

onset and progression of kidney disease in elders are incompletely characterized, but include older age, black race, diabetes, hypertension and cardiovascular disease [3].

One potentially under-appreciated risk factor for kidney function decline is low serum albumin concentration. Previous studies have shown even small decrements in levels of serum albumin concentration to be strongly associated with cardiovascular disease, heart failure and mortality in vulnerable populations, such as elderly and HIV-infected individuals [4–6]. Limited research has linked low albumin levels to kidney function decline. Investigations in the Cardiovascular Health Study found that serum albumin was independently associated with higher risk of kidney function decline, whereas several inflammatory markers had no significant associations [7]. However, the study did not have concurrent measures of urine albumin concentrations, so it could not discern the contribution of urine losses of albumin—an established prognostic marker of kidney disease and potential confounder. Tangri demonstrated that serum albumin concentrations are an important component of a multi-marker predictive model for progression to end-stage renal disease (ESRD) in a cohort of Canadian adults with known chronic kidney disease (CKD) [8]. Recently, we demonstrated that serum albumin levels are an important predictor of kidney function decline in HIV-infected individuals, independent of albuminuria and known liver disease [9].

It remains unclear whether the associations of low serum albumin levels with kidney function decline reflect underlying inflammation, urine albumin, chronic illness or some combination of factors. To our knowledge, no study in a racially diverse cohort of elders has jointly examined the associations of serum and urine albumin concentration with kidney function decline independently of inflammatory markers. In this study, we hypothesized that serum albumin would be an important prognostic biomarker for kidney function decline and CKD risk in an elderly, bi-racial cohort, the Health, and Body Composition Study (Health ABC), and that the associations would be independent and complementary to urine albumin levels.

MATERIALS AND METHODS

Study population

Health ABC enrolled 3075 high-functioning men and women in generally good health between the ages of 70 and 79 years. Recruitment took place in Memphis, TN and Pittsburg, PA between April 1997 and June 1998; inclusion required that the participant planned to remain in the area for at least 3 years. Other inclusion criteria were the ability to perform activities of daily living, walk a quarter of a mile and climb 10 steps, and the absence of life-threatening illness. For this analysis, we included 2598 of the original participants who had serum albumin, urine albumin, baseline cystatin C and at least one follow-up measure of cystatin C. Further details of the Health ABC design and methods have been described previously [10].

Serum albumin

Serum albumin levels were measured at the Health ABC Core Laboratory at the University of Vermont, where the concentration of serum albumin in blood samples was determined using the bromocresol green method (Vitros; Orthoclinical Diagnostics Inc., Rochester, NY, USA). We analyzed serum albumin concentrations as a continuous variable [per standard deviation (SD)] and a categorical variable divided into quartiles ($>$4.21, 4.01–4.21, 3.81–4.00, $\leq$3.80). Since urine albumin values are heavily right skewed, urine albumin was log transformed to the Base 2 and treated as a continuous variable (per doubling); we also dichotomized urine albumin to creatinine ratio (ACR) at 30 mg/g versus lesser values, and categorized urine ACR into quartiles. Secondary predictors included C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) modeled as log transformed to the Base 2 continuous variables.

Outcomes

We determined estimated glomerular filtration (eGFR) rate using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for cystatin C (eGFRcys). Cystatin C was measured at the baseline visit, Year 3 and Year 10. We chose cystatin C because it is less biased by muscle mass than creatinine, and also because creatinine measurement methods changed during follow-up of Health ABC. We evaluated three potential outcomes: first, we examined eGFRcys as the continuous outcome of annual change expressed as mL/min/1.73 m^2 per year; second, we examined rapid kidney function decline defined as a 30% or more decline in eGFR from baseline, as has been recommended [11]; and third, we examined incident reduced eGFR, defined as a final eGFR $<$60 mL/min/1.73 m^2 and a rate of decline of at least 1 mL/min/1.73 m^2 per year.

Covariates

For this study, candidate covariates included sociodemographic factors (age, sex, race, clinical site and education level); lifestyle factors (current smoking and alcohol use); and comorbid conditions [body mass index (BMI), diabetes (defined by use of hypoglycemic agents, self-report, fasting plasma glucose $>$126 mg/dL or an oral glucose tolerance test $>$200 mg/dL), use of antihypertensive medications, systolic blood pressure, diastolic blood pressure, prevalent heart failure, coronary artery disease, peripheral arterial disease and chronic obstructive pulmonary disease].

Analysis

For continuous outcomes of kidney function decline, we used linear-mixed models with random intercepts and slopes to estimate and compare linear trends in eGFR over time. Rapid kidney function decline was assessed as a dichotomized outcome at $>$30% decline. For this outcome, we estimated odds ratios using multivariate logistic regression. The change in eGFR was calculated from an ordinary least squares model that takes the observed slope of eGFR over all time points. Incident CKD was also evaluated as a dichotomized outcome for patients reaching the threshold of $<$60 mL/min/1.73 m^2. To prevent this outcome from being reached by small changes in eGFR, we required that participants have at least a 1 mL/min/1.73 m^2 annual decline in eGFR, improving the specificity of the

Table 1. Characteristics of elders in the health aging and body composition study by serum albumin quartiles

Parameter	Serum albumin (g/dL)				
	Q1	Q2	Q3	Q4	All
Range	>4.21	4.01–4.21	3.81–4.00	≤3.80	
n	510	566	646	875	2598
Age	73 (3)	74 (3)	73 (3)	74 (3)	74 (3)
Male	290 (57)	284 (50)	299 (46)	380 (43)	1253 (48)
African American	185 (36)	209 (37)	254 (39)	374 (43)	1022 (39)
eGFR-cysC	72 (18)	73 (18)	73 (18)	73 (18)	73 (18)
eGFR<60	131 (26)	133 (24)	137 (21)	211 (24)	612 (24)
Urine ACR[a]	9.7 [5.2–25.7]	8.6 [4.9–19.3]	8.2 [4.6–19.6]	6.9 [3.9–16.6]	8.1 [4.4–19.8]
Urine albumin[a]	10.6 [4.9–27.6]	8.9 [4.6–20.1]	9.5 [3.8–24.5]	8.7 [4.1–21.2]	9.2 [4.2–22.5]
Urine ACR >30	116 (23)	88 (16)	104 (16)	128 (15)	436 (17)
Smoking					
Current	236 (46)	270 (48)	299 (46)	393 (45)	1198 (46)
Alcohol					
Current	102 (20)	126 (22)	155 (24)	177 (20)	560 (22)
General health					
Fair	61 (12)	61 (11)	99 (15)	136 (16)	357 (14)
Poor	4 (1)	8 (2)	2 (0.3)	3 (0.3)	17 (0.8)
Prevalent HF	18 (4)	10 (2)	12 (2)	23 (3)	64 (3)
Prevalent CAD	113 (23)	120 (21)	135 (21)	167 (20)	535 (21)
BMI	26.8 (4.3)	27.2 (4.2)	27.4 (5.0)	27.8 (5.1)	27.4 (4.8)
CRP[a]	1.48 [0.92–2.65]	1.56 [0.96–2.91]	1.74 [0.99–3.18]	1.88 [1.05–3.47]	1.66 [0.98–3.06]
IL-6[a]	1.61 [1.13–2.47]	1.70 [1.16–2.60]	1.79 [1.17–2.76]	1.94 [1.37–2.93]	1.78 [1.21–2.72]
TNF-α	3.40 (1.62)	3.43 (1.89)	3.39 (1.46)	3.50 (1.71)	3.44 (1.68)
Cholesterol	212 (41)	206 (39)	200 (35)	197 (37)	203 (38)
LDL	126 (36)	124 (35)	120 (31)	118 (35)	122 (35)

[a]Median [interquartile range].
HF, heart failure; CAD, coronary artery disease; LDL, low-density lipoprotein.

outcome. We also excluded individuals with eGFR <60 mL/min/1.73 m^2 at baseline. The statistical analysis of this outcome was performed by Poisson regression offset for time, thus allowing us to model the incidence rate ratio. We performed similar analyses for the inflammatory markers CRP, IL-6 and TNF-α, using the same outcomes and statistical methods.

Each outcome was evaluated as a series of models. The first model in each analysis was adjusted for demographic characteristics and clinical risk factors; the second model followed with adjustment for inflammatory markers and self-reported health; and, urine albumin was added to the serum albumin analyses in a third model.

All analyses were performed using IBM SPSS Statistics (Version 23.0, IBM Corp., Armonk, NY, USA) and Stata (StatCorp 2013, Stata Statistical Software: Release 13, StataCorp LP, College Station, TX, USA). A $P < 0.05$ was considered statistically significant for all analyses including interaction terms.

RESULTS

Among the 2598 participants included in this analysis, the mean eGFR was 73 mL/min/1.73 m^2 and the mean ACR was 8.1 mg/g (Table 1). The mean age was 74 years, 39% were African American and 48% were male. Across quartiles of baseline albumin, prevalence of diabetes, hypertension, smoking, alcohol use, coronary artery disease, peripheral arterial disease and CKD appeared similar, as was mean eGFR. Persons with lower serum albumin levels on average had lower urine albumin concentrations.

As a linear variable, lower levels of serum albumin concentration were associated with greater decline in eGFR (Table 2). This association remained statistically significant and minimally attenuated when adjusted for demographic risk factors, inflammatory markers, self-reported health status and albuminuria. When divided into quartiles, lower serum albumin levels were strongly associated with eGFR decline in the sequentially adjusted models. Urine albumin did not appear to attenuate the association of serum albumin concentration with eGFR decline. A higher urine ACR as a linear variable, dichotomized and divided into quartiles was also independently associated with kidney function decline after adjustment.

We assessed the association between serum albumin concentration and rapid kidney function decline ($n = 451/2598$) (Table 3). As a linear variable, each SD decrease of the serum albumin concentration was associated with a 19% higher odds of rapid decline in an unadjusted model, and there was minimal attenuation in the fully adjusted model. When categorized into quartiles, serum albumin concentrations ≤3.80 g/dL were significantly associated with rapid kidney function decline relative to levels >4.20 g/dL with minimal attenuation after adjustment. The association of urine albumin levels with rapid kidney function decline did not appear to attenuate the association of serum albumin with kidney function decline. Urine ACR was significantly associated with rapid kidney function decline in the fully adjusted model. Levels >30 mg/g were strongly and independently associated with rapid kidney function decline, as well as levels >20.20 mg/g relative to levels ≤4.00 mg/g.

Table 2. Longitudinal associations of serum and urine albumin with kidney function decline

Outcome = eGFR decline (mL/min/1.73 m^2/year)	Unadjusted β (95% CI)	Model 1[a] β (95% CI)	Model 2[b] β (95% CI)	Model 3[c] β (95% CI)
Serum albumin				
per SD decrease = 0.31	−0.07 (0.01, −0.16)	−0.13 (−0.04, −0.22)**	−0.11 (−0.01, −0.20)**	−0.12 (−0.03, −0.22)**
Quartiles				
>4.21	0 (ref)	0 (ref)	0 (ref)	0 (ref)
4.01–4.20	−0.23 (−0.50, 0.04)	−0.31 (−0.58, −0.03)*	−0.26 (−0.55, 0.02)	−0.26 (−0.56, 0.03)
3.81–4.00	−0.06 (−0.32, 0.20)	−0.17 (−0.45, 0.10)	−0.11 (−0.40, 0.18)	−0.21 (−0.51, 0.08)
≤3.80	−0.24 (−0.49, 0.02)	−0.38 (−0.65, −0.11)*	−0.32 (−0.61, 0.04)*	−0.35 (−0.64, −0.05)*
Urine ACR				
Urine ACR (per doubling)	−0.09 (−0.13, −0.05)*	−0.07 (−0.12, −0.03)**	−0.09 (−0.14, −0.05)*	−0.08 (−0.17, 0.01)
Urine ACR >30 mg/g	−0.60 (−0.86, −0.33)*	−0.53 (−0.80, −0.26)*	−0.60 (−0.88, −0.32)*	−0.47 (−0.82, −0.13)**
Quartiles				
≤4.00	0 (ref)	0 (ref)	0 (ref)	0 (ref)
4.01–7.89	−0.23 (−0.46, 0.01)	−0.17 (−0.40, 0.06)	−0.16 (−0.39, 0.08)	−0.05 (−0.33, 0.24)
7.90–20.20	−0.33 (−0.56, −0.10)**	−0.24 (−0.47, −0.01)**	−0.24 (−0.48, −0.0002)**	−0.05 (−0.38, 0.27)
>20.20	−0.56 (−0.83, −0.29)*	−0.40 (−0.67, −0.13)**	−0.47 (−0.76, −0.18)**	−0.16 (−0.62, 0.30)

[a]Model 1: demographics and risk factors; model adjusted for age, gender, race, site, DM, SBP, HTN meds, smoking, prevalent cardiovascular disease, high-density lipoprotein, low-density lipoprotein.
[b]Model 2: inflammation and health; model further adjusted for CRP, IL-6, TNF-α and self-reported health status.
[c]Model 3: further adjusted for urine albumin (or serum albumin).
*P < 0.001.
**P < 0.05.
CI, confidence interval.

Table 3. Longitudinal associations of serum and urine albumin concentrations with rapid kidney function decline

Outcome = rapid eGFR decline >30% (451/2598 = 17%)	*n*	No. of patients rapid decline	Unadjusted OR (95% CI)	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)
Serum albumin						
per SD decrease = 0.31	2598	451	1.19 (1.09, 1.27)*	1.20 (1.09, 1.29)*	1.18 (1.07, 1.27)**	1.19 (1.09, 1.28)**
Quartiles						
>4.21	510	77	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.01–4.20	567	98	1.21 (0.83, 1.73)	1.21 (0.84, 1.76)	1.18 (0.81, 1.71)	1.23 (0.84, 1.80)
3.81–4.00	646	91	0.99 (0.69, 1.43)	1.01 (0.69, 1.48)	0.97 (0.66, 1.42)	1.00 (0.68, 1.46)
≤3.80	875	185	1.58 (1.14, 2.19)**	1.62 (1.15, 2.28)**	1.53 (1.08, 2.16)**	1.59 (1.12, 2.26)**
Urine ACR						
Urine ACR (per doubling)			1.20 (1.14, 1.27)*	1.17 (1.10, 1.24)*	1.17 (1.10, 1.24)*	1.18 (1.11, 1.25)*
Urine ACR (>30 mg/g)	436	119	2.27 (1.75, 2.93)*	2.00 (1.52, 2.65)*	1.98 (1.50, 2.62)*	2.06 (1.55, 2.74)*
Quartiles						
≤4.00	677	90	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.01–7.89	662	112	1.27 (0.92, 1.74)	1.26 (0.91, 1.74)	1.25 (0.90, 1.72)	1.31 (0.94, 1.81)
7.90–20.20	631	100	1.12 (0.80, 1.55)	1.05 (0.75, 1.46)	1.03 (0.74, 1.45)	1.09 (0.78, 1.54)
>20.20	598	146	2.14 (1.58, 2.90)*	1.86 (1.34, 2.57)*	1.81 (1.30, 2.51)*	1.93 (1.39, 2.69)*

[a]Model 1: demographics and risk factors; model adjusted for age, gender, race, site, DM, SBP, HTN meds, smoking, prevalent cardiovascular disease, high-density lipoprotein, low-density lipoprotein and eGFR.
[b]Model 2: inflammation and health; model further adjusted for CRP, IL-6, TNF-α and self-reported health status.
[c]Model 3: further adjusted for urine albumin (or serum albumin).
*P < 0.001.
**P < 0.05.
CI, confidence interval; OR, odds ratio.

Similar results were found for associations of serum and urine albumin concentrations with incident reduced eGFR ($n = 556/1986$) (Table 4). The associations of both serum and urine ACR with incident CKD were minimally attenuated by measured risk factors, self-reported health and inflammatory markers. In separate analyses using a binary clinical threshold of serum albumin ≤3.5 g/dL ($n = 211$), we found an 83% (24–170%) higher risk of rapid kidney function decline and 48% (13–94%) higher risk of incident reduced eGFR relative to levels >4.2 g/dL in the fully adjusted model.

The inflammatory markers assessed in this analysis did not have consistent associations with kidney function decline (Table 5). None of the inflammatory markers was significantly associated with kidney function decline in the fully adjusted models. Only high CRP levels were significantly associated with rapid decline. All three inflammatory markers—CRP, IL-6 and

Table 4. Longitudinal associations of serum and urine albumin concentrations with incident reduced eGFR

Outcome = incident CKD (556/1986=28%)						
	n	No. of patients incident CKD	Unadjusted IRR (95% CI)	Model 1[a] IRR (95% CI)	Model 2[b] IRR (95% CI)	Model 3[c] IRR (95% CI)
Serum albumin			IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
per SD decrease = 0.31	1986	556	1.09 (0.84–0.98)**	1.12 (1.06–1.19)*	1.12 (1.05–1.18)**	1.13 (1.06–1.19)**
Quartiles						
>4.21	379	105	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.0–4.20	434	123	1.04 (0.83–1.30)	1.13 (0.91–1.40)	1.04 (0.82–1.31)	1.03 (0.81–1.31)
3.81–4.00	509	127	0.94 (0.75–1.17)	0.99 (0.79–1.24)	0.94 (0.74–1.19)	0.98 (0.77–1.26)
≤3.80	664	201	1.18 (0.96–1.45)	1.32 (1.07–1.62)**	1.26 (1.01– 1.56)**	1.29 (1.03–1.62)**
Urine ACR						
Urine ACR (per doubling)			1.09 (1.05–1.14)*	1.08 (1.04–1.13)*	1.07 (1.03–1.12)*	1.08 (1.04–1.13)*
Urine ACR (>30 mg/g)	271	108	1.79 (1.51– 2.13)*	1.49 (1.25–1.77)*	1.51 (1.25–1.81)*	1.56 (1.30–1 .88)*
Quartiles						
≤4.00	554	135	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
4.01–7.89	533	138	1.09 (0.89–1.35)	1.04 (0.85–1.27)	0.91 (0.73–1.13)	0.94 (0.76–1.17)
7.90–20.20	496	136	1.18 (0.96–1.46)	1.04 (0.85–1.28)	0.95 (0.77–1.17)	0.99 (0.80–1.22)
>20.20	381	143	1.84 (1.50–2.25)*	1.48 (1.21–1.82)*	1.38 (1.11–1.71)*	1.44 (1.16–1.79)*

[a]Model 1: demographics and risk factors; model adjusted for age, gender, race, site, DM, SBP, HTN meds, smoking, prevalent cardiovascular disease, high-density lipoprotein, low-density lipoprotein and eGFR.
[b]Model 2: inflammation and health; model further adjusted for CRP, IL-6, TNF-α and self-reported health status.
[c]Model 3: further adjusted for urine albumin (or serum albumin).
*P < 0.001.
**P < 0.05.
CI, confidence interval; IRR, incidence rate ratio.

Table 5. Longitudinal associations of inflammatory markers with kidney function decline, rapid kidney function decline and incident CKD

Outcome = eGFR decline (mL/min/1.73 m^2/year)						
			Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
CRP (per doubling)	—	—	−0.01 (−0.10, 0.07)	−0.02 (−0.09, 0.08)	−0.03 (−0.12, 0.07)	−0.04 (−0.13, 0.05)
IL-6 (per doubling)	—	—	−0.02 (−0.12, 0.07)	0.01 (−0.09, 0.11)	−0.001 (−0.11, 0.11)	0.03 (−0.08, 0.14)
TNF-α (per doubling)	—	—	0.07 (−0.10, 0.23)	0.17 (0.001, 0.35)**	0.18 (0.0004, 0.36)**	0.18 (−0.003, 0.37)
Outcome = rapid eGFR decline >30%						
	n	No. of patients with rapid decline				
CRP (per doubling)	2598	451	1.19 (1.08, 1.30)*	1.17 (1.06, 1.30)**	1.14 (1.01, 1.27)**	1.14 (1.02, 1.29)**
IL-6 (per doubling)	2598	451	1.17 (1.03, 1.32)**	1.15 (1.00, 1.31)**	1.00 (0.86, 1.17)	0.96 (0.82, 1.12)
TNF-α (per doubling)	2598	451	1.18 (0.98, 1.44)	1.34 (1.06, 1.68)**	1.30 (1.03, 1.65)**	1.25 (0.99, 1.59)
Outcome = incident CKD						
	n	No. of patients with incident CKD				
CRP (per doubling)	1986	556	1.15 (1.08, 1.22)*	1.11 (1.04, 1.18)**	1.06 (0.98, 1.14)	1.06 (0.98, 1.15)
IL-6 (per doubling)	1986	556	1.25 (1.16, 1.35)*	1.14 (1.05, 1.24)**	1.05 (0.95, 1.15)	1.04 (0.94, 1.15)
TNF-α (per doubling)	1986	556	1.80 (1.54, 2.10)*	1.40 (1.20, 1.63)*	1.36 (1.17, 1.59)*	1.30 (1.11, 1.53)**

[a]Model 1: demographics and risk factors; model adjusted for age, gender, race, site, DM, SBP, HTN meds, smoking, prevalent cardiovascular disease, high-density lipoprotein, low-density lipoprotein and eGFR.
[b]Model 2: inflammation and health; model further adjusted for CRP, IL-6, TNF-α and self-reported health status.
[c]Model 3: further adjusted for urine albumin.
*P < 0.001.
**P < 0.05.

TNF-α—were initially associated with incident reduced eGFR; however, when adjusted for serum and urine albumin, only TNF-α retained a significant association with the outcome.

DISCUSSION

We found serum albumin concentrations to be strongly associated with eGFR decline, rapid eGFR decline and incident CKD. These findings were independent of albuminuria, self-reported health, biomarkers of inflammation, as well as demographic and clinical risk factors for kidney disease progression. Urine ACR was also significantly associated with eGFR decline, rapid decline and incident CKD in each fully adjusted model. None of the inflammatory markers was consistently associated with kidney function outcomes after adjustment for urine albumin and serum albumin.

Serum albumin concentration is a well-known predictor of mortality in patients with CKD. Only a few studies have examined serum albumin as a risk factor for the development of ESRD [12–14]. In a 2011 retrospective cohort analysis of 1800 men and women from the UK, Wagner *et al.* found that serum albumin levels were an essential component of a multivariable risk model for mortality in patients with ESRD [12]. Specifically, the authors found that higher serum albumin concentrations, defined as a continuous variable, were associated lower risk of mortality within 3 years of starting dialysis. A second retrospective study of 1000 chronic dialysis patients in Ireland dichotomized serum albumin levels at 3.5 g/dL, and found the lower category to be associated with higher mortality risk in adjusted analyses [13]. One other study of 109 dialysis patients found similar associations of albumin and mortality, which appeared to be mediated by cardiovascular events [15].

Few studies have examined associations of serum albumin with kidney function decline. However, in one study of eight inflammatory markers, including serum albumin, serum albumin was the only laboratory measure associated with kidney function decline [7]. We previously found serum albumin to be a strong and independent risk factor for kidney function decline in HIV-infected women [9], and those associations were only minimally attenuated by albuminuria. No other studies, to our knowledge, have examined serum albumin as an independent risk factor for the development of kidney function decline, rapid decline and incident CKD in a diverse population of elders, accounting for both inflammatory factors and urine albumin. Because serum albumin is a widely available clinical laboratory measurement, it may serve as a useful marker to help identify individuals at higher risk of CKD development in clinical practice.

The underlying mechanisms for these associations are unclear. To our knowledge, there is no direct physiological basis for low serum albumin to cause the development of CKD. Serum albumin levels may be reduced for one of several reasons: liver damage and disease may decrease production; they may decrease as a negative acute phase reactant or in response to inflammation; and substantial and sustained albuminuria can lead to lower serum concentrations. Uncommonly low serum albumin can also reflect malnutrition, but the only malnourished state that consistently produces lower serum albumin is kwashiorkor, a rare disease in the developing world [16]. In this study, albuminuria is clearly not the explanation for these associations since baseline concentrations of urine albumin were low, albuminuria was similar across quartiles of serum albumin at baseline and the associations were not attenuated when adjusted for urine albumin. Inflammation would appear to be the most likely explanation for our findings; however, we evaluated the association of several inflammatory markers—CRP, TNF-α and IL-6—with kidney function decline. IL-6 was not associated with any of the outcomes, while CRP and TNF-α had inconsistent associations. A similar study in Health ABC investigating the associations of these three inflammatory markers with cardiovascular disease also found inconsistent results [17], suggesting that these inflammatory markers do not capture the physiological processes that underlie the associations of serum albumin with adverse outcomes in Health ABC.

We hypothesize that the strong relationship between lower serum albumin and kidney function decline in this study must be multi-factorial, representing general ill health. We could not adjust for prevalence and severity of liver disease in this study, as this may represent one reason why individuals have lower serum albumin and decreased kidney function. Lower albumin concentrations may also reflect much broader abnormalities in processes of inflammation, thrombosis and microvascular function than can be captured by the markers available in this cohort [18–20]. Lower serum albumin and kidney function decline may also be related by multiple factors that are currently poorly understood. These findings are consistent with the results from our previous study of HIV-infected women [9] as well as other studies of serum albumin in ESRD [12, 13].

This study had several strengths. It had a large sample size in a well-characterized cohort with rigorously attained clinical data. The data span 10 years with multiple measurements of cystatin C over that time period. Our study also had several limitations. The cohort was limited to elders and therefore our results may not be generalizable to the younger adult population. Most individuals had preserved kidney function at baseline, and we could not evaluate whether results generalize to populations with more advanced CKD, or with ESRD outcomes. We also cannot fully explain the physiological basis for these findings.

In summary, we found that lower levels of serum albumin are strongly and independently associated with eGFR decline, rapid eGFR decline and incident CKD in a population of well-functioning, community dwelling elders. These findings were independent of albuminuria, three markers of inflammation and other known risk factors for kidney disease progression. Several studies have evaluated utilizing serum albumin as a risk factor for ESRD in both the general and HIV-infected populations [12, 21, 22]. Our findings suggest that serum albumin may further aid clinicians in risk-stratifying patients for the development of kidney disease. Additional studies are required to understand the biological mechanisms linking low serum albumin with kidney function decline.

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CONFLICT OF INTEREST STATEMENT

None declared.

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Obesity and synergistic risk factors for chronic kidney disease in African American adults: the Jackson Heart Study

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ABSTRACT

Background. African Americans are at high risk for chronic kidney disease (CKD). Obesity may increase the risk for CKD by exacerbating features of the metabolic syndrome and promoting glomerular hyperfiltration. Whether other factors also affecting these pathways may amplify or mitigate obesity–CKD associations has not been investigated.

Methods. We studied interactions between obesity and these candidate factors in 2043 African Americans without baseline kidney disease enrolled in the Jackson Heart Study. We quantified obesity as body mass index (BMI), sex-normalized waist circumference and visceral adipose volume measured by abdominal computed tomography at an interim study visit. Interactions were hypothesized with (i) metabolic risk factors (dietary quality and physical activity, both quantified by concordance with American Heart Association guidelines) and (ii) factors exacerbating or mitigating hyperfiltration (dietary protein intake, *APOL1* risk status and use of renin–angiotensin