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ORIGINAL ARTICLE

Association of serum uromodulin with mortality and cardiovascular disease in the elderly—the Cardiovascular Health Study

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ABSTRACT

Background. Uromodulin (UMOD) is released by renal tubular cells into the serum (sUMOD) and urine. Lower urine UMOD has been linked to mortality and cardiovascular disease but much less is known about sUMOD. We evaluated the association of sUMOD with these outcomes in community-dwelling older adults.

Methods. We measured sUMOD in a random subcohort of 933 participants enrolled in the Cardiovascular Health Study. The associations of sUMOD with all-cause mortality, incident heart failure (HF) and incident cardiovascular disease (CVD; myocardial infarction, stroke and mortality due to coronary disease or stroke) were evaluated using multivariable Cox regression, adjusting for study participants' demographics, estimated glomerular filtration rate (eGFR), albuminuria and CVD risk factors. Generalized additive models with splines were used to address the functional form of sUMOD with outcomes. Due to nonlinear associations of sUMOD with all outcomes, 2.5% of the values on either end of the sUMOD distribution were excluded from the analyses, limiting the range of sUMOD to 34.3–267.1 ng/mL.

Results. The mean age was 78 ± 5 years, 40% were male, sUMOD level was 127 ± 64 ng/mL, eGFR was 63 mL/min/1.73 m^2 and 42% had CKD defined as eGFR <60 mL/min/1.73 m^2. Patients in the lower sUMOD quartiles had lower eGFR and higher albuminuria ($P < 0.01$, respectively). During a median follow-up of 9.9 years, 805 patients died, 283 developed HF and 274 developed CVD. In multivariable analysis, higher sUMOD was significantly associated with a lower hazard for mortality {hazard ratio [HR] 0.89 [95% confidence interval (CI) 0.80–0.99] per 1 standard deviation (SD) higher sUMOD}, CVD [HR 0.80 (95% CI 0.67–0.96)] and the composite endpoint [HR 0.88 (95% CI 0.78–0.99)]; the association with HF was not statistically significant [HR 0.84 (95% CI 0.70–1.01)].

Conclusion. Higher sUMOD is independently associated with a lower risk for mortality and CVD in older adults.

Keywords: cardiovascular disease, chronic kidney disease, Tamm–Horsfall protein, tubular function, uromodulin

BACKGROUND

Chronic kidney disease (CKD) is a major public health problem with approximately 26 million US adults affected overall [1] and with a prevalence of >45% in people >70 years of age. CKD is a strong risk factor for all-cause mortality and cardiovascular disease (CVD) [2] and understanding the mechanisms by which CKD causes CVD could be important for prevention of CVD. A number of recent studies suggest that loss of tubular integrity may be one of the mechanisms through which CKD promotes CVD [3–5]. However, there are no accepted noninvasive biomarkers to assess tubular function or integrity. Among multiple biomarkers that have been evaluated in the last several years, uromodulin (UMOD) has shown some promise. It is exclusively produced by cells in the thick ascending limb of the loop of Henle and secreted into both the tubular lumen and the blood [6]. Both serum UMOD (sUMOD) and urinary UMOD (uUMOD) have been associated with tubular atrophy [7]. Higher levels of uUMOD have been associated with lower

overall mortality in prior studies, including in the Cardiovascular Health Study (CHS) [8, 9].

In contrast to the urine, where UMOD forms multimers [10], UMOD can be detected as a monomer in serum [11]. Two recent studies in patients selected for coronary angiography found associations of higher sUMOD with lower overall and cardiovascular mortality independent of estimated glomerular filtration rate (eGFR) and other CVD risk factors [12, 13]. To our knowledge, these findings have not been evaluated in broader populations. The elderly non-CKD population has a high degree of tubular atrophy [14]. Therefore the associations of sUMOD and adverse outcomes in the elderly population are of particular interest.

Within the CHS, a large community-based cohort of older adults, we examined the association between sUMOD and mortality, heart failure (HF) and atherosclerotic CVD outcomes over an extended follow-up period.

MATERIALS AND METHODS

Study participants

The CHS is an observational, community-based cohort study that included men and women ≥65 years of age from four US communities: Forsyth County, NC, Sacramento County, CA, Washington County, MD and Pittsburgh, PA. It was primarily designed to assess the prevalence and incidence of CVD as well as risk factors for CVD in a nonselected, general elderly population. A total of 5888 Medicare-eligible, noninstitutionalized participants were enroled, including 5201 persons (4957 non-Black, 244 Black) in 1989–90 and an additional 687 Blacks in 1992–93. Participants were recruited from random samples of Medicare eligibility lists and from age-eligible members of the same household. All gave informed consent for participation and local institutional review boards approved study methods. The baseline examination included a medical history, physical examination, laboratory testing and assessment for the presence of CVD. Participants were seen for yearly study visits until 1998–99 and interviewed by telephone between the study visits. After 1998–99, participants were contacted by telephone every 6 months.

Study design

In a prior study we assayed uUMOD in a random subcohort of 958 participants among the 4143 CHS participants who returned for the 1996–97 study visit and provided urine samples [8]. In order to maintain consistency, we chose to measure sUMOD in this same subcohort. As 25 lacked adequate serum for measuring sUMOD, our final sample size for the random subcohort was 933.

Exposure

Serum samples were obtained at the 1996–97 study visits and stored at −70°C until they were thawed. sUMOD measurements were performed at the University of Cincinnati Children's Hospital Medical Center using a commercial enzyme-linked immunosorbent assay (ELISA; Euroimmun Medizinische Labordiagnostika, Lübeck, Germany) as described previously based on the manufacturer's instructions [15]. This assay is based on a colorimetric sandwich immunoassay using a polyclonal antibody against human UMOD as the capture antibody and a biotinylated polyclonal antibody against human UMOD as the detection antibody. Validation data provided by the manufacturer of the ELISA are intra-assay coefficient of variation (CV) 1.8–3.2%, interassay CV 6.6–7.8%, mean linearity recovery 97% and lower limit of detection 2.0 ng/mL.

We correlated sUMOD with uUMOD using uUMOD measurements as detailed in a prior publication [8]. In brief, uUMOD was measured in 2014 at the University of Cincinnati Children's Hospital Medical Center using a commercially available ELISA kit (MD Bioproducts, St. Paul, MN, USA).

Outcomes

Primary study outcomes, including mortality, incident HF and incident atherosclerotic CVD [i.e. myocardial infarction (MI), stroke or death from either coronary heart disease or cerebrovascular disease (CVD mortality)] [16, 17]—were assessed until June 2015 using well-established ascertainment methods published previously [18]. In brief, all-cause mortality was assessed by active surveillance of medical records, death certificates, obituaries, Centers for Medicare and Medicaid Services databases and from next-of-kin interviews. Cardiac disease diagnoses and causes of death were adjudicated by physician members of the Cardiac and Stroke Events Committee of the CHS, upon review of hospital and medical records, symptoms and signs, complementary diagnostic tests (e.g. electrocardiograms, head computed tomography and magnetic resonance imaging, cardiac enzymes and other laboratory tests), autopsy reports when available), and proxy interviews.

Covariates

Information was collected on a variety of sociodemographic characteristics, risk factors for CVD and markers of kidney function. These factors included age, sex, race, clinical site, body mass index (BMI), educational status, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C formula [19], albumin:creatinine ratio (ACR), prevalent diabetes (defined by the use of hypoglycemic agents, fasting plasma glucose >126 mg/dL or nonfasting glucose ≥200 mg/dL), self-reported smoking status, systolic blood pressure (SBP), serum cholesterol, C-reactive protein (CRP), lipid-lowering therapy, antihypertensive medication use and prevalent HF or CVD. All covariates were assessed at the time of sUMOD measurement.

Statistical analysis

We described the population overall and across sUMOD quartiles using means and standard deviations for continuous variables and percentages for binary and categorical variables. We compared the distribution of variables across sUMOD quartiles using the chi-square test for categorical variables and a linear trend for continuous variables. We tested the correlation between sUMOD and uUMOD using Pearson's correlation

coefficient among 933 participants with both measurements available.

Generalized additive models with splines were used to address the functional form of sUMOD with outcomes. To formally test for nonlinearity, we used permutation tests. We subsequently restricted our results to the linear range due to nonlinearity at the extremes of sUMOD (see 'Results' section). Cox proportional hazards models were used to examine the association of sUMOD with study outcomes of HF, CVD, mortality and the composite of CVD and mortality. Prevalent events were excluded for analysis of the corresponding outcome. Models were adjusted in a nested way: unadjusted; Model 1 adjusted for baseline demographic/clinical parameters (age, sex, race, clinical site, BMI and educational status); Model 2 included Model 1 plus eGFR and ACR; Model 3 included Model 2 plus diabetes, smoking status, SBP, serum cholesterol, CRP, lipid-lowering therapy, antihypertensive medication use and prevalent HF and CVD. Whereas the analysis for mortality was adjusted for both prevalent HF and CVD, the analysis for incident HF was only adjusted for CVD and vice versa. Analyses were performed using R version 3.4.1 (R Project for Statistical Computing, Vienna, Austria). We did not adjust for multiple testing.

RESULTS

Population characteristics

Among the 933 participants, the mean serum concentration of sUMOD was 127 ± 64 ng/mL (range 6.2–634.1). There were no major differences between the random subcohort and the total CHS cohort participants that presented to this visit (Supplementary data, Table S1). Participants were on average 78 ± 5 years of age, 40% were male and 15% were black. The mean eGFR was 63 ± 19 mL/min/1.73 m^2. Individuals in the lower sUMOD quartiles were older, more likely to be male and white and had a higher baseline prevalence of diabetes, hypertension, HF, MI and stroke (Table 1). Participants with lower sUMOD levels also had lower eGFRs and higher fasting glucose, CRP and ACR (Table 1). Participants with lower sUMOD levels had lower uUMOD levels (Table 1). The correlation between sUMOD and uUMOD was 0.33 [95% confidence interval (CI) 0.27–0.38].

sUMOD and outcomes

Splines from general additive models suggested nonlinearity between sUMOD and all four outcomes at the extremes of sUMOD levels (Supplementary data, Figure S1). Permutation tests confirmed the better fit of a polynomial form of the association compared with a linear association (P = 0.003 for mortality, 0.021 for HF, 0.038 for CVD and 0.026 for the composite endpoint). Therefore we excluded 2.5% of the values on either end of the sUMOD distribution to model the association linearly between sUMOD in the range of 34.3–267.1 ng/mL and hazards for each outcome (Figure 1). There were 805 (86%) deaths, 283 (33%) cases of HF and 274 (36%) CVD events during a median follow-up period of 9.9 (95% CI 0.3–19.1) years (Table 2). The composite outcome was reached in 673 (87%) patients. Of note, the number of events for the composite outcome is lower compared with overall deaths, because patients with prevalent HF or CVD at baseline were excluded from the composite outcome analysis.

In univariate analyses, higher sUMOD was associated with a lower hazard for all-cause mortality [hazard ratio (HR) 0.73 (95% CI 0.67–0.80) per 1 SD higher sUMOD; Table 2], HF [HR 0.68 (95% CI 0.59–0.80)], CVD [HR 0.68 (95% CI 0.58–0.79)] and the composite outcome [HR 0.76 (95% CI 0.69–0.84)]. The association was attenuated when adjusting for demographics and eGFR/ACR. In the fully adjusted multivariable models, higher sUMOD was independently associated with a lower hazard for all-cause mortality [HR 0.89 (95% CI 0.80–0.99)], CVD [HR 0.80 (95% CI 0.67–0.96)] and the composite outcome [HR 0.88 (95% CI 0.78–0.99)] and a trend for HF [HR 0.84 (95% CI 0.07–1.01)] (Table 2 and Figure 1).

DISCUSSION

The results of our study in an elderly, community-based US cohort demonstrate that the association of sUMOD with mortality and CVD is linear within the middle 95% of the sUMOD range, with lower sUMOD concentrations independently associated with higher risk for all-cause mortality and CVD.

Higher concentrations of markers linked to the tubular system such as urine neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) have been associated with mortality and CVD in elderly cohorts [20, 21]. However, these markers represent tubular injury and are therefore primarily used to evaluate acute kidney injury (AKI) rather than kidney outcomes in stable community settings. NGAL and KIM-1 are also expressed in other tissues and upregulated in special clinical conditions such as in proinflammatory states [22, 23] and therefore lack specificity to reflect tubular function due to their nonrenal determinants. In contrast, UMOD is secreted into the urine and blood exclusively by the tubular cells of the ascending limb of the loop of Henle and has been associated with tubular atrophy, suggesting its value as a noninvasive marker of tubular integrity [7].

The underlying mechanisms explaining the association of low sUMOD levels with a higher risk for mortality and CVD are not completely understood. Basic research suggests that interstitial and circulatory UMOD deficiency lead to a proinflammatory state via various mechanisms such as activation of the interleukin 23 (IL-23)–IL-17 axis, neutrophilic granulopoiesis and regulation of myeloid progenitor cells [24, 25]. It has also been shown that in the renal interstitium UMOD can inhibit proinflammatory neutrophil chemokine secretion from the proximal tubule, thus potentially ameliorating the recovery of renal tissue in the setting of AKI [26]. Episodes of AKI are associated with an increased risk for CVD and mortality [27]. In clinical studies, circulatory sUMOD was inversely correlated with markers of inflammation (CRP and IL-1β), independent of eGFR, even in patients without CKD [12, 13]. Since higher sUMOD is associated with a lower risk for mortality and CVD, it is possible that sUMOD may have a systemic anti-inflammatory effect. Furthermore, lower sUMOD levels were associated with higher odds for coronary artery calcification in

Table 1. Baseline participant characteristics by quartiles of sUMOD

Variable	Total cohort ($n = 933$)	Quartile 1 ($n = 234$)	Quartile 2 ($n = 233$)	Quartile 3 ($n = 233$)	Quartile 4 ($n = 233$)
sUMOD range (ng/mL)	–	≤83.3	>83.3–118.4	>118.4–162.3	>162.3
sUMOD (ng/mL)	127.2 (63.6)	57.5 (17.4)	100.4 (9.9)	138.6 (13.6)	212.4 (51.2)
Demographics					
Age (years)	78.1 (4.8)	79.5 (5.33)	78.4 (4.95)	77.4 (4.3)	77.2 (4.2)
Male, %	39.7	48.7	41.6	38.2	30.0
Race Black, %	15.3	12.0	11.6	19.3	18.5
Site, %					
Wake Forest	23.2	17.1	27.0	24.9	23.6
UC Davis	28.5	26.9	28.3	30.5	28.3
Johns Hopkins	21.8	27.4	21.0	18.5	20.2
Pittsburgh	26.6	28.6	23.6	26.2	27.9
Laboratory measures					
CKD (eGFR <60 mL/min/1.73 m^2), %	41.7	69.7	45.1	31.8	20.2
eGFR (mL/min/1.73 m^2)	63.4 (18.6)	49.9 (19.4)	63.0 (15.7)	68.0 (15.6)	72.7 (15.0)
ACR >30 mg/g Cr, %	20.5	33.9	19.6	15.7	11.8
ACR (mg/g)	13.9 (4.3)	22.6 (4.9)	13.9 (4.3)	11.3 (3.0)	9.8 (2.6)
Urinary uromodulin (μg/mL)	30.5 (19.8)	22.9 (16.0)	28.7 (16.5)	31.9 (19.5)	38.4 (23.1)
Fasting glucose (mg/dL)	107.4 (34.6)	113.1 (35.7)	104.2 (23.4)	108.1 (39.0)	104.3 (37.5)
CRP (mg/dL)	2.5 (3.0)	3.0 (3.0)	2.5 (3.0)	2.5 (3.0)	2.0 (3.0)
Total cholesterol (mg/dL)	201.4 (38.8)	196.6 (43.3)	201.8 (37.8)	203.3 (38.1)	204.0 (35.5)
Serum albumin (g/dL)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)	3.8 (0.3)
CVD and prevalent risk factors					
Systolic BP (mmHg)	137.0 (21.0)	138.3 (21.7)	136.3 (21.6)	136.4 (17.1)	137.0 (23.0)
Diastolic BP (mmHg)	69.8 (11.0)	67.5 (13.4)	69.8 (10.1)	70.7 (9.9)	71.1 (9.9)
BMI (kg/m^2)	26.9 (4.7)	27.7 (5.1)	26.9 (4.9)	26.8 (4.2)	26.3 (4.4)
Diabetes, %	25.3	19.7	12.0	14.2	9.4
Hypertension, %	60.0	71.1	60.3	59.7	48.9
Heart failure, %	9.2	17.5	8.6	6.0	4.7
Cardiovascular disease, %	17.5	26.9	18.5	12.4	12.0
Medication use, %					
Lipid lowering	12.0	13.2	12.4	10.3	12.0
Antihypertensive	55.4	73.5	59.2	52.8	36.1
Lifestyle factors					
Smoking, %					
Current	7.4	5.2	7.4	9.7	7.5
Former	41.6	46.5	43.0	39.2	37.4
Never	51.0	48.3	49.4	51.1	55.1

Values are presented as mean (SD) unless stated otherwise. CVD is defined as a history of MI and/or stroke prior to baseline assessment. Cr, creatinine; BP, blood pressure.

patients with type 1 diabetes, suggesting that sUMOD may be protective against vascular calcification, another risk factor for mortality and CVD [28]. Since uUMOD has been shown to be a proxy for renal tubular mass [29], sUMOD may also serve as a proxy for tubular health and thereby capture the risk for both CKD and its progression independent of glomerular function [30]; CKD in turn is associated with mortality and CVD [31]. However, whether sUMOD reflects tubular mass in a comparable manner to uUMOD requires further evaluation. Given that sUMOD has been associated with tubular atrophy, it may also incorporate the risk of tubular disorders such as hyperkalemia and calcium–phosphorus dysbalance [32, 33], which are related to CVD and mortality.

In our cohort, the correlation of sUMOD and uUMOD was only moderate, suggesting that the two biomarkers cannot be used interchangeably. This is supported by the fact that the association of sUMOD with mortality and CVD has thus far been consistent among different cohorts [12, 13], but not in the case of uUMOD [8, 9, 34]. It is possible that uUMOD may be associated with mortality and CVD via different mechanisms. uUMOD deficiency leads to renal salt loss via, among other mechanisms, reduced activity of sodium–potassium–chloride[2] and renal outer medullary potassium channels, polyuria, decreased eGFR and reduced renin biosynthesis [6]. In addition, uric acid reabsorption is increased in the proximal tubule, leading to hyperuricemia [35]. A recent study in UMOD knockout mice confirmed these observations in young animals [36]. In contrast, in aged mice, they detected reduced urinary volume, hypertension and upregulation of the renin–angiotensin–aldosterone system (RAAS). Hyperuricemia, hypertension and RAAS activation are risk factors for mortality and CVD [37–39]. It remains unclear, however, whether these changes are pathophysiologically related to uUMOD deficiency and deserve further research.

In our analysis, we excluded participants with the extreme 2.5% sUMOD values at both ends, because the assumption of linearity of the HR in Cox regression analysis was violated. There are possible explanations for this observation. While we

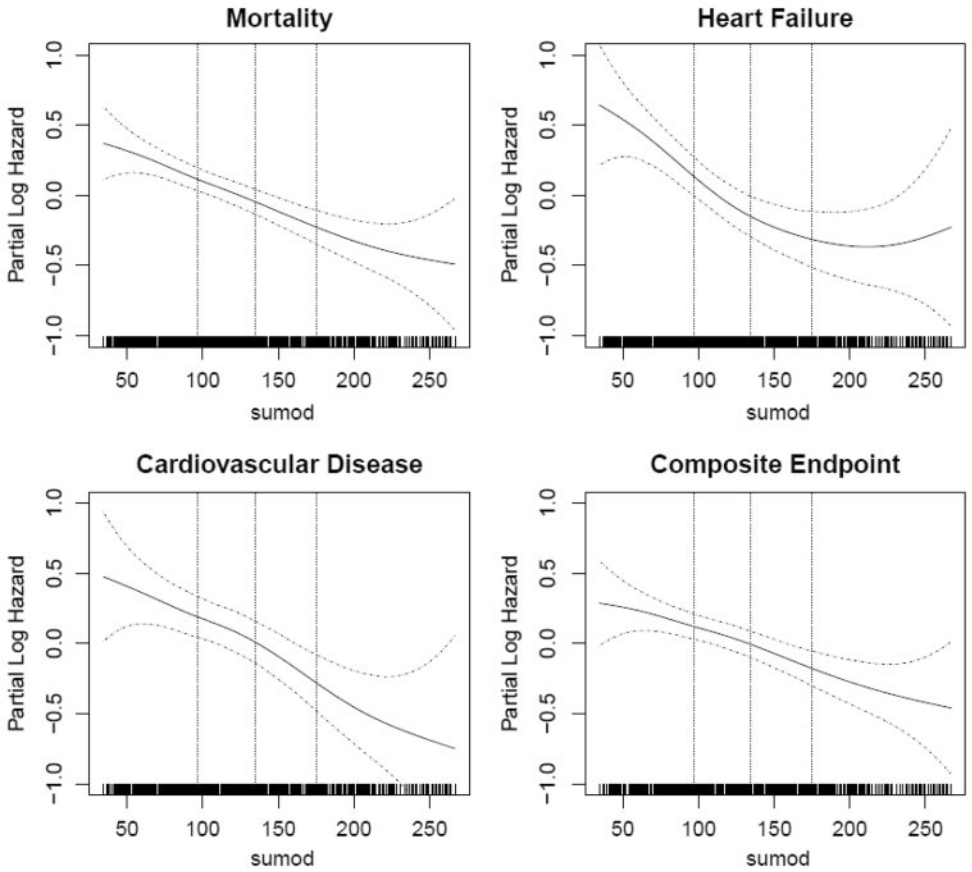

FIGURE 1: Penalized splines for sUMOD adjusted for demographic parameters, eGFR, albuminuria, cardiovascular risk factors and prevalent CVD at baseline. sUMOD (in ng/mL) on the *x*-axis and the partial hazard on a logarithmic scale on the *y*-axis. The solid black line indicates the partial log hazard; the two dotted lines around the black line indicate its 95% CI. Ticks on the *x*-axis represent individual participants. Vertical dotted lines indicate quartiles according to sUMOD levels. About 2.5% of values on both ends of sUMOD levels have been removed from the plot due to nonlinearity, limiting the data range in this plot to 34.3–267.1 ng/mL.

Table 2. Associations of sUMOD with mortality and cardiovascular outcomes

sUMOD (ng/mL)	Number of events	Incidence per 1000 person-years (95% CI)	Univariate, HR (95% CI)	Plus adjusted for demographics, HR (95% CI)[b]	Plus adjusted for eGFR and ACR, HR (95% CI)[c]	Plus adjusted for CVD RF and prevalent disease, HR (95% CI)[d]
Mortality ($n = 933$)	805	8.3 (7.7–9.0)	0.73 (0.67–0.80)	0.77 (0.70–0.84)	0.85 (0.77–0.94)	0.89 (0.80–0.99)
Incident HF ($n = 847$)	283	3.5 (2.0–4.2)	0.68 (0.59–0.80)	0.71 (0.61–0.84)	0.78 (0.66–0.93)	0.84 (0.70–1.01)
Incident CVD ($n = 770$)	274	3.7 (3.1–4.5)	0.68 (0.58–0.79)	0.70 (0.60–0.82)	0.76 (0.64–0.90)	0.80 (0.67–0.96)
Composite[a] ($n = 770$)	673	9.1 (8.3–10.1)	0.76 (0.69–0.84)	0.80 (0.72–0.88)	0.85 (0.76–0.95)	0.88 (0.78–0.99)

Multivariable Cox proportional hazards regression analysis for the sUMOD range of 34.3–267.1 ng/mL. HR given for 1 SD higher sUMOD (SD 63.6 ng/mL).
[a]Composite: mortality or incident CVD (MI, stroke of death from CVD). [b]Adjusted for age, sex, race, clinic site, BMI and level of education. [c]Adjusted for age, sex, race, clinic site, BMI, level of education, eGFR and log ACR. [d]Adjusted for age, sex, race, clinic site, BMI, level of education, eGFR and log ACR, diabetes, smoking status, SBP, serum cholesterol, log serum C-reactive protein, lipid-lowering medication, antihypertensive medication, prevalent chronic HF and CVD (mortality), prevalent CVD (incident HF) and prevalent HF (incident CVD). RF, risk factor.

cannot rule out a statistical artifact due to the small number of observations in these extreme sUMOD ranges, 2.5% of the participants with the highest sUMOD levels could also have a truly increased mortality and CVD risk due to overexpression of sUMOD. It has been proposed that very high sUMOD levels may lead to salt-sensitive hypertension, which could associate with an increased CVD risk [40]. On the other hand, the relatively reduced mortality and CVD risks of participants with very low sUMOD levels remain elusive.

The present study significantly adds to the literature, as it is the first of which we are aware that has evaluated the relationship of sUMOD with CVD outcomes and mortality in the general elderly population. We noted more attenuation of the results in comparison with the prior studies in those with coronary disease [12, 13]. This might be due to the fact that, in contrast to prior studies, we additionally adjusted for ACR and prevalent CVD [31]. Furthermore, the baseline characteristics of our cohort differed from the other studies, with our cohort

being older and having lower levels of sUMOD and eGFR; it is possible that as kidney function declines, eGFR incorporates more of the risk related to sUMOD or overall kidney health.

Our study has several strengths. To our knowledge, this is the first study that has evaluated the relationship of sUMOD with outcomes in an elderly, community-based cohort that presumably has a high prevalence of tubular atrophy. The CHS is a well-characterized cohort with detailed ascertainment of risk factors and adjudicated outcomes. An outcome assignment of 100% was reached for the outcomes of interest. Limitations include the long storage time of the samples used for sUMOD measurements. Although no deleterious effect of storage time on sUMOD levels has been reported, we cannot rule out degradation of the protein over time. If so, then there may be misclassification of the exposure variable and dilution of the results to the null.

In conclusion, sUMOD is associated with adverse CVD outcomes and overall mortality in the elderly independent of demographic variables, eGFR, ACR and cardiovascular risk factors. Additional studies are needed to reproduce these results in the general population.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

We declare that the results presented in this article have not been published previously in whole or part, except in abstract format.

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Association of motivations and barriers with participation and performance in a pedometer-based intervention

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ABSTRACT

Background. A randomized trial of a pedometer-based intervention with weekly activity goals led to increased walking among dialysis patients. However, the association of participant-expressed motivations and barriers to participation and performance in such an intervention has not been determined.

Methods. Thirty dialysis patients were randomized to a 12-week pedometer-based intervention with weekly step goals. Participants were asked about motivations and barriers to the increasing activity via weekly semi-scripted telephone interviews. We examined the association of these motivations and barriers with achieving weekly goals, reaching overall targets and increasing steps through multivariable linear and logistic regression analyses adjusted for age, sex, body mass index, dialysis modality and baseline steps.

Results. The most common motivations were desire to maintain/improve functional ability (30%) and activity (30%). The most common barriers were health-related (33%). Motivation to maintain/improve functional ability was associated with achieving weekly goals 17.9% more often [95% confidence interval (CI) 1.7–34.2] and with a greater increase in steps (1524 steps; 95% CI 61–2989) than those lacking this motivation. Experiencing a health-related barrier was not associated with