Serum albumin concentration and risk of end-stage renal disease: the REGARDS study

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ABSTRACT

Background. Serum albumin concentration is a commonly available biomarker with prognostic value in many disease states. It is uncertain whether serum albumin concentrations are associated with incident end-stage renal disease (ESRD) independently of urine albumin-to-creatinine ratio (ACR).

Methods. A longitudinal evaluation was performed of a population-based community-living cohort from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Participants were ≥ 45 years of age at study entry and had serum albumin, creatinine, cystatin C and spot urine ACR measured at the baseline visit ($n = 19\,633$). Estimated glomerular filtration rate (eGFR) was from the Chronic Kidney Disease Epidemiology Collaboration combined creatinine-cystatin C equation. Baseline serum albumin concentration was the predictor variable, and hazard ratios (HRs) for incident ESRD (from US Renal Data System linkage) were calculated in sequentially adjusted models.

Results. Age at study entry was 63.9 ± 9.7 years, 62% of the participants were female and 40% were black. Mean eGFR at baseline was 83.3 ± 20.8 mL/min/1.73 m². Over a median 8-year follow-up, 1.2% ($n = 236$) developed ESRD. In models adjusted for baseline eGFR, ACR and other ESRD risk factors, the HR for incident ESRD was 1.16 [95% confidence interval (CI) 1.01–1.33] for each standard deviation (0.33 g/dL) lower serum albumin

concentration. The HR comparing the lowest (<4 g/dL) and highest quartiles (≥ 4.4 g/dL) of serum albumin was 1.61 (95% CI 0.98–2.63). Results were qualitatively similar among participants with eGFR <60 and ≥ 60 mL/min/1.73 m², and those with and without diabetes.

Conclusions. In community-dwelling US adults, lower serum albumin concentration is associated with higher risk of incident ESRD independently of baseline urine ACR, eGFR and other ESRD risk factors.

Keywords: albumin, biomarkers, ESRD, population-based cohort, urine albumin-to-creatinine ratio

INTRODUCTION

Serum albumin concentration is a widely available clinical biomarker with prognostic value for numerous health outcomes. The association of serum albumin concentration with vascular disease has been extensively investigated, and lower concentrations have been associated with risk for the development of coronary heart disease, heart failure and cardiovascular mortality in several prospective studies across a variety of populations [1–3].

These associations may reflect many processes, including increased catabolism in inflammatory states, reduced production in settings of diminished protein and calorie intake and

increased urinary albumin losses in overtly proteinuric kidney disease [4, 5]. Lower serum albumin concentration is a marker of increased mortality risk in chronic kidney disease (CKD) [6], persons on dialysis [7] and renal transplant recipients [8]. Less is known about the association of serum albumin concentration with the risk of progressive CKD. High urine albumin excretion is associated with low serum albumin concentrations, and is a well-established risk factor for CKD progression. However, whether serum albumin concentration itself is associated with CKD progression, and whether any such putative association is independent of urine albumin excretion is uncertain.

The purpose of this analysis is to test whether lower serum albumin is associated with incident end-stage renal disease (ESRD) among a community-dwelling population of black and white adults in the USA. *A priori*, we hypothesized that lower serum albumin concentration would be associated with incident ESRD, and that the association would remain even after adjustment for urine albumin-to-creatinine ratio (ACR).

MATERIALS AND METHODS

Study design

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study is a prospective, population-based cohort study of black and white adults 45 years and older in the USA. REGARDS was designed to study factors associated with high stroke mortality in the stroke belt of the Southeastern USA and among black persons [9]. An ancillary study added measurement of serum albumin and ESRD linkage and was initiated during REGARDS enrollment [10].

Participants

REGARDS enrolled 30 239 persons from January 2003 until October 2007, with oversampling of residents of the Southeastern USA and black individuals [11]. Fifty-six percent of the sample was recruited from eight Southeastern states (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas and Louisiana), with the remainder coming from the other 40 contiguous states and the District of Columbia. Black persons made up 42% of the study population [11]. An ancillary study added measurements of serum albumin and other variables among participants enrolled starting in May 2004; thus, the first 8608 enrolled participants did not have these measurements [12]. Recruitment was conducted through a combination of mail and telephone contact. Age, sex, race, smoking status, antihypertensive medication use, antidiabetes medication use and history of cardiovascular disease were obtained from a telephone interview. Each participant completed a single in-home visit at which blood pressure, height and weight were measured, blood and urine samples were taken, and an electrocardiogram was performed. The study was approved by the institutional review boards of all participating institutions, and all participants gave written informed consent. A total of 10 553 participants (including the 8608 mentioned above) were excluded from this analysis because of missing data for serum albumin, creatinine, cystatin C or urine ACR. An additional 53 persons who reported being

on dialysis at the time of enrollment or who were identified as initiating dialysis prior to the baseline visit through US Renal Data System (USRDS) were excluded, resulting in a final study sample of 19 633 (Figure 1).

Serum albumin

Albumin was measured in serum using colorimetric reflectance density on the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA). The interassay coefficients of variation were 1.7% at 2.4 g/dL and 0.9% at 4.6 g/dL.

Incident ESRD

Incident ESRD was ascertained from linkage to the USRDS, which collects information on persons initiating dialysis or receiving kidney transplants. The current analysis included ESRD cases identified through 3 June 2014. Mortality was assessed in a secondary analysis as a competing risk for incident ESRD and was ascertained from 6-month interval follow-up by telephone or mail with participants' proxies, and confirmed with review of death certificates or the Social Security death index. Deaths were identified through 3 June 2014.

Other measurements

The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined creatinine-cystatin C equation [13]. Serum creatinine was measured at the University of Vermont, and was calibrated to an isotope-dilution mass spectroscopic standard. Cystatin C was measured by particle-enhanced immunonephelometry (Dade Behring, now Siemens, Munich, Germany, N Latex on BNII) [14]. Urine albumin was measured on a random spot urine sample with the BNII ProSpec nephelometer from Dade Behring (now Siemens) at the University of Minnesota,

FIGURE 1: Study flowchart with exclusion criteria.

with an observed assay range from 2.4–76.9 mg/L on initial sampling, and interassay coefficients of variation of 2.2% at 109.9 mg/L and 4.3% at 12.7 mg/L. A rate-blanked Jaffé procedure with the Modular-P analyzer from Roche/Hitachi (Roche Diagnostics, Rotkreuz, Switzerland) was used to measure urine creatinine. Initial sampling showed an observed assay range of 1–650 mg/dL, and interassay coefficients of variation were 2.4% at 66.6 mg/dL and 7.8% at 15.6 mg/dL [12]. High-sensitivity C-reactive protein (CRP) was measured by particle-enhanced immunonephelometry using the BNII nephelometer from Dade Behring (now Siemens) with interassay coefficients of variations of 2.1%–5.7%. Total and high-density lipoprotein (HDL) cholesterol were measured by colorimetric reflectance spectrophotometry using the Ortho Vitros Clinical Chemistry System 950IRC from Johnson & Johnson Clinical Diagnostics [15].

Definitions of other covariates

We defined prevalent cardiovascular disease by evidence of coronary heart disease (self-reported myocardial infarction, coronary artery bypass graft, angioplasty or stent; or electrocardiographic evidence of prior infarction based on the Minnesota classification [16]) or self-reported history of stroke. Diabetes was defined as fasting venous blood glucose ≥ 126 mg/dL, non-fasting venous blood glucose ≥ 200 mg/dL or self-report of anti-diabetes medication use. Smoking status was determined from self-report of current, past or never smoking.

Statistical analysis

Baseline characteristics are reported as count (percentage), mean [standard deviation (SD)] or median [interquartile range (IQR)] for the whole sample and by quartile of serum albumin. Significance testing for differences in baseline characteristics among albumin quartiles were performed using chi-squared tests for dichotomous and categorical variables and ANOVA for continuous variables. Cumulative ESRD incidence and rate were calculated by serum albumin quartile. Quartiles were unequal because serum albumin was rounded to the nearest 0.1 g/dL.

Cox proportional hazards regression was used to determine hazard ratio (HR) [95% confidence interval (CI)] of incident ESRD per SD lower serum albumin in unadjusted and sequential multivariable adjusted models. The first model adjusted for demographic variables (age, sex and race) and estimated GFR (eGFR). The second model also adjusted for body mass index (BMI), systolic blood pressure, antihypertensive medication use, smoking status, prevalent cardiovascular disease, diabetes, logarithm of CRP, total cholesterol and HDL cholesterol. A final model added adjustment for the logarithm of urine ACR. Cubic spline regression analysis with serum albumin concentration as the predictor variable was performed. This was adjusted for the variables as in the final model above, and knots were placed at the quartiles. Proportional hazards assumptions were tested for age, eGFR, logarithm of urine ACR and serum albumin, and were not violated. The analyses were repeated using the Fine and Gray method to evaluate death as a competing risk [17]. In sensitivity analyses, the main models were repeated

using the CKD-EPI creatinine equation, because cystatin C concentration may be affected by inflammation [18].

Multiplicative interactions between serum albumin and eGFR rate category (<60 or ≥ 60 mL/min/1.73 m²), urine ACR categories (<30 , 30–300 or >300 mg/g), diabetes status, race and sex were calculated individually, and stratified analyses were conducted for those with two-sided $P < 0.10$. All analyses were conducted using SAS Version 9.4 (Cary, NC, USA).

RESULTS

Characteristics of participants by quartile of serum albumin are presented in Table 1. Among the 19 633-person study sample, the mean age (SD) was 63.9 ± 9.7 years. Women made up 62% of the sample, and 40% were black. Diabetes mellitus was present in 20%, 53% took antihypertensive medications, 17% had coronary heart disease and 5% had cerebrovascular disease. More than half the participants were prior or current smokers. Mean serum albumin was 4.2 ± 0.3 g/dL. Median serum albumin was 4.2 g/dL, the 25th percentile was 4.0 g/dL and the 75th percentile was 4.4 g/dL. Figure 2 shows the distribution of serum albumin level and fitted normal curve. The mean eGFR was 83.3 mL/min/1.73 m², and 14% of participants had an eGFR <60 mL/min/1.73 m² at baseline. Urine ACR of 30–300 mg/g was present in 12% of participants, and >300 mg/g was present in 2%. [Supplementary Table S1](#) compares baseline characteristics of the included and excluded subjects. Excluded subjects were older (mean age 66.6 years), a lower proportion was female (43%), and they had lower mean eGFR (78.2 mL/min/1.73 m²), among other differences.

Persons in the lower serum albumin quartiles tended to be older, and were more likely to be female and black. Coronary heart disease, cerebrovascular disease, diabetes mellitus and antihypertensive medication use were more prevalent in the lower albumin quartiles. A higher proportion of never-smokers was present in the lower two albumin quartiles. Systolic blood pressure was slightly higher and diastolic blood pressure slightly lower, with lower serum albumin. BMI was higher in the lower serum albumin quartiles. Persons in the lowest serum albumin quartile also had lower eGFR and higher prevalence of both micro- and macroalbuminuria. Serum albumin concentration was inversely related to the logarithm of urine ACR, with Pearson correlation coefficient -0.09 ($P < 0.001$).

Median follow-up was 8 years. Figure 3 shows the cumulative incidence of ESRD (censoring at death) by serum albumin quartile. In unadjusted analysis, lower serum albumin concentrations were strongly associated with risk of ESRD (Table 2). The unadjusted HR (95% CI) for incident ESRD per SD (0.33 g/dL) lower serum albumin was 2.51 (95% CI 2.22–2.84). The HR decreased to 1.52 (95% CI 1.34–1.73) when adjusted for age, race, sex and baseline eGFR. Additional adjustment for BMI, systolic blood pressure, antihypertensive medication use, smoking status, cardiovascular disease, diabetes mellitus, logarithm of CRP and cholesterol resulted in an HR of 1.40 (95% CI 1.23–1.29). When urine ACR was additionally added to the model, the HR was 1.16 (95% CI 1.01–1.33). HRs (95% CIs) for covariates in the final model are given in [Supplementary Table S2](#).

Table 1. Characteristics and outcomes of the study population^a

	All	Serum albumin quartile (g/dL)			
		Q1 (< 4.0)	Q2 (4.0–4.1)	Q3 (4.2–4.3)	Q4 (≥ 4.4)
Number ^b	19 633	4832	4509	4596	5696
Demographics					
Age (years) (SD)	63.9 (9.7)	65.9 (10.1)	64.8 (9.6)	63.6 (9.3)	61.9 (9.2)
Women, <i>n</i> (%)	12 104 (62)	3257 (67)	2870 (64)	2809 (61)	3168 (56)
Black race, <i>n</i> (%)	7888 (40)	2430 (50)	1860 (41)	1729 (38)	1869 (33)
Comorbid conditions and history					
History of coronary heart disease, <i>n</i> (%)	3200 (17)	927 (20)	748 (17)	702 (16)	823 (15)
History of stroke, <i>n</i> (%)	1060 (5)	323 (7)	239 (5)	223 (5)	275 (5)
Diabetes mellitus, <i>n</i> (%)	3891 (20)	1302 (27)	924 (21)	797 (17)	868 (15)
Antihypertensive medication use, <i>n</i> (%)	9974 (53)	2680 (58)	2308 (53)	2257 (51)	2729 (50)
Smoking status, <i>n</i> (%)					
Never	9300 (48)	2259 (47)	2218 (49)	2158 (47)	2665 (47)
Former	7394 (38)	1800 (37)	1650 (37)	1778 (39)	2166 (38)
Current	2867 (15)	760 (16)	624 (14)	639 (14)	844 (15)
Physical examination					
Systolic BP (mmHg) (SD)	127 (16)	128 (17)	126 (16)	126 (16)	126 (16)
Diastolic BP (mmHg) (SD)	76 (10)	76 (10)	76 (10)	76 (9)	77 (10)
BMI (kg/m ²) (SD)	29.4 (6.3)	30.8 (7.3)	29.9 (6.5)	29.1 (5.8)	28.1 (5.3)
Kidney function					
eGFR, CKD-EPI cys C-creat (mL/min/1.73 m ²) (SD)	83.3 (20.8)	78.5 (22.7)	82.6 (20.6)	84.6 (19.6)	86.8 (19.4)
eGFR <60 mL/min/1.73 m ² , <i>n</i> (%)	2651 (14)	973 (20)	625 (14)	527 (11)	526 (9)
Laboratory data					
Serum creatinine (mg/dL) (SD)	0.9 (0.3)	0.9 (0.4)	0.9 (0.3)	0.9 (0.2)	0.9 (0.2)
Serum cystatin C (mg/L) (SD)	1.0 (0.3)	1.1 (0.4)	1.0 (0.3)	0.9 (0.3)	0.9 (0.3)
CRP (mg/L), median [IQR]	2.2 [0.9, 5.1]	3.2 [1.3, 7.5]	2.4 [1.0, 5.4]	2.0 [0.9, 4.7]	1.6 [0.8, 3.6]
Urine ACR, median [IQR]	7.2 [4.6, 14.9]	7.6 [4.6, 18.5]	7.0 [4.5, 14.3]	7.0 [4.6, 13.8]	7.5 [4.8, 14.3]
Urine ACR 30–300 mg/g, <i>n</i> (%)	2260 (12)	617 (13)	506 (11)	481 (10)	656 (12)
Urine ACR >300 mg/g, <i>n</i> (%)	489 (2)	259 (5)	96 (2)	76 (2)	58 (1)
Calculated LDL cholesterol (mg/dL) (SD)	112.8 (35.1)	105.4 (33.5)	110.5 (33.5)	115.1 (34.6)	119.3 (36.6)
Total cholesterol (mg/dL) (SD)	191.9 (40.3)	181.0 (38.3)	188.5 (38.3)	194.6 (39.4)	201.5 (41.7)
HDL cholesterol (mg/dL) (SD)	53.1 (16.4)	51.5 (15.7)	52.6 (15.9)	53.6 (16.2)	54.6 (17.1)
Outcomes					
Death, <i>n</i> (%)	2875 (15)	1064 (22)	668 (15)	552 (12)	590 (11)
Incident ESRD, <i>n</i> (%)	236 (1)	142 (3)	47 (1)	22 (0.5)	25 (0.4)
Incident ESRD rate (per 100 000 person-years)		373.9	128.7	59.3	55.1

^aP-values for differences in baseline characteristics across albumin quartiles was 0.01 for smoking status, and <0.001 for all others.

^bQuartiles are unequal because the laboratory rounded serum albumin to nearest 0.1 g/dL.

eGFR, estimated glomerular filtration rate using the CKD-EPI combined cystatin C-creatinine equation; LDL, low-density lipoprotein.

In analyses of serum albumin categorized by quartiles, incident ESRD in the lowest compared with the highest quartile revealed an unadjusted HR of 6.80 (95% CI 4.45–10.41) (Table 2). Adjustment for age, sex, race and baseline eGFR reduced the HR to 2.26 (95% CI 1.46–3.49). The final model, with additional adjustment for urine ACR, resulted in an HR of 1.61 (95% CI 0.98–2.63). Results were unchanged when analyses were repeated with baseline eGFR estimated using the CKD-EPI creatinine equation (data not shown).

Figure 4 shows the cubic spline regression results adjusted for Model 3 variables. For the lower tail of the serum albumin distribution the curve is flat, but the risk estimate for ESRD decreases steadily with higher serum albumin concentrations in the rest of the distribution.

Multiplicative interaction testing of serum albumin with baseline eGFR categories (<60 versus ≥60 mL/min/1.73 m²) revealed a P-value of 0.07, and with diabetes status also had a P-value of 0.07. Each SD lower serum albumin was associated with an HR for incident ESRD of 1.14 (95% CI 0.97–1.33) and

FIGURE 2: Distribution of serum albumin in study participants.

1.61 (95% CI 1.21–2.15) among participants with eGFR <60 and ≥60 mL/min/1.73 m², respectively (Table 3). The strength of association between serum lower albumin quartiles and incident ESRD was markedly higher among those with

FIGURE 3: Cumulative incidence of ESRD by serum albumin quartile.

Table 2. Association of serum albumin with incident ESRD

	HRs (95% CIs)			
	Unadjusted	Model 1	Model 2	Model 3
Continuous				
Per SD lower serum albumin (0.33 g/dL)	2.51 (2.22–2.84)	1.52 (1.34–1.73)	1.40 (1.23–1.59)	1.16 (1.01– 1.33)
Categorical				
Q1 (<4.0 g/dL)	6.80 (4.45–10.41)	2.26 (1.46–3.49)	2.37 (1.48–3.79)	1.61 (0.98–2.63)
Q2 (4.0–4.1 g/dL)	2.34 (1.44–3.80)	1.62 (1.01–2.61)	1.73 (1.05–2.87)	1.69 (1.03–2.78)
Q3 (4.2–4.3 g/dL)	1.08 (0.61–1.91)	0.79 (0.45–1.38)	0.89 (0.49–1.59)	0.91 (0.51–1.60)
Q4 (≥4.4 g/dL) (ref)	1.00	1.00	1.00	1.00

Model 1: adjusted for age, sex, race and baseline eGFR.

Model 2: adjusted for Model 1 variables, in addition to BMI, systolic blood pressure, antihypertensive medication use, smoking status, baseline cardiovascular disease, diabetes status, logarithm of CRP, and total and HDL cholesterol.

Model 3: adjusted as in Model 2, in addition to logarithm of urine ACR.

FIGURE 4: Cubic spline regression analysis of the relationship between serum albumin concentration and incident ESRD. Adjusted for age, sex, race, eGFR, BMI, systolic blood pressure, antihypertensive medication use, smoking status, cardiovascular disease, diabetes, logarithm of CRP, total cholesterol, HDL cholesterol and logarithm of urine ACR.

eGFR ≥ 60 compared with <60 mL/min/1.73 m² (Table 3). Among those with diabetes, the fully adjusted HR per SD lower serum albumin was 1.29 (95% CI 1.08–1.55), whereas it was 1.22 (95% CI 0.99–1.49) in those without diabetes (Supplementary Table S3). There was no evidence of effect modification by urine ACR categories (<30 , 30 – 300 , >300 mg/g), sex or race (P-values for interaction 0.25, 0.73 and 0.99, respectively).

Among the 19 633 study participants, there were 2875 deaths during follow-up. Twenty-two percent of participants in the lowest albumin quartile died during follow-up, compared with 11% in the highest albumin quartile. Fine and Gray subdistribution hazard models using death as a competing risk for incident ESRD in continuous and categorical analyses revealed no substantial changes in risk estimates.

DISCUSSION

In this study of community-dwelling black and white adults in the USA, lower serum albumin concentration was independently associated with higher incident ESRD risk. This association persisted after adjustment for factors associated with

Table 3. Association of serum albumin with incident ESRD stratified by baseline eGFR

HRs (95% CIs)								
	Unadjusted Baseline eGFR<60 mL/min/1.73 m ²	Model 1 Model 1 60 mL/min/1.73 m ²	Model 2	Model 3	Unadjusted Baseline eGFR≥60 mL/min/1.73 m ²	Model 1 Model 1 60 mL/min/1.73 m ²	Model 2	Model 3
Continuous								
Per SD lower serum albumin (0.33 g/dL)	1.84 (1.64–2.15)	1.48 (1.27–1.74)	1.38 (1.18–1.61)	1.14 (0.97–1.33)	2.39 (1.89–3.03)	2.29 (1.81–2.89)	2.12 (1.66–2.72)	1.61 (1.21–2.15)
Categorical								
Q1 (<4.0 g/dL)	2.98 (1.89–4.72)	1.86 (1.17–2.98)	1.68 (1.01–2.80)	1.11 (0.65–1.88)	12.7 (3.88–41.58)	12.1 (3.66–40.24)	11.4 (3.34–38.73)	7.36 (2.20–24.63)
Q2 (4.0–4.1 g/dL)	1.39 (0.82–2.36)	1.33 (0.77–2.31)	1.44 (0.83–2.50)	1.39 (0.82–2.40)	4.61 (1.28–16.58)	4.54 (1.25–16.47)	4.76 (1.31–17.32)	3.96 (1.12–14.09)
Q3 (4.2–4.3 g/dL)	0.61 (0.31–1.19)	0.53 (0.27–1.03)	0.53 (0.27–1.05)	0.54 (0.28–1.05)	3.29 (0.87–12.42)	3.33 (0.89–12.45)	3.72 (0.98–14.02)	3.32 (0.91–12.09)
Q4 (≥4.4 g/dL) (ref)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Model 1: adjusted for age, sex, race and baseline eGFR rate.

Model 2: adjusted for Model 1 variables, in addition to BMI, systolic blood pressure, antihypertensive medication use, smoking status, baseline cardiovascular disease, diabetes status, logarithm of CRP, and total and HDL cholesterol.

Model 3: adjusted as in Model 2, in addition to logarithm of urine ACR.

kidney disease, including diabetic and cardiovascular comorbidities, baseline eGFR, CRP and notably, urine ACR.

Serum albumin was strongly associated with ESRD risk in unadjusted analysis; an association that was attenuated but not extinguished when adjusted for age, baseline eGFR and other risk factors. Additional adjustment for urine ACR attenuated the remaining association, but did not eliminate it. Based on the categorical analyses, this increased risk seems to be present for serum albumin levels below the median, but not above. We conclude that lower serum albumin is independently associated with incident ESRD risk, and this association is not entirely explained by greater urine ACR.

Notably, the association between serum albumin concentration and incident ESRD was stronger in the subgroup of participants with baseline eGFR ≥ 60 mL/min/1.73 m², despite the lower ESRD incidence in this group. This initially surprising finding is related to the low ESRD absolute risk among those with eGFR ≥ 60 mL/min/1.73 m², which can be demonstrated with incidence rates (see [Supplementary Table S4](#)). In the higher eGFR group, the unadjusted incidence rate ratio between highest and lowest serum albumin quartiles is over 10, whereas the incidence difference is 88 per 100 000 person-years. In comparison, among those with eGFR < 60 mL/min/1.73 m² the incidence rate ratio is only 3, but the incidence difference is 1178 per 100 000 person-years. Thus, while the strength of association is more striking in the higher eGFR group, the importance as a prognostic factor may be more relevant to those with lower eGFR given the much higher absolute risk. [Supplementary Table S5](#) shows incidence rates for subgroups defined by eGFR and urine ACR categories, demonstrating similar findings regarding risk ratios and differences in these subgroups.

To our knowledge, this is the first study to demonstrate an association between serum albumin concentrations and ESRD while accounting for urine ACR in a community-dwelling adult population. A prior analysis of the Cardiovascular Health Study demonstrated that lower serum albumin was associated with decline in eGFR, rather than ESRD, in a community-based cohort of persons aged 65 years and older [19]. That study focused on inflammatory markers and found that the association of markers with CKD progression was unique for serum albumin, and was not observed with C-reactive protein (CRP), interleukin-6 (IL-6), or other systemic markers of inflammation. However, urine ACR was not measured and so it remained unclear if the unique associations of serum albumin with CKD progression were perhaps marking greater urine albumin loss. Subsequently, an equation to estimate risk of progression to ESRD in patients with established CKD was developed and validated in populations with prevalent CKD. It was found that lower serum albumin, in addition to higher urine ACR, helped to predict incident ESRD in persons with CKD Stages 3–5 [20, 21]. A recent analysis of the Chronic Renal Insufficiency Cohort found lower serum albumin was associated with higher risk of ≥ 50% decline in eGFR or incident ESRD among persons with eGFR 20–70 mL/min/1.73 m², independent of urine ACR and inflammatory markers [22]. In addition, a recent study in community-living elders showed that serum albumin was

associated with incident CKD; however, there were insufficient ESRD events to evaluate this outcome in that study [23]. Thus, our study extends the literature in several ways. We confirm that the association of lower serum albumin concentration with ESRD risk is not merely a reflection of greater urine ACR. We extend prior observations that evaluated CKD progression to a hard, clinically relevant incident ESRD endpoint, and we demonstrate that this association is not limited to persons with CKD at baseline, but that serum albumin concentration is also a risk marker for CKD in the general population.

The CKD-EPI creatinine-cystatin C combined equation was chosen for the primary analysis because of superior accuracy over equations based on either creatinine or cystatin C alone across widely ranging kidney function [24]. However, serum cystatin C concentration is increased in inflammatory states, and is inversely correlated with serum albumin concentration [25], and thus the non-GFR-related relationship between serum albumin level and incident ESRD may be attenuated when using cystatin C to estimate baseline GFR. This did not appear to significantly impact the results, as the main analyses were minimally affected by using the CKD-EPI creatinine equation for baseline eGFR.

While mechanisms are uncertain, there are several possible explanations for the inverse association between serum albumin concentration and incident ESRD risk. First, lower serum albumin concentration may hold information about the true baseline GFR, beyond what can be derived from eGFR equations that incorporate demographics, serum cystatin C and creatinine. This possibility is supported by the original development and validation of the Modification of Diet in Renal Disease (MDRD) Study estimating equation, which showed that lower serum albumin concentration was associated with lower measured GFR, and inclusion of serum albumin concentration, in addition to other serum markers, improved the accuracy of the GFR estimating equation [26]. Subsequent data suggested that the eGFR equation performance was not materially influenced by dropping serum albumin and retaining age, gender, race and creatinine, resulting in the so-called '4-variable MDRD equation'. The relationship between serum albumin concentration and true GFR may be due, in part, to increased tubular creatinine secretion at lower serum albumin concentrations [27]. Also, lower serum albumin concentration may reflect renal tubular dysfunction impairing protein reabsorption from the filtrate [28], and thus may reflect tubular damage predisposing to development and progression of clinically apparent renal disease. However, this would likely have been reflected by greater urine ACR, and we found that the association of low serum albumin with ESRD events was independent of urine ACR. Serum albumin concentration may also provide additional information on the inflammatory milieu, beyond what is contained in the serum CRP concentration. However, prior studies in the general population have found that serum albumin is uniquely associated with CKD progression, an association that is not found with other serum markers of inflammatory stress [19]. The general nutritional state of an individual, influenced by factors that affect renal disease such as overall health, comorbidities and inflammation, may also link serum albumin level with renal outcomes. Thus, despite several appealing

hypotheses, the mechanisms linking lower serum albumin with ESRD events remain obscure.

While mechanisms remain uncertain, these findings may have clinical implications. Serum albumin concentrations are strongly associated with ESRD events in unadjusted analysis, and modestly associated in fully adjusted analysis. Prior studies in populations with CKD suggest that they are predictive of ESRD independent of other CKD risk factors. Serum albumin measurements are nearly ubiquitously available, typically inexpensive and precisely measured by the clinical laboratory. These data suggest that measurement of serum albumin may add information about risk for CKD progression and ESRD on top of urine ACR, eGFR and other clinical risk factors. Individuals with lower serum albumin may benefit from closer surveillance and aggressive treatment of CKD risk factors in an effort to abate CKD progression.

This study has many strengths, including the use of a large, community-dwelling, geographically diverse population; the high prevalence of black race; the linkage with USRDS, which identifies nearly all incident ESRD cases; and the availability of baseline albuminuria and cystatin C measurement. The study also has important limitations. The study sample excluded persons of races other than black and white. The relative imprecision of the serum albumin measurements, measured to the nearest 0.1 g/dL, may have caused underestimation of the correlation between serum albumin concentration and incident ESRD. Additionally, despite most exclusions being due to enrollment before serum albumin measurement was added to the REGARDS protocol, differences between excluded and included subjects were found, which may limit generalizability. Although the association remained after adjustment for the included covariates, given the degree of attenuation with the adjustments, residual confounding from unadjusted and/or unmeasured covariates could perhaps explain the observed association. Etiology of progressive CKD and ESRD incidence were not available in this study. We were not able to perform sensitivity analyses using other kidney disease outcomes, such as decline in eGFR.

In conclusion, we show that lower serum albumin, an inexpensive and widely available biomarker, is associated with incident ESRD in community-dwelling adults. This association is independent of CKD risk factors, baseline eGFR and urine ACR.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](http://ndt.online).

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AUTHORS' CONTRIBUTIONS

J.H.I., M.G.S., O.M.G. and C.P.W. were responsible for the study design; J.H.I., O.M.G., M.C., S.E.J., J.L., W.M., P.M., M.J.S., M.G.S., D.G.W. and C.P.W. carried out data interpretation; O.M.G. and R.K. performed statistical analyses. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work. C.P.W., J.H.I. and O.M.G. take responsibility that this study has been reported honestly, accurately and transparently, and that no important aspects of the study have been omitted.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or in part.

REFERENCES

- Danesh J, Collins R, Appleby P *et al.* Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 1998; 279: 1477–1482
- Gopal DM, Kalogeropoulos AP, Georgiopoulou VV *et al.* Serum albumin concentration and heart failure risk The Health, Aging, and Body Composition Study. *Am Heart J* 2010; 160: 279–285
- Kuller LH, Eichner JE, Orchard TJ *et al.* The relation between serum albumin levels and risk of coronary heart disease in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1991; 134: 1266–1277
- Fanali G, di Masi A, Trezza V *et al.* Human serum albumin: from bench to bedside. *Mol Aspects Med* 2012; 33: 209–290
- de Mutser R, Grootendorst DC, Indemans F *et al.* Association between serum albumin and mortality in dialysis patients is partly explained by inflammation, and not by malnutrition. *J Ren Nutr* 2009; 19: 127–135
- Menon V, Greene T, Wang X *et al.* C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005; 68: 766–772
- Kalantar-Zadeh K, Kilpatrick RD, Kuwae N *et al.* Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrol Dial Transplant* 2005; 20: 1880–1888
- Guijarro C, Massy ZA, Wiedeker MR *et al.* Serum albumin and mortality after renal transplantation. *Am J Kidney Dis* 1996; 27: 117–123
- Howard VJ, Cushman M, Pulley L *et al.* The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology* 2005; 25: 135–143
- Warnock DG, McClellan W, McClure LA *et al.* Prevalence of chronic kidney disease and anemia among participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study: baseline results. *Kidney Int* 2005; 68: 1427–1431
- Howard G, Lackland DT, Kleindorfer DO *et al.* Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA Intern Med* 2013; 173: 46–51
- Warnock DG, Muntner P, McCullough PA *et al.* Kidney function, albuminuria, and all-cause mortality in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis* 2010; 56: 861–871
- Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; 367: 20–29
- Peralta CA, Shlipak MG, Judd S *et al.* Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 2011; 305: 1545–1552
- Cushman M, McClure LA, Howard VJ *et al.* Implications of increased C-reactive protein for cardiovascular risk stratification in black and white men and women in the US. *Clin Chem* 2009; 55: 1627–1636
- Prineas RJ, Crow RS, Blackburn HW. *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification.* J. Wright, 1982, Boston, Massachusetts, USA
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509
- Stevens LA, Schmid CH, Greene T *et al.* Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009; 75: 652–660
- Keller C, Katz R, Sarnak MJ *et al.* Inflammatory biomarkers and decline in kidney function in the elderly: the Cardiovascular Health Study. *Nephrol Dial Transplant* 2010; 25: 119–124
- Tangri N, Stevens LA, Griffith J *et al.* A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011; 305: 1553–1559
- Tangri N, Grams ME, Levey AS *et al.* Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA* 2016; 315: 164–174
- Amdur RL, Feldman HI, Gupta J *et al.* Inflammation and progression of CKD: the CRIC Study. *Clin J Am Soc Nephrol* 2016; 11: 1546–1556
- Lang J, Petrovic S, Gutierrez OM *et al.* Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders. *Nephrol Dial Transplant* 2017 [Epub ahead of print 2017 Aug 23]
- Fan L, Inker LA, Rossert J *et al.* Glomerular filtration rate estimation using cystatin C alone or combined with creatinine as a confirmatory test. *Nephrol Dial Transplant* 2014; 29: 1195–1203
- Shlipak MG, Katz R, Kestenbaum B *et al.* Rate of kidney function decline in older adults: a comparison using creatinine and cystatin C. *Am J Nephrol* 2009; 30: 171–178
- Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
- Horio M, Imai E, Yasuda Y *et al.* Lower serum albumin level is associated with higher fractional excretion of creatinine. *Clin Exp Nephrol* 2014; 18: 469–474
- Otaki Y, Watanabe T, Takahashi H *et al.* Comorbid renal tubular damage and hypoalbuminemia exacerbate cardiac prognosis in patients with chronic heart failure. *Clin Res Cardiol* 2016; 105: 162–171

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