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Urinary sodium excretion and kidney failure in non-diabetic chronic kidney disease

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Abstract

Current guidelines recommend under 2g/day sodium intake in chronic kidney disease, but there are few studies relating sodium intake to long-term outcomes. Here we evaluated the association of mean baseline 24-hour urinary sodium excretion with kidney failure and a composite outcome of kidney failure or all-cause mortality using Cox regression in 840 participants enrolled in the Modification of Diet in Renal Disease Study. Mean 24-hour urinary sodium excretion was 3.46 g/day. Kidney failure developed in 617 and the composite outcome was reached in 723. In the primary analyses there was no association between 24-hour urine sodium and kidney failure [HR 0.99 (95% CI 0.91–1.08)] nor on the composite outcome [HR 1.01 (95% CI 0.93–1.09),] each per 1g/day higher urine sodium. In exploratory analyses there was a significant interaction of baseline proteinuria and sodium excretion with kidney failure. Using a 2-slope model, when urine sodium was under 3g/day, higher urine sodium was associated with increased risk of kidney failure in those with baseline proteinuria under 1g/day, and lower risk of kidney failure in those with baseline proteinuria of 1g/day or more. There was no association between urine sodium and kidney failure when urine sodium was 3g/day or more. Results were consistent using first baseline and time-dependent urine sodium. Thus, we noted no association of urine sodium with kidney failure. Results of the exploratory analyses need to be verified in additional studies and the mechanism explored.

Keywords

24-h urinary sodium excretion; kidney failure; CKD

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Disclosure

All authors declared no conflicts.

Introduction

Data from clinical trials and observational studies have convincingly demonstrated that increased sodium intake leads to higher blood pressure. [1, 2] Current guidelines therefore recommend low sodium intake for management and prevention of hypertension. The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends a sodium intake of less than 2 gram per day, but acknowledges that this recommendation is based primarily on data in the general population and not on hard clinical endpoints, as well as on the inference that interventions which reduce blood pressure will reduce progression of kidney disease; therefore it was given a 1C recommendation.[3]

There are fewer data, particularly trial data, relating sodium intake to the long term outcomes of cardiovascular disease (CVD), mortality and kidney failure. A recent meta-analysis[4] in the general population has suggested a modest effect of reduced salt intake on CVD outcomes, but observational data in the general population and in individuals with diabetes have created some controversy in that low sodium intake has been associated with higher risk of mortality and kidney failure.[5–8] In patients with chronic kidney disease (CKD), studies have shown that low sodium intake reduces urinary excretion of protein, which in turn is a risk factor of kidney disease progression.[2, 9] The benefit of low sodium has been particularly noted in those treated with renin-angiotensin-aldosterone system (RASS) inhibitors.[10–13]

There are no studies of which we are aware in non diabetic CKD, with multiple measures of baseline and follow up urinary sodium, long term follow up and with a large number of kidney failure outcomes. We therefore evaluated the association of 24-h urinary sodium excretion with kidney failure and a composite outcome of kidney failure or all cause mortality in the long term follow up of the Modification of Diet in Renal Disease (MDRD) Study. In exploratory analyses we also evaluated whether the association of urine sodium with kidney failure varies by glomerular filtration rate (GFR), level of proteinuria, and ACE inhibitor use given their potential relationships with both sodium intake and with kidney failure.[2, 8, 11–14] We also evaluated interactions by blood pressure target and protein intake targets given the randomized nature of the study.

Results

Baseline characteristics and follow-up 24-h urinary sodium excretion

Mean (SD) age was 51.7 ± 12.4 years, 60% were male and 85% white. 24% of the cohort had polycystic kidney disease, 31% had glomerular diseases, and 45% were classified as having other forms of kidney disease. Five percent of participants had a history of diabetes and 13% had a history of CVD. Mean (SD) measured GFR was 32.5 ±12.0 ml/min/1.73 m^2, median (25^{th}, 75^{th}) 24-h proteinuria was 0.32 (0.07, 1.51) g/d, mean (SD) 24-h urinary sodium excretion was 3.46 ± 1.13 g/d, and 36% of participants were receiving ACE inhibitors at baseline (Table 1).

Participants in the higher quartiles of urinary sodium excretion were more likely to be male, have a history of diabetes, have higher body mass index (BMI), measured GFR, and

proteinuria, and lower levels of high density lipoprotein (HDL) cholesterol. Urinary excretion of creatinine was similar in each of the quartiles.

24-hour urinary sodium excretion and long-term outcomes

Median follow-up time was 6 years (range, 0.25 to 18.61 years) for kidney failure. 617 (9.53 per 100-patient years) developed kidney failure and 723 (11.17 per 100-patient years) reached the composite outcome of kidney failure or all-cause mortality. In quartiles 1 to 4, the event rates per 100-patient years for kidney failure were 9.68, 9.48, 10.81, and 8.33; and 10.93, 11.27, 12.68, and 9.98 for the composite outcome, respectively.

In unadjusted and adjusted Cox regression models, there was no association between urine sodium with kidney failure or the composite outcome (Table 2 and Figure 1). There was also no deviation from linearity in these relationships. Results were similar using only the first baseline and cumulative mean time-dependent values for 24-h urinary sodium excretion (Supplementary Table S1).

Interactions

Figure 2 demonstrates the adjusted hazards ratios and interaction *p*-values for 24-h urine sodium and kidney failure overall and in subgroups. There was a significant interaction between 24 hour urine sodium and urinary protein excretion ($p = 0.019$ in the adjusted model) for kidney failure. The optimal knot for the 2-slope model for urine sodium corresponded to 3 g/d. Table 3 shows the hazard ratios for kidney failure and the composite outcome in the subgroups with baseline urine protein level < 1 g/d and ≥ 1 g/d. When 24-h urinary sodium excretion < 3 g/d, a 1 g/d higher urine sodium was associated with a 72% increased risk of kidney failure [HR 1.72 (95% CI, 1.31– 2.24)] in those with baseline proteinuria < 1 g/day, and a 39% lower risk of kidney failure [HR 0.61 (95% CI, 0.42 – 0.89)] in those with baseline proteinuria ≥1 g/day. In contrast, after adjustment, there was no association between 24-h urinary sodium excretion and kidney failure in those with urine sodium ≥ 3 g/d. Figure 3 demonstrates these results graphically. Results were for the most part consistent with the composite outcome (Table 3), and in sensitivity analyses using first baseline and cumulative mean time-dependent 24-h urinary sodium excretion (Supplementary Table S2 and S3, respectively).

Discussion

In the current study we demonstrate no association between 24-hour urinary sodium excretion with either kidney failure or a composite outcome of kidney failure and mortality. These relationships were robust in multivariable analyses and despite several sensitivity analyses including time dependent analyses. In exploratory analyses, we noted an interaction with urine protein, whereby in individuals consuming less than 3 grams of sodium per day, higher urinary sodium was associated with increased risk of kidney failure in those with baseline proteinuria < 1 g/d and lower risk of kidney failure in those with baseline proteinuria ≥ 1 g/d. We did not note any interactions of urinary sodium with baseline GFR, ACE inhibitor use, or blood pressure and protein intake randomization targets.

It is well accepted that sodium intake has an effect on blood pressure and randomized trials of lowering sodium intake have resulted in decreases in blood pressure.[1] This has led to recommendations in both the general population and CKD to reduce sodium intake. [3, 15] There are few clinical trial data however on the effect of sodium intake on either mortality or CVD outcomes. In the general population sodium lowering trials have at most a modest effect on reducing CVD outcomes,[4] perhaps related to the requirement for long follow up and large studies to achieve adequate statistical power for these outcomes. Recent observational studies in patients with diabetes, CVD and the general population have added controversy to this topic by demonstrating higher CVD and kidney failure outcomes in those with lowest sodium intake. In patients with both type 1 and type 2 diabetes, observational studies have demonstrated that low sodium intake may be associated with increased risk of all-cause mortality and CVD mortality.[7, 8] In addition, low sodium intake was also associated with kidney failure in those with macroalbuminuria.[8] In a post hoc analysis of individuals at high CVD risk enrolled in The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) (N=28,000) trials, a J-shaped relationship was noted between CVD events and sodium intake.[5] Similar J-shaped results were also reported in a general population study of 3681 individuals.[6] It has been argued that several of these studies may have been biased by inaccurate assessment of sodium intake due to estimation by spot urine samples,[5] inaccuracy of 24 hour urine sample collections[6] and small sample sizes.[8] Either way, the results have suggested that there is more to be learned in this area and that there may be individuals who are at higher risk of sodium restriction.[16]

Patients with CKD have a high prevalence of hypertension and are at particularly high risk for mortality as well as progression of kidney disease;[17, 18] therefore evaluation of the effect of sodium intake is of critical public health importance in this population. Unfortunately there are very few observational studies of sodium intake, and no RCT's with long term hard outcomes in this population. In the Ramipril Efficiency in Nephropathy (REIN) study, lower sodium intake defined as 24-h urinary sodium/creatinine excretion < 100 mEq/g (approximately 2.87 grams sodium per day) was associated with slower progression in those treated with ramipril; however no data are provided on the control group.[13] In a combined analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) and The Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trials, low sodium intake, defined as the first tertile of 24-h urinary sodium/creatinine ratio, was only of benefit in those treated with an angiotensin receptor blocker (ARB). Our study adds to this literature by providing the most comprehensive assessment of sodium intake compared to the published literature, and the ability to evaluate a large number of long term outcomes. Our primary results demonstrated there was no association between 24-h urine sodium with either kidney failure or the composite outcome in a large cohort of predominantly non-diabetes CKD patients. There are several potential interpretations of our results. First it is possible that indeed sodium intake is not a risk factor for progression of kidney disease, or stated differently is a relatively minor risk factor compared to other established risk factors for progression of CKD. Our results are consistent with data from the African American Study of Kidney Disease and Hypertension (AASK) and a recent analysis of individuals

with type 2 diabetes without macroalbuminuria from the ONTARGET study, in which urine sodium was not associated with progression of kidney disease in adjusted analyses. [19, 20] Second, it is possible that given prior data which suggest that both high sodium and low sodium may be associated with adverse outcomes through different mechanisms, the effect of each may negate the other. We did not however note any overt deviations from linearity or U shaped relationships. Third, given the strong interrelationships of sodium intake with blood pressure and proteinuria, and the difficulty of distinguishing confounding versus mediating relationships in observational studies, it is possible we may have missed a significant relationship.

In exploratory analyses, we however noted an interaction of urine sodium with proteinuria such that when urine sodium < 3 g/day, higher urine sodium was associated with increased risk of kidney failure in those with proteinuria < 1 gram per day, but lower risk of kidney failure in those proteinuria ≥ 1 g/d. The former is consistent with our *apriori* hypothesis that high sodium may be detrimental, but the latter findings were unexpected. There are several potential explanations for the latter result. First, patients with higher levels of proteinuria are at increased risk for hypoalbuminemia with redistribution of extracellular fluid from the vascular to the interstitial compartment, and in the setting of lower salt intake may be at particular risk for episodes of decreased kidney perfusion and possibly acute kidney injury (AKI). Acute kidney injury in turn is now recognized as a risk factor for progression of kidney disease.[21] Unfortunately, AKI was not one of the primary outcomes ascertained in the MDRD Study, therefore we could not explore this hypothesis further. Second, low salt intake may stimulate activation of the sympathetic nerve system as well as RAAS,[22] and particularly in those with proteinuria, may be associated with progression of kidney disease. Third, in diabetic nephropathy, Vallon et al. have hypothesized that low salt intake may actually promote hyperfiltration, which in theory may be deleterious to residual nephrons.[23] It remains to be determined whether this is also true in non diabetic CKD. Lastly, despite adjustment for all variables that we thought may be potential confounders, we cannot rule out the possibility of residual confounding such that individuals with proteinuria who are consuming less sodium are sicker and therefore more likely to have progression of kidney disease.

There are several strengths of our study. First, we had accurate ascertainment of the exposure variable given the availability of 3–4 24-hour urine collections at baseline as well many 24 urine collections in follow-up which allowed time dependent analyses. Other studies have relied either on spot urines[5] or one 24 hour urine collection to assess urinary sodium excretion.[6] Second, the 24-hour urine collections appeared adequate by creatinine excretion criteria. Third, we had detailed ascertainment of risk factors and outcomes and the ability to evaluate long term outcomes of kidney failure and mortality, which are the primary outcomes of interest in patients with CKD. Fourth, given that the MDRD Study was a randomized trial we were able to evaluate interactions with randomized groups. Limitations include the fact that the MDRD Study excluded individuals with type 1 diabetes, type 2 diabetes treated with insulin, and individuals with advanced vascular disease; therefore the results may not be generalizable to all patients with CKD.

In conclusion, 24-hour urinary sodium excretion was not associated with kidney failure or a composite outcome in a large group of individuals with predominantly non- diabetic CKD. In exploratory analyses we noted an interaction with proteinuria which needs to be evaluated and reproduced in additional studies. Our results should to be confirmed in other forms of kidney disease and the mechanisms underlying the associations investigated. Ultimately, randomized trials in CKD should be undertaken to evaluate the relationship of sodium intake to the clinically important outcomes of kidney failure, CVD and mortality.

Methods

Participants and Measurement

Details of MDRD study have been described previously.[24] The MDRD study was a randomized controlled trial conducted from January 1989 to January 1993, and designed to evaluate the effect of dietary protein restriction and strict blood pressure control on the progression of kidney disease. The trial included CKD patients with age 18 to 70 years and with serum creatinine level 1.4–7.0 mg/dL in men or 1.2–7.0 mg/dL in women. The exclusion criteria were pregnancy, type 1 diabetes, insulin-dependent type 2 diabetes, glomerulonephritis caused by autoimmune diseases, obstructive uropathy, renal artery stenosis, proteinuria with protein greater than 10 g/d, mean arterial pressure greater than 125 mm Hg, and prior kidney transplantation. A total of 840 participants were randomized.

Glomerular filtration rate was measured by using urinary iothalamate clearance. After a 3-month baseline period, participants with GFR 25–55 mL/min/1.73 m^2 entered study A and participants with GFR 13–24 mL/min/1.73 m^2 entered study B. Participants in study A were randomized to a usual protein (1.3 g/kg/d) or low protein (0.58 g/kg/d) diet. In study B, participants were randomly assigned to a low protein diet (0.58 g/kg/d) or a very low protein diet (0.28 g/kg/d) supplemented with a mixture of keto-acids and amino acids. Participants both in study A and study B were randomly assigned to either a usual blood pressure target or low blood pressure target. The low target blood pressure was a mean arterial pressure (MAP) less than 92 mm Hg (equivalent to a blood pressure less than 125/75 mm Hg) for patients 18 – 60 years old and less than 98 mm Hg for patients more than 61 years old. The usual target blood pressure was a MAP less than 107 mm Hg (equivalent to a blood pressure of 140/90 mmHg) for patients 18 – 60 years old and less than 113 mm Hg for patients more than 61 years old. Dietary sodium intake was not restricted in either study. All labs were measured at the MDRD Study Central Biochemistry Laboratory (Department of Biochemistry, Cleveland Clinic Foundation, Cleveland, OH).

Exposure Variable

The mean baseline 24-h urinary sodium excretion for each participant was calculated from either three (n=200) or four (n=640) 24-h urine collections during the baseline period. In sensitivity analyses, we used the first baseline measurement of urinary sodium excretion as dietary sodium may have changed during the baseline period and cumulative mean time-dependent values for 24-h urinary sodium excretion during follow-up to account for changes in sodium intake during follow-up. For each participant, a median (25^{th}, 75^{th}) of 33 (25, 39)

24-h urinary sodium excretions were measured during follow-up. 24 hour urine sodium excretion is a good proxy for sodium intake in the steady state.

Outcomes

Our primary outcomes were kidney failure (defined as initiation of dialysis or transplantation), and given any possibility of competing risk due to mortality, a composite of kidney failure or all-cause mortality. Kidney failure outcomes were obtained from the United States Renal Data System (USRDS) and survival status from the National Death Index (NDI). Both outcomes were ascertained through December 31, 2007. We define survival time for each participant as time from randomization to kidney failure, death or administrative censoring at December 31st, 2007 whichever comes first. Data collection procedures were approved by the Cleveland Clinic and Tufts Medical Center Institutional Review Boards.

Covariates

Covariates included demographic factors (age, race and sex); comorbid conditions (cardiovascular disease-defined as either coronary artery disease, cerebral vascular disease, or peripheral vascular disease, and diabetes); cause of kidney disease (polycystic kidney disease, glomerular disease or other); kidney measures (measured GFR and urine protein); other cardiovascular and kidney related risk factors (smoking, BMI), systolic blood pressure (SBP), low density lipoprotein (LDL) cholesterol, HDL cholesterol); medications (ACE inhibitors and diuretics); MDRD Study A or B, and randomization assignments. All covariates were measured at the last visit prior to randomization. 24-h urine creatinine was used to assess accuracy of the urine collections.

Statistical Analysis

The distribution of demographic data and laboratory variables were compared across quartiles of mean 24-h urinary sodium excretion using the χ^2-test for categorical variables and the Kruskal-Wallis test or Mann-Whitney U test for continuous variables, as appropriate.

Restricted cubic splines were used to explore the association of urine sodium with kidney failure and composite outcome in unadjusted and adjusted analyses. Cox proportional hazards regression models were used to evaluate the relationship between 24-h urinary sodium excretion and kidney failure and composite outcome in the primary analysis. The following potential confounding covariates were included in all models: age, baseline GFR, sex, race, smoking, diabetes, history of CVD, BMI, SBP, LDL cholesterol, HDL cholesterol, log urine protein, cause of kidney disease, ACE inhibitor use, diuretic use, MDRD study A or B, and randomization groups.

We then performed exploratory analysis to evaluate the following pre-specified interactions with 24-h urine sodium excretion using multivariable Cox regression models: level of GFR based on MDRD Study A or B; baseline urine protein level (< 1 g/d or ≥ 1 g/d) based on the fact that in the MDRD Study lower target blood pressure reduced progression of kidney disease in those with proteinuria >1 g/d;[25] ACE inhibitor use, and randomization to usual or

low BP target as well as randomization to usual, low protein, or very low protein diet. When the interaction was significant, we used restricted cubic splines to explore the functional form of urine sodium on kidney failure by allowing a different form by the interaction variable. The splines plotted for the model with urine protein interaction suggested a 2-slope model. We searched for the corresponding optimal knot based on models with the lowest −2 log likelihood.

All analyses were performed using SAS software (version 9.3, SAS Institute, Cary, NC), and R project for Windows (version 2.15.1 and 2.13.1). All hypothesis tests were 2-sided, and statistical significance defined as a p -value < 0.05.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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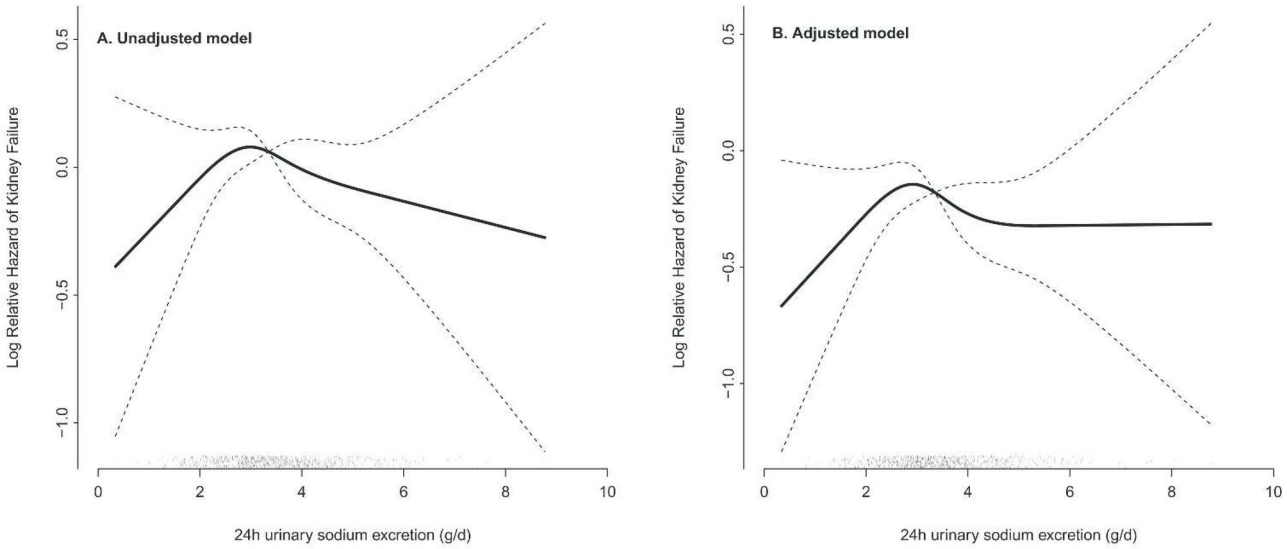

Figure 1. Unadjusted and adjusted restricted cubic splines for mean baseline 24-h urinary sodium excretion and kidney failure in the entire cohort

Splines were plotted using 4 default knots. *p*-value for nonlinearity of urine sodium were 0.251 in unadjusted model and 0.191 in adjusted model. Dashed lines indicate 95% CIs, and rugs at the bottom show location of each value for 24-h urine sodium. Splines were adjusted for age, sex, race, cause of kidney disease, measure GFR, log urine protein, BMI, SBP, LDL cholesterol, HDL cholesterol, smoking, diabetes, history of CVD, ACE inhibitor use, diuretic use, MDRD study A or B, and randomization to blood pressure and dietary protein target.

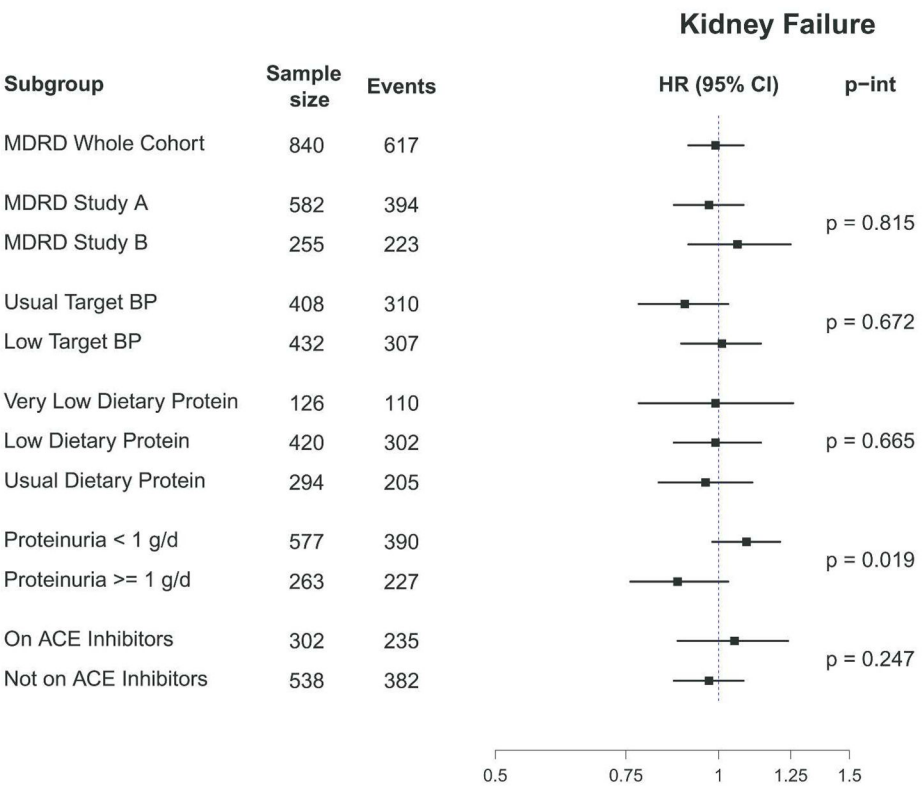

Figure 2. Forest plot of mean baseline 24-h urinary sodium excretion and kidney failure in the entire cohort and subgroups

Hazard ratios (HRs) (95% CI) were per 1 g/d higher urine sodium, and HRs were log scale. *p*-int was *p*-value for the interaction. The hazard ratios were adjusted for age, sex, race, cause of kidney disease, measure GFR, log urine protein, BMI, SBP, LDL cholesterol, HDL cholesterol, smoking, diabetes, history of CVD, ACE inhibitor use, diuretic use, MDRD study A or B, and randomization to blood pressure and dietary protein target.

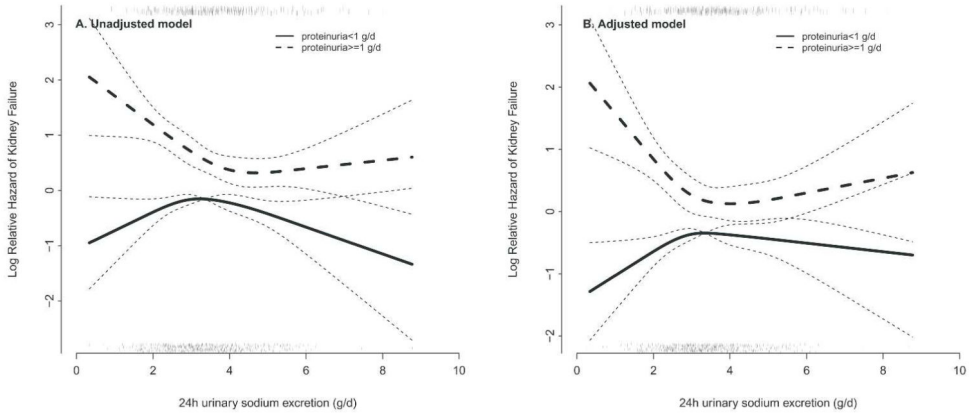

Figure 3. Unadjusted and adjusted restricted cubic splines for mean baseline 24-h urinary sodium excretion and kidney failure stratified by baseline proteinuria

Splines were plotted using 4 default knots. *p*-value for nonlinearity of urine sodium were 0.005 in unadjusted model and 0.003 in adjusted model. Thin dashed lines indicate 95% CIs, and rugs at the bottom and top showed location of each value for 24-h urine sodium in those with baseline urine protein < 1g/d and ≥ 1 g/d, respectively. Splines were adjusted for age, sex, race, cause of kidney disease, measure GFR, log urine protein, BMI, SBP, LDL cholesterol, HDL cholesterol, smoking, diabetes, history of CVD, ACE inhibitor use, diuretic use, MDRD study A or B, and randomization to blood pressure and dietary protein target, and interaction between urine sodium and baseline urine protein.

Table 1

Baseline characteristics by baseline mean 24-hour urinary sodium excretion

Variable	Overall n=840	24-h urinary sodium excretion, g/d				*p*-value for linear trend
		Quartile 1 n=210	Quartile 2 n=210	Quartile 3 n=210	Quartile 4 n=210	
24-h Urinary sodium excretion (g/d)	3.46 ± 1.13	2.14 ± 0.44	3.05 ± 0.17	3.70 ± 0.21	4.96 ± 0.78	NA
Age (y)	51.7 ± 12.4	51.1 ± 12.7	52.4 ± 12.8	53.3 ± 12.3	50.1 ± 11.6	0.408
Men (%)	60.5	37.6	52.9	67.1	84.3	<0.001
White (%)	85.0	81.0	84.3	87.6	87.1	0.047
Kidney diseases diagnosis (%)						
Polycystic kidney disease	23.8	27.1	26.7	22.9	18.6	0.020
Glomerular disease	31.4	25.7	32.4	29.5	38.1	
Other	44.8	47.1	41.0	47.6	44.3	
BMI (kg/m^2)	27.1 ± 4.4	24.9 ± 3.8	26.4 ± 4.2	27.7 ± 4.1	29.5 ± 4.3	<0.001
Systolic BP (mmHg)	131.9 ± 17.6	129.9 ± 17.5	132.5 ± 17.8	132.9 ± 18.9	132.4 ± 15.9	0.077
Diastolic BP (mmHg)	81.0 ± 10.1	79.4 ± 9.9	80.7 ± 9.9	81.2 ± 10.4	82.6 ± 10.0	0.001
Diabetes (%)	5.1	3.3	2.4	7.1	7.6	0.010
History of CVD (%)	13.1	9.5	15.2	16.2	11.4	0.522
Current smoker (%)	9.8	8.6	9.1	10.0	11.5	0.291
LDL (mg/dL)	147.4 ± 41.3	146.7 ± 41.3	153.0 ± 44.1	146.4 ± 38.0	143.6 ± 41.2	0.450
HDL (mg/dL)	39.9 ± 14.3	45.2 ± 16.4	41.0 ± 13.4	37.8 ± 13.5	35.4 ± 11.5	<0.001
mGFR (ml/min/1.73m^2)	32.5 ± 12.0	30.4 ± 12.8	31.6 ± 11.7	31.6 ± 11.6	36.5 ± 11.0	<0.001
Urinary protein excretion (g/d)	0.32 (0.07, 1.51)	0.25 (0.07, 1.03)	0.19 (0.06, 1.24)	0.53 (0.07, 1.69)	0.53 (0.08, 2.00)	0.002
Urinary creatinine excretion (g/d)	1.40 (1.06, 1.70)	1.31 (1.05, 1.74)	1.31 (1.05, 1.63)	1.42 (1.08, 1.74)	1.33 (1.05, 1.64)	0.884
Usual target blood pressure (%)	48.6	46.7	45.7	49.5	52.3	0.174
Low target blood pressure (%)	51.4	53.3	54.3	50.5	47.6	
ACEi (%)	36.0	32.4	34.3	40.5	36.7	0.198
Diuretic (%)	40.5	33.8	39.5	46.7	41.9	0.038

Note: data presented as mean ± SD, percent or median (25^{th}, 75^{th}). Conversion factors for units: urinary sodium excretion in mEq/d to g/d, ×0.02299; cholesterol, LDL and HDL cholesterol in mg/dL to mmol/L, ×0.02586; mGFR in mL/min/1.73m^2 to mL/s/1.73m^2, ×0.01667.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; mGFR, measure glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitors.

Table 2

Association of mean baseline 24-h urinary sodium excretion with kidney failure and the composite outcome of kidney failure or mortality in entire cohort

		Unadjusted model		Adjusted model*	
	Event N(%)	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Kidney failure	617 (73.5)	0.98 (0.91, 1.05)	0.538	0.99 (0.91, 1.08)	0.863
Composite outcome	723 (86.1)	1.00 (0.94, 1.06)	0.926	1.01 (0.93, 1.09)	0.804

Hazard ratios (HRs) were per 1 g/d higher urine sodium.

*Adjusted for age, sex, race, cause of kidney disease, measured GFR, log urine protein, BMI, SBP, LDL cholesterol, HDL cholesterol, smoking, diabetes, history of CVD, ACE inhibitor use, diuretics use, MDRD study A or B, and randomization to BP and dietary protein target.

Table 3

Association of mean baseline 24-h urinary sodium excretion with kidney failure and composite outcome by baseline urinary protein excretion

	Unadjusted model						Adjusted model**			
	24-h urine sodium < 3 g/d			24-h urine sodium ≥ 3 g/d			24-h urine sodium < 3 g/d		24-h urine sodium ≥ 3 g/d	
	Event*	HR (95% CI)	*P*-value	Event*	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Kidney failure										
Baseline urine protein excretion < 1 g/d	145	1.37 (1.05, 1.78)	0.020	245	0.85 (0.74, 0.97)	0.021	1.72 (1.31, 2.24)	<0.001	0.86 (0.73, 1.02)	0.084
Baseline urine protein excretion ≥ 1 g/d	68	0.57 (0.40, 0.81)	0.002	159	0.93 (0.80, 1.08)	0.322	0.61 (0.42, 0.89)	0.012	0.97 (0.82, 1.16)	0.779
Composite outcome of kidney failure or all-cause mortality										
Baseline urine protein excretion < 1 g/d	171	1.42 (1.11, 1.81)	0.005	305	0.88 (0.78, 1.00)	0.048	1.60 (1.26, 2.05)	<0.001	0.90 (0.78, 1.04)	0.170
Baseline urine protein excretion ≥ 1 g/d	74	0.58 (0.41, 0.80)	0.001	173	0.93 (0.80, 1.07)	0.312	0.64 (0.45, 0.93)	0.019	0.97 (0.82, 1.15)	0.760

Hazard ratios (HRs) were per 1 g/d higher urine sodium. Interaction *p*-value between baseline urine sodium and proteinuria were < 0.001 for kidney failure and the composite outcome in adjusted models.

*Event numbers are applicable for unadjusted and adjusted models.

**Adjusted for age, sex, race, cause of kidney disease, measured GFR, log urine protein, BMI, SBP, LDL cholesterol, HDL cholesterol, smoking, diabetes, history of CVD, ACE inhibitor use, diuretics use, MDRD study A or B, and randomization to BP and dietary protein target.