Sodium Intake and Renal Outcomes: A Systematic Review

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BACKGROUND
Sodium intake is an important determinant of blood pressure; therefore, reduction of intake may be an attractive population-based target for chronic kidney disease (CKD) prevention. Most guidelines recommend sodium intake of <2.3 g/day, based on limited evidence. We reviewed the association between sodium intake and renal outcomes.

METHODS
We reviewed cohort studies and clinical trials, which were retrieved by searching electronic databases, that evaluated the association between sodium intake/excretion and measures of renal function, proteinuria, or new need for dialysis.

RESULTS
Of 4,337 reviewed citations, seven (n = 8,129) were eligible, including six cohort studies (n = 7,942) and one clinical trial (n = 187). Four studies (n = 1,787) included patients with CKD. All four cohort studies reported that high intake (>4.6 g/day) was associated with adverse outcomes (vs. moderate/low), while none reported an increased risk with moderate intake (vs. low). Three studies (n = 6,342) included patients without CKD. Two cohort studies (n = 6,155) reported opposing directions of association between low (vs. moderate) sodium intake and renal outcomes, and one clinical trial (n = 187) reported a benefit from low intake (vs. moderate) on proteinuria but an adverse effect on serum creatinine.

CONCLUSIONS
Available, but limited, evidence supports an association between high sodium intake (>4.6 g/day) and adverse outcomes. However, the association with low intake (vs. moderate) is uncertain, with inconsistent findings from cohort studies. There is urgent need to clarify the long-term efficacy and safety of currently recommended low sodium intake in patients with CKD.

Keywords: blood pressure; chronic kidney disease; clinical epidemiology; hypertension; nutrition.

doi:10.1093/ajh/hpt294

Chronic kidney disease (CKD), which is characterized by proteinuria and/or reduction in glomerular filtration rate (GFR), affects as many as one in eight adults[1] and is associated with increased mortality and morbidity.[2] More than 1.8 million people worldwide receive renal replacement therapy (RRT) for end-stage kidney disease (ESKD). Given the burden of CKD and its covert presentation, population-based interventions that target modifiable risk factors for CKD are needed. In general, CKD shares risk factors with cardiovascular disease (CVD), and hypertension is a major risk factor for CKD. High sodium intake is associated with increased blood pressure and randomized controlled trials report a modest reduction in blood pressure with reduction of sodium intake from moderate to moderate–low levels.[3,4] Based on this evidence, which links sodium intake with blood pressure, but without direct evidence linking sodium intake to CKD, some guidelines recommend sodium restriction to prevent the development and progression of CKD.

Most current guidelines, for both the general population and specific populations such as those with CKD or ESKD, recommend a daily sodium intake of <2.3 g/day[5–10] (<100 mmol of sodium, <6 g of salt) and some recommend even lower intake (<1.5 g/day;[11] Figure 1). However, these guidelines are extrapolated from studies of populations without CKD, where outcome measures were blood pressure or CV events, or are based on small, short-term studies that include measures of renal function.[13] Moreover, recent evidence suggests that the association between sodium intake and CVD may be J-shaped,[14] with an increased risk at the low levels recommended by current guidelines.[15] A recent report from the Institute of Medicine found insufficient evidence to recommend intakes of 1.5–2.3 g/day in populations with kidney disease.[16]

Given these considerations, we systematically reviewed cohort studies and clinical trials to determine the independent association between sodium intake and creatinine-based measures of renal function and proteinuria in people with and without CKD.

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Initially submitted October 18, 2013; date of first revision November 23, 2013; accepted for publication December 18, 2013; online publication February 7, 2014.

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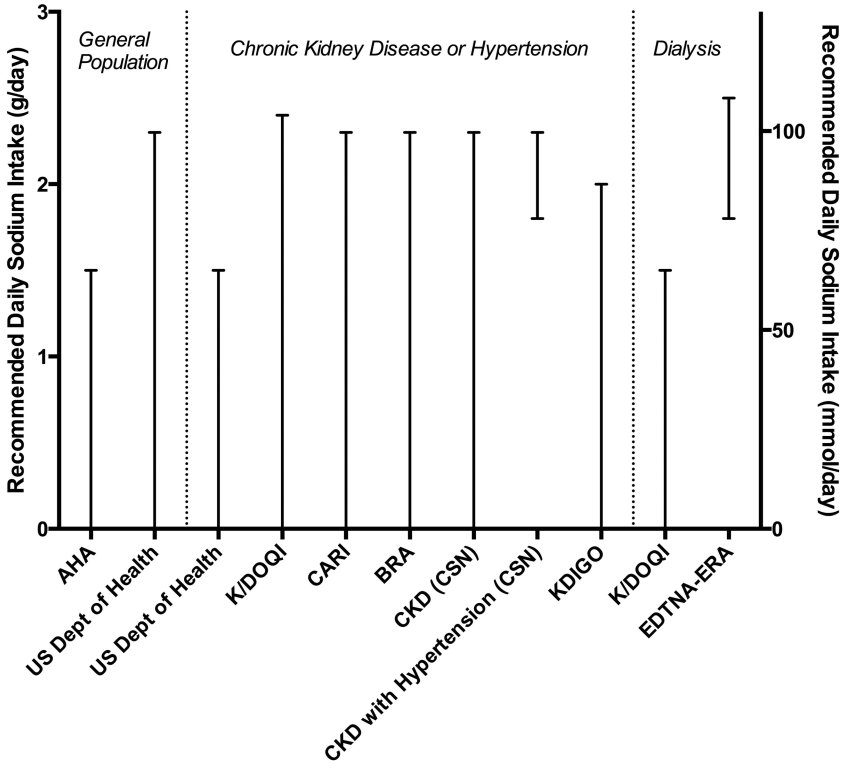

Figure 1. Guidelines on dietary sodium intake. Recommend range of intake plotted; guidelines that do not include a recommended lower limit plotted as recommended range (e.g., <2.3,g/day plotted as 0–2.3 g/day). X-axis = target population (organization issuing guideline). Abbreviations: AHA, American Heart Association (2012);[11] US Dept of Health, US Department of Health and Human Services (2010);[8] K/DOQI, National Kidney Foundation Disease Outcomes Quality Initiative (2004);[5] CARI, Caring for Australasians with Renal Impairment (2005);[7] BRA, British Renal Association (2011);[12] CSN, Canadian Society of Nephrology (2008);[10] KDIGO, Kidney Disease Improving Global Outcomes (2012);[9] EDTNA-ERA, European Dialysis and Transplantation Nurses Association/European Renal Care Association (2002).[6]

SUBJECTS AND METHODS

Search strategy

Two investigators (A.S., M.O'D.) searched the following electronic databases: the Cochrane Central Register of Controlled Trials, MEDLINE (Ovid), Embase, CINAHL, PsycINFO, Health Technology Assessment, PubMed, and Abstracts of Reviews of Effects (DARE) for articles published from January 1966 to June 2012 (Supplementary Table S1).

Eligibility criteria

We included cohort studies (retrospective and prospective) and clinical trials that evaluated the association between sodium ingestion or excretion and renal outcomes. The outcome measures included creatinine-based measures of renal function (including estimated glomerular filtration rate (eGFR), serum creatinine and creatinine clearance, doubling of creatinine, diagnosis of ESKD and/or the need for dialysis) and proteinuria (including nonspecific proteinuria, 24-hour urinary albumin excretion (UAE), 24-hour urinary protein excretion, urine albumin-to-creatinine ratio (ACR), and urine protein-to-creatinine ratio (PCR)). Studies that reported quantified measures of sodium intake/excretion (including urinary estimates of sodium, dietary recall, and food-frequency questionnaires (FFQs)) and at least one of the selected renal outcomes were eligible. All studies were required to include 50 or more participants and to have a minimum total follow-up of 3 months.

Cross-sectional studies were excluded, as were studies that included only patients on dialysis or with a renal transplant at the start of the study period, as they are considered a separate population since the primary outcomes of interest in all subjects were present at baseline. Studies that evaluated a multicomponent dietary or lifestyle intervention were not eligible, unless the independent effect of sodium intake/excretion was reported.

Data collection

Two investigators (A.S., M.O'D.) independently reviewed full-text articles that met the eligibility criteria; disagreements regarding eligibility were resolved by consensus. Data on study type and design, population characteristics, sodium estimation (method of assessment, actual measurement, and categories of intake (low, moderate, and high)), and outcome variables were extracted by A.S. and confirmed by two other reviewers (M.O'D., C.C.). We defined low sodium intake as that recommended by guidelines (<2.3 g/day), moderate intake as 2.3–4.6 g/day, and high intake as twice the upper limit recommended by guidelines (>4.6 g/day). A positive association was defined as worsening renal outcomes (i.e., a worsening of renal function or an increase

in proteinuria), with increasing sodium intake/excretion and an inverse association defined conversely. Studies were classified as being of populations with CKD if the population was defined as CKD in the primary paper or if the mean eGFR was <60 ml/min/1.73 m^2. As renal outcomes differed between studies, we report the renal outcomes as defined in the study manuscript.

Risk of bias

Using standardized risk-of-bias tools, including the Newcastle-Ottawa scale[17] and the Cochrane collaboration's tool for assessing risk of bias,[18] two investigators (A.S., M.C.) reviewed all eligible studies.

Analysis

Due to known heterogeneity in the methods of sodium estimation and the number of different renal outcomes, we decided *a priori* not to perform metaanalysis or to generate quantitative summary estimates. Instead we planned to present a qualitative summary in tabular format, with studies divided into those of patients with and those without chronic kidney disease (CKD). When studies reported multiple adjusted effects, data from the most adjusted model was recorded.

RESULTS

Of 4,337 citations, seven studies (n = 8,129) fulfilled the eligibility criteria (Supplementary Figure S1), including one retrospective cohort study[19] (n = 57), five prospective cohort studies[20–24] (n = 7,885), and one clinical trial[25] (n = 187). Four studies (n = 1,787) included only participants with CKD;[19–21,24] three studies (n = 6,342) included only participants without CKD.[22,23,25] Sodium intake was estimated by 24-hour urinary sodium collection in six studies[19–21,23–25] and FFQ in one study.[22]

All seven studies reported outcomes for creatinine-based measures of renal function,[19–25] and six studies reported outcomes for proteinuria.[19–22,24,25] Table 1 describes the population and method of sodium estimation included in each study, and Supplementary Table S2 summarizes the methodological characteristics of studies included in this review.

Overall, the risk of bias was low in the included observational studies (Supplementary Table S3), but three of the six cohort studies reported only unadjusted estimates for renal outcomes.[19,20,24] Similarly, the risk of bias was low in the included clinical trial (Supplementary Table S4). Due to differing study designs and outcomes, we were unable to assess for publication bias using a funnel plot.

Table 1. Details of included studies

	Study						
Parameter	Cianciaruso *et al.* 1998[19]	Lin *et al.* 2010[22]	Amaha *et al.* 2010[20]	Thomas *et al.* 2011[23]	Vegter *et al.* 2012[21]	Lambers Heerspink *et al.* 2012[24]	He *et al.* 2009[25]
Population	57	3,348	53	2,807	500	1,177	187
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Trial
Country	Italy	United States	Japan	Finland	Italy	Multiple	United Kingdom
Age, years	μ48–52	μ67	μ64 ± 10	μ38–39	μ52–56	30–70	μ50
Hypertension, %	22.8	54.4	N/A	44.5–53.6	NA	NA	100
Proteinuria, %	100	6.1	NA	35	100	100	0
Reduced glomerular filtration rate, %	100	NA	100	NA	100	100	0
Cardiovascular disease, %	NA	6.2	NA	6.4–9.2	NA	NA	0
Diabetes, %	12.3	23.7	0	100	0	100	0
ACE/ARB therapy, %	NA	15.6	NA	24–28.9	100	42.4	0
Diuretic therapy, %	NA	NA	NA	8.1–10.0	NA	61	0
Measure of sodium	Six 24-hour urine sodium	Five food frequency questionnaires	Two 24-hour urine sodium	One 24-hour urine sodium	Five 24-hour urine sodium[a]	Five 24-hour urine sodium[a]	Six 24-hour urine sodium
Sodium intake, g/day	μ3.7	1.7–2.4*	μ2.8	μ3.5	μ2.8–5.6	μ4.2	μ3.0
Length of follow-up, years	μ3.6	10	1	10*	μ2.2	μ2.5	0.3
Completed follow-up, %	100	100	100	100	100	100	100

Abbreviations: *, median; μ, mean; ACE/ARB, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy; NA, not available or reported in primary paper.

[a]Mean of five 24-hour urine collections.

Studies of populations with CKD

Four studies (n = 1,787) reported the association between sodium intake and renal function,[19–21,14] and four studies (n = 1,787) reported the association between sodium intake and proteinuria[19–21,24] in patients with CKD at baseline (Table 2).

Retrospective cohort studies. One study (n = 57) reported that high sodium intake (>4.6 g/day) was associated with a greater decline in creatinine clearance and a greater increase in proteinuria compared with low sodium intake (<2.3 g/day) over a mean follow-up of 3 years. Patients with moderate sodium intake (2.3–4.6 g/day) were excluded.[19]

Prospective cohort studies. One study (n = 500) reported that high sodium intake (>4.6 g/day) was associated with the highest risk of ESKD and a greater increase in urinary PCR compared with moderate sodium intake (2.3–4.6 g/day) and low sodium intake (<2.3 g/day) over a mean follow-up of 26.2 months. There was no significant difference between moderate and low sodium intake for risk of ESKD.[21] A second study (n = 53), which did not include a group with low sodium intake (overall mean intake 2.8 ± 0.7 g/day), reported that higher sodium intake was associated with an increased rate of decline in renal function and increased proteinuria over a 1-year follow-up.[20] A third study (n = 1,177) reported that the lowest third of sodium intake (mean 3.4 g/day, in the moderate range of intake) was associated with the lowest risk of doubling of serum creatinine or ESKD and ESKD alone, in ARB-treated subjects only, and the greatest reduction in 24-hour ACR over 30 months of follow-up.[24]

Clinical trials. No eligible studies were identified.

Studies of populations without CKD

Three studies (n = 6,342) reported the association between sodium intake and renal function,[22,23,25] and two studies (n = 3,535) reported the association between sodium intake and proteinuria[22,25] in patients without CKD at baseline (Table 3).

Retrospective cohort studies. No eligible studies were identified.

Prospective cohort studies. One study (n = 3,348) reported that moderate intake (median 2.4 g/day, range 2.3–4.9 g/day) was associated with an increased risk of decline in GFR, but no change in proteinuria, compared with low intake (median 1.7 g/day, range 1.1–1.7 g/day).[22] A second study (n = 2,807) reported that low sodium intake (<2.3 g/day) was associated with the highest cumulative incidence of ESKD and did not report on proteinuria.[23]

Clinical trials. A crossover trial (n = 187) that included patients with mild hypertension who were randomized to low sodium intake (2.5 g/day) or moderate sodium intake (3.8 g/day for 6 weeks each) reported lower serum creatinine (82.3 ± 14.7 μmol/L vs. 83.8 ± 15.0 μmol/L; $P = 0.013$) but higher UAE (median 10.2 mg/24 hours vs. 0.9 mg/24 hours; $P < 0.001$) and ACR (median 0.81 mg/mmol vs. 0.66 mg/mmol; $P < 0.001$) following randomization to moderate or low intake at 6 weeks after follow-up for each regimen.[25]

DISCUSSION

In patients with established CKD, we report consistent associations between high sodium intake (>4.6 g/day) and a decline in both creatinine-based measures of renal function (GFR) and an increase in proteinuria. However, there was no convincing evidence that low intake (<2.3 g/day) was more renoprotective than moderate intake (2.3–4.6 g/day), which is consistent with the findings of the Institute of Medicine.[16] In patients without CKD, findings were more inconsistent, with two prospective cohort studies reporting opposing directions of association between sodium intake and renal function[22,23] and one short-term crossover clinical trial reporting different short-term effects of low sodium intake on creatinine and proteinuria compared with moderate intake.[25]

Current guidelines recommend that patients with CKD consume <2.3 g/day or <1.5 g/day of sodium (Figure 1). Hypothetical benefits to low sodium intake include a reduction in the rate of decline in renal function and prevention of CV events, as patients with CKD are at increased CV risk.[26] Evidence included in our review supports the contention that high sodium intake (>4.6 g/day) is an important risk factor for decline in renal function in patients with CKD,[19–21,24] although the evidence base is limited, as we identified only four studies (n = 1,787) that evaluated this association. None of these studies reported more adverse renal outcomes with moderate compared with low intake, meaning that we did not find observational evidence to support the <2.3 g/day recommended threshold.

No trials in patients with established CKD were identified. In patients without established CKD, a short-term crossover trial reported that low sodium intake compared with moderate intake was associated with an increase in creatinine but reduction in measures of proteinuria.[25] This finding raises the possibility that sodium intake may have different effects on GFR and proteinuria, which needs to be further determined in longer term studies. A major finding of our review was the absence of randomized controlled trials in a population defined by established CKD that evaluate the effect of low sodium intake (recommended by current guidelines) compared with moderate intake on renal outcomes. In recognition of the uncertainty, there are two ongoing clinical trials comparing low sodium intake with moderate/usual intake in patients with CKD.[27,28]

A previous systematic review reported no evidence of a detrimental effect from reduced sodium intake and a link between sodium exposure and kidney tissue injury. The review also suggested dietary sodium restriction, without a specific guideline on the level of restriction, in patients with CKD.[13] Our study, which shows consistent evidence of increased risk with high intake (>4.6 g/day), but no evidence of a difference in risk between low (<2.3 g/day) and moderate intakes (2.3–4.6 g/day), differs from that paper in a number of ways. First, most of the studies (six of seven) included in our review were published subsequent to that 2006 review.[20–25] Second, by excluding small studies and by

Table 2. Characteristics and findings of studies of patients with chronic kidney disease

Author, year	Association	Summary of findings
Measures of renal function		
Retrospective cohort studies		
Cianciaruso *et al*. 1998[19]	Positive[a]	Unadjusted analyses reported a greater decline in creatinine clearance in the high sodium group (>4.6 g/day, μ5.3 g/day) compared with the low sodium group (<2.3 g/day, μ1.9 g/day).
Effect size: Mean decline in creatinine clearance 0.51 ± 0.09 ml/min in the high sodium group compared with 0.25 ± 0.07 ml/min in the low sodium group ($P < 0.05$).		
Prospective cohort studies		
Amaha *et al*. 2010[20]	Positive[a]	Unadjusted analyses reported a higher rate of decline in renal function with increasing sodium (2–5 g/day).
Effect size: Correlation between the rate of renal function decline (dl/mg/month) and dietary salt intake, $r = -0.287$ ($P = 0.037$).		
Vegter *et al*. 2011[21]	Positive[a]	Multivariable analyses reported an increase in risk of ESKD per 2.3 g/day of sodium; unadjusted analyses reported increased risk of ESKD with high sodium vs. low and moderate sodium but no difference between low and moderate sodium.
Effect size: HR for progression to ESKD (i) per 2.3 g/day, HR 1.61 (1.15–2.24); (ii) high sodium (>5.8 g/day) vs. low (<2.9 g/day), HR 3.3 (1.7–6.4); (iii) high sodium vs. moderate (2.9–5.8 g/day), HR 2.4 (1.4–4.1); (iv) moderate sodium vs. low, HR 1.4 (0.8–2.4).		
Lambers Heerspink *et al*. 2012[24]	Positive[a]	Unadjusted analyses reported the lowest risk of doubling of creatinine or ESKD in the lowest third of intake (μ3.5 g)
Effect size: HR for doubling of creatinine or ESKD in the lowest third (μ3.5 g/day) vs. the highest third (μ4.8 g/day), HR 0.75 (0.53–1.05).		
Clinical trials: No eligible clinical trials were identified.		
Measures of proteinuria		
Retrospective cohort studies		
Cianciaruso *et al*. 1998[19]	Positive[b]	Unadjusted analyses reported a progression in proteinuria with high sodium (>4.6 g/day, μ5.3 g/day) but reduction with low sodium (<2.3 g/day, μ1.9 g/day).
Effect size: Proteinuria increased with high sodium (1.5 ± 0.2 g/day to 2.4 ± 0.4 g/day; $P < 0.01$) and decreased with low sodium (2.9 ± 0.3 g/day to 1.9 ± 0.3 g/day; $P<0.005$).		
Prospective cohort studies		
Amaha *et al*. 2010[20]	Positive[b]	Unadjusted analyses reported a linear association between urinary protein excretion and sodium intake.
Effect size: Correlation between urinary protein excretion (g/day) and dietary salt intake (g/day), $r = 0.528$ ($P < 0.0001$).		
Vegter *et al*. 2011[21]	Positive[b]	Unadjusted analyses reported a linear association between increasing urine PCR and increasing sodium excretion.
Effect size: Urine PCR decreased from baseline by 31% with low sodium (<2.9 g/day; $P < 0.001$), 25% with medium sodium (2.9–5.8 g/day; $P<0.001$), and 20% with high sodium (>5.8 g/day; $P = 0.036$). There was a significant trend to less proteinuria reduction with increasing intake ($P = 0.012$).		
Lambers Heerspink *et al*. 2012[24]	Positive[b]	Unadjusted analyses reported the greatest decline in 24-hour UACR in the lowest third of sodium intake (μ3.5 g)
Effect size: Decline in 24-hour UACR was 44 mg/g in the lowest third of sodium intake (μ3.5 ± 1.8g), 16 mg/g in the middle third (μ4.1 ± 1.9 g), and 21 mg/g in the highest third (μ4.8 ± 2.1 g).		
Clinical trials: No eligible clinical trials were identified.		

Abbreviations: ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HR, hazard ratio (95% confidence interval); OR, odds ratio (95% confidence interval); μ, mean; PCR, protein to creatinine ratio; UACR, urine albumin to creatinine ratio.

[a]Positive association defined as lower measure of renal function with higher sodium intake.

[b]Positive association defined as higher measure of proteinuria with higher sodium intake.

Table 3. Characteristics and findings of studies of patients without chronic kidney disease

Author, year	Association	Summary of findings
Measures of renal function		
Retrospective cohort studies: No eligible retrospective cohort studies were identified.		
Prospective cohort studies		
Lin *et al.* 2010[22]	Positive[a]	Multivariable analyses reported a linear association between risk of GFR decline and increasing sodium.
Effect size: Odds for ≥30% decline in GFR over 10 years for high sodium (median, 2.4 g/day (2.3–4.9 g/day)) vs. low sodium (median, 1.7g/day (1.1–1.7 g/day)) was OR 1.53 (1.11–2.09).		
Thomas *et al.* 2011[23]	Inverse[b]	Multivariable analyses reported a linear association between decreased incidence of ESKD and sodium intake.
Effect size: Highest sodium intake associated with lowest incidence of ESKD ($P < 0.001$).		
Clinical trials		
He *et al.* 2009[25]	Inverse[b]	Unadjusted analyses reported lower serum creatinine with sodium supplementation (3.8 g/day) than placebo (2.5 g/day).
Effect size: Serum creatinine while on sodium supplementation group was 82.3 ± 14.7 μmol/l compared with 83.8 ± 15.0 μmol/l while on placebo ($P = 0.013$).		
Measures of proteinuria		
Retrospective cohort studies: No eligible retrospective cohort studies were identified.		
Prospective cohort studies		
Lin *et al.* 2010[22]	None	Multivariable analyses reported no association between proteinuria and sodium intake (high vs. low quartile).
Effect size: Odds for the onset of microalbuminuria over 10 years comparing upper to lower quartile was OR 0.94 (0.63–1.41).		
Clinical trials		
He *et al.* 2009[25]	Positive[c]	Unadjusted analyses reported higher UAE and ACR with sodium supplementation (3.8 g/day) than placebo (2.5 g/day).
Effect Size: Median 24hr UAE was 10.2mg (IQR 6.8–18.9mg) while on sodium supplementation (3.8 g/day) and 9.1mg (IQR 6.6–14.0mg) while on placebo (2.5g/day) and an 11% reduction in UAE on switching from sodium supplementation to placebo ($P < 0.001$).		

Abbreviations: ACR, albumin to creatinine ratio; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; IQ, interquartile range; μ, mean; OR, odds ratio (95% confidence interval); PCR, protein to creatinine ratio; UAE, urinary albumin excretion.

[a]Positive association defined as lower measure of renal function with higher sodium intake.

[b]Inverse association defined as higher measure of renal function with higher sodium intake.

[c]Positive association defined as higher measure of proteinuria with higher sodium intake.

confining our review to cohort studies and clinical trials that evaluated the independent association between sodium intake and renal outcomes, our eligibility criteria were stricter. We excluded small studies, as they are more likely to provide spurious results. We included a crossover clinical trial with a total follow-up that met the minimum criteria.[25] Third, we included only studies with a follow-up of at least 3 months to determine the effect of sodium intake on longer-term change in renal outcomes. More than half of the studies included in the previous review included intervention periods of <1 month or were of cross-sectional design. If we excluded studies with <1 year follow-up, no clinical trial would have been eligible for inclusion in this review and the overall results would not have changed significantly.

In general populations, most prospective cohort studies report an association between high sodium intake and hypertension,[29,30] and randomized controlled trials have found that low sodium intake reduces blood pressure compared with moderate or high intake.[4,5,31] Such evidence has been interpreted as representing a compelling case for sodium restriction in patients with CKD, especially in those with hypertension. However, this interpretation assumes that all interventions that lower blood pressure will translate into a reduced rate of renal function decline, an assumption that has been challenged by studies published in the last 10 years. We know, for example, that there are between-class differences in antihypertensive therapies on the rate of disease progression for a given blood pressure reduction.[32] In particular, medications that inhibit the renin–angiotensin–aldosterone system (RAAS) appear to have renoprotective effects independent of blood pressure lowering.[33] Of note, low sodium intake (<3 g/day) has been associated with activation of the RAAS, and increased RAAS activity is associated with a higher incidence of glomerular fibrosis and increased intraglomerular pressure.[34] Therefore, low sodium intake appears to have competing renal effects, that is, both a reduction in blood pressure, which is expected to be renoprotective, and an increase in RAAS activity, which is expected to have adverse renal effects.

In addition, salt sensitivity is reported to be more prevalent in patients with CKD due to a reduced capability to excrete sodium, meaning that a given sodium load may additionally increase blood pressure in patients with CKD who may also lose

the nocturnal dip in blood pressure.[35] However, salt sensitivity was not defined, measured, or reported in any of the included studies. Four studies suggested a trend toward increased blood pressure with increasing sodium intake[21–23,25] and two studies adjusted for blood pressure in their analyses,[21,22] one of which was performed in a population with CKD.[21] Additional studies are needed to investigate this further.

Regarding prevention of CV events, recent evidence suggests that the association between sodium intake and CV events may be J-shaped in a secondary prevention population, with the lowest CV risk associated with moderate sodium intake.[14] It is unclear if the presence of CKD modifies this association, although a retrospective cohort study of patients with ESKD, which was not included in our review as it did not meet eligibility criteria, reported an increased all-cause and CV mortality with low sodium intake.[15] The kidney is important in the control of salt and water homeostasis, and patients with CKD may be particularly vulnerable to the effects of extremes of sodium intake. It is plausible, if not likely, that patients with CKD have sodium intake requirements that are different from those of patients without CKD, mandating stand-alone studies in this important population.

Multiple methods were used to estimate sodium intake in the studies included in this review. The criterion standard for estimating sodium intake was seven or more 24-hour urine collections conducted over several months.[36] Twenty-four–hour urine collections were completed in most studies (six of seven),[19–21,23–25] and only one study performed a single collection.[23] Single measurements of sodium intake are less reliable and susceptible to regression dilution bias due to interindividual day-to-day variations in intake. Even with stable day-to-day intake, there are rhythmic changes in sodium excretion and retention that are independent of blood pressure, body water, and sodium intake, and this may affect the reliability of 24-hour urine collection, which is a problem for individual-level measurement of sodium intake.[37] Measurement bias may influence absolute estimates of sodium intake and affect the strength of association between sodium intake and renal outcomes. Similarly, the FFQs used in one study[22] may be less accurate and may also be prone to recall bias and, therefore, are also not optimal. Restriction of our analysis to studies that used 24-hour urinary measures did not alter our conclusions but further reduced the already modest number of studies.

The main strength of this review was the standardized, guideline-adherent approach to study identification and data summarization. The main limitation of our review was the small number of studies identified and the small sample sizes included. We identified only one eligible clinical trial; no trial included a population that was defined by established CKD. Two clinical trials of patients with congestive heart failure who were managed with fluid restriction and high-dose diuretics, with high serum creatinine measurements, were considered ineligible, as sodium intake was assessed using a food diary and physician interview (not a quantified assessment).[38,39] In addition, the patients were not considered to be typical of the general population with CKD, despite increased serum creatinine measurements, as all had heart failure and received high-dose diuretics. Both trials reported adverse renal outcomes with low sodium intake (1.8 g/day); however, these patients may be particularly sensitive to the effects of dietary sodium intake and are not representative of the general population with CKD. We also identified two other similar trials, but they were subsequently excluded after the recent retraction of a metaanalysis of sodium trials in patients with heart failure.[40] Moreover, due to the heterogeneity in study design, population, outcome measure, and method of measuring sodium intake, we were unable to metaanalyze data. Another challenge in performing our review was the varying methods that were used to measure renal function. A combination of these factors likely contributed to the inconsistency in our findings.

In summary, our review identified a major deficit in the evidence base to support current guidelines on sodium intake in patients with CKD. While there is reasonable evidence to support an association between high sodium intake and adverse renal outcomes, there is no convincing evidence that low sodium intake is associated with better renal outcomes than moderate intake in patients with and without established CKD. Low-sodium diets are difficult for patients, especially renal patients who have other dietary considerations, and have important knock-on implications for other dietary factors. Until further research prospectively compares low vs. moderate levels of sodium intake in populations with CKD, ideally in RCTs, it would be prudent to recommend moderate levels of salt intake rather than low or very low intakes.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflict of interest to disclose. The results presented in this article have not been published previously in whole or part, except in abstract format.

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