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Original Article

Association between sodium intakes with the risk of chronic kidney disease: evidence from a meta-analysis

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Abstract: *Objective*: Inconsistent results regarding the association between sodium intake and the risk of chronic kidney disease (CKD) have been reported. Thus, we conducted a meta-analysis to summarize the evidence from epidemiological studies of sodium with the risk of CKD. *Methods*: Pertinent studies were identified by searching of PubMed and Web of Science. The random effect model was used to combine the results. Meta-regression and subgroups analyses were used to explore potential sources of between-study heterogeneity. Publication bias was estimated using Egger's regression asymmetry test. *Results*: Finally, 9 articles involving 5638 CKD cases were included in this meta-analysis. Pooled results suggested that highest sodium intake level versus lowest level was significantly associated with the risk of CKD [summary relative risk (RR) = 1.088, 95% CI = 1.009-1.193, I^2 = 78.1%], especially among Europe [summary RR = 1.097, 95% CI = 1.009-1.205], but not in the America. The association was also found in the prospective studies [summary RR = 1.096, 95% CI = 1.007-1.192], but not in the cross-sectional studies. No evidence of significant publication bias was found. *Conclusions*: Higher sodium intake might increase the risk of CKD.

Keywords: Sodium, chronic kidney disease, meta-analysis

Introduction

Chronic Kidney Disease (CKD) is an epidemic and a worldwide public health problem. The increasing incidence and prevalence can be attributed to changing demographics of the general population coupled with earlier detection of CKD. However, increases in the prevalence of obesity, diabetes [1-3] and hypertension [4, 5], known traditional cardiovascular risk factors, accounts for the majority of increase in the prevalence of CKD. The presence of kidney disease is associated with higher morbidity and mortality and increased health care utilization. Control of blood pressure, strict glycemic control and blocking of the renin angiotensin aldosterone axis are some of the proven strategies in preventing and slowing the progression of CKD [6-9]. However, in most cases, even with adoption of these strategies, the incidence and prevalence of CKD continues to rise. Thus the strategy of adopting traditional risk factor modifications alone is not sufficient. This emphasizes the need for different therapeutic targets, such as dietary sodium intake, should be advocated for the primary prevention of CKD.

It has been hypothesized that greater intake of sodium may be associated with an elevated risk of CKD [10]. Up to date, a number of epidemiologic studies have been published to explore the relationship between sodium intake and CKD risk. However, the results are not consistent. Therefore, we conducted a meta-analysis to (1) first assess the CKD risk for the highest vs. lowest categories of sodium intake; (2) assess the heterogeneity among studies and publication bias.

Methods

Search strategy

A computerized literature search was conducted in PubMed and Web of Knowledge, through December 31, 2014, by two independent investigators. We searched the relevant studies with

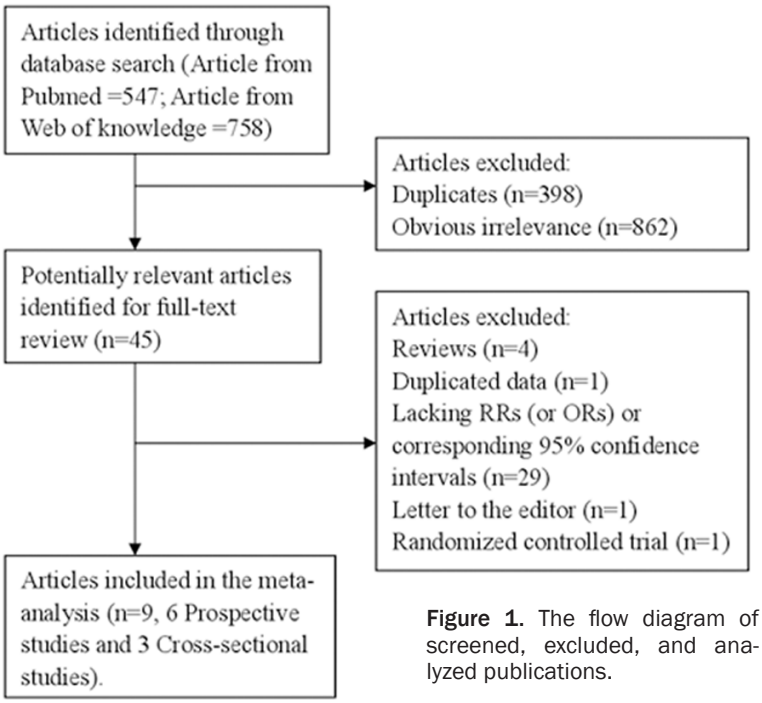

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

the following text word and/or Medical Subject Heading terms: 'sodium' or 'salt' or 'dietary' combined with 'chronic kidney disease' or 'glomerular filtration rate (GFR)' or 'serum creatinine' or 'creatinine clearance' or 'proteinuria' without restrictions. Moreover, we reviewed the reference lists from retrieved articles to search for further relevant studies. Disagreements between the two investigators were resolved by consensus with a third reviewer.

Inclusion criteria

Each identified study was independently reviewed by two investigators to determine whether an individual study was eligible for inclusion in this meta-analysis. The inclusion criteria are as follows: (1) using a prospective design or case-control design or cross-sectional design; (2) the exposure of interest was sodium; (3) the outcome of interest was CKD; (4) multivariate-adjusted relative risk (RR) with 95% confidence interval (CI) was provided. Accordingly, the following exclusion criteria were also used: (1) reviews and (2) repeated or overlapped publications. CKD defined as estimated GFR <60 mL/minute/1.73 m^2 or estimated GFR ≥60 ml/min/1.73 m^2 with albuminuria. Measures of sodium intake included 24 hour urine, food frequency questionnaire, and dietary recall or timed urine samples.

Data extraction

The following data were collected from all studies independently by two investigators: the first author's last name, publication year, country where the study was performed, the design type (case-control study, cohort study, cross-sectional study), measures of sodium intake, duration of follow-up for prospective studies, highest category of sodium intake, sample size and number of cases, variables adjusted for in the analysis, RR (OR) estimates with corresponding 95% CI for sodium, respectively. For studies that reported results from various covariate analyses, we abstracted the estimates based on the model that included the most potential confounders. If there was disagreement between the two investigators about eligibility of the article, it was resolved by consensus with a third reviewer.

Statistical analysis

The pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RR with 95% CI for sodium intake and CKD risk. A random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [11]. The I^2 of Higgins & Thompson [12] were used to assess heterogeneity. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively [13]. Meta-regression and subgroup analysis were conducted to explore potential sources of heterogeneity [14]. Publication bias was estimated using Egger's regression asymmetry test [15]. A study of influence analysis [16] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the

Table 1. Characteristics of studies on sodium intake and chronic kidney disease risk

Study, year	Country	Study design	Duration of follow-up	Defined of CKD	Participants (No. of cases)	Age Mean (SD)	Measures of sodium intake	Highest category of sodium intake	RR (95%CI)	Quality score
Crews et al. 2014	United States	Cross-sectional	NA	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	2058 (1189)	48.2 (9.5)	24 hour food intake information	Sodium >1143 mg/1,000 kcal	1.37 (0.70-2.70)	5
Fan et al. 2014	United States	Prospective	6 years	estimated by GFR and level of proteinuria	617 (159)	51.7 (12.4)	24 hour urine sodium	24-h urine sodium was ≥3 g/day	0.97 (0.82-1.16)	7
Humalda et al. 2014	Netherlands	Prospective	8.5 years	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	241 (75)	50.7 (10.5)	24 hour urine sodium	24-h urinary Na/creatinine: ≥153 mmol/g	1.37 (0.96-1.96)	8
Koo et al. 2014	Korea	Cross-sectional	NA	CKD was defined as 24-hr urine protein 150 mg/day (proteinuria) or more and/or estimated GFR < 60 mL/min/1.73 m^2	1363 (400)	48.8 (15.0)	24 hour urine sodium	24 UNa ≥90 mEq/day	2.44 (1.25-4.77)	6
McQuarrie et al. 2014	United Kingdom	Prospective	8.5 years	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	488 (154)	51.1 (16.8)	24 hour urine sodium	24-h urinary Na/creatinine: ≥160 mmol/g	1.03 (0.99-1.06)	7
Nerbass et al. 2014	Brazil	Prospective	4 years	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	1733 (1039)	72.9 (9.0)	24 hour urine sodium	Na intake >100 mmol/day	1.35 (1.02-1.79)	8
Ortega et al. 2014	Spain	Prospective	11 months	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	120 (72)	68 (15)	24 hour urine sodium	24 UNa ≥138 mEq/l	1.04 (1.01-1.09)	7
Sharma et al. 2013	United States	Cross-sectional	NA	CKD defined as estimated GFR <60 mL/minute/1.73 m^2 or estimated GFR ≥60 ml/min/1.73 m^2 with albuminuria.	31507 (2333)	45.0 (0.4)	24 hour recall and evaluated in quartiles	Sodium Intake >4267 mg/day	0.79 (0.66-0.96)	6
Thomas et al. 2011	Finland	Prospective	10 years	estimated GFR and log albumin excretion rate	2807 (217)	39 (12)	24 hour urine sodium	Na intake >104.6 mmol/day	2.15 (1.49-3.11)	8

Abbreviations: CI=confidence interval; RR=relative risk; GFR= glomerular filtration rate; Na= not available.

Table 2. Summary risk estimates of the association between sodium intake and chronic kidney disease risk

Subgroups	No. (cases)	No. studies	Risk estimate (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
All studies	5638	9	1.088 (1.009-1.193)	78.1	0.000
Study design					
Prospective	1716	6	1.096 (1.007-1.192)	76.7	0.001
Cross-sectional	3922	3	1.309 (0.642-2.667)	83.1	0.003
Geographic locations					
America	4720	4	1.025 (0.800-1.314)	72.4	0.012
Europe	518	4	1.097 (1.009-1.205)	82.9	0.001
Measures of sodium intake					
24 hour food intake	2116	7	1.123 (1.024-1.231)	78.3	0.000
Others	3522	2	0.942 (0.570-1.558)	57.9	0.123

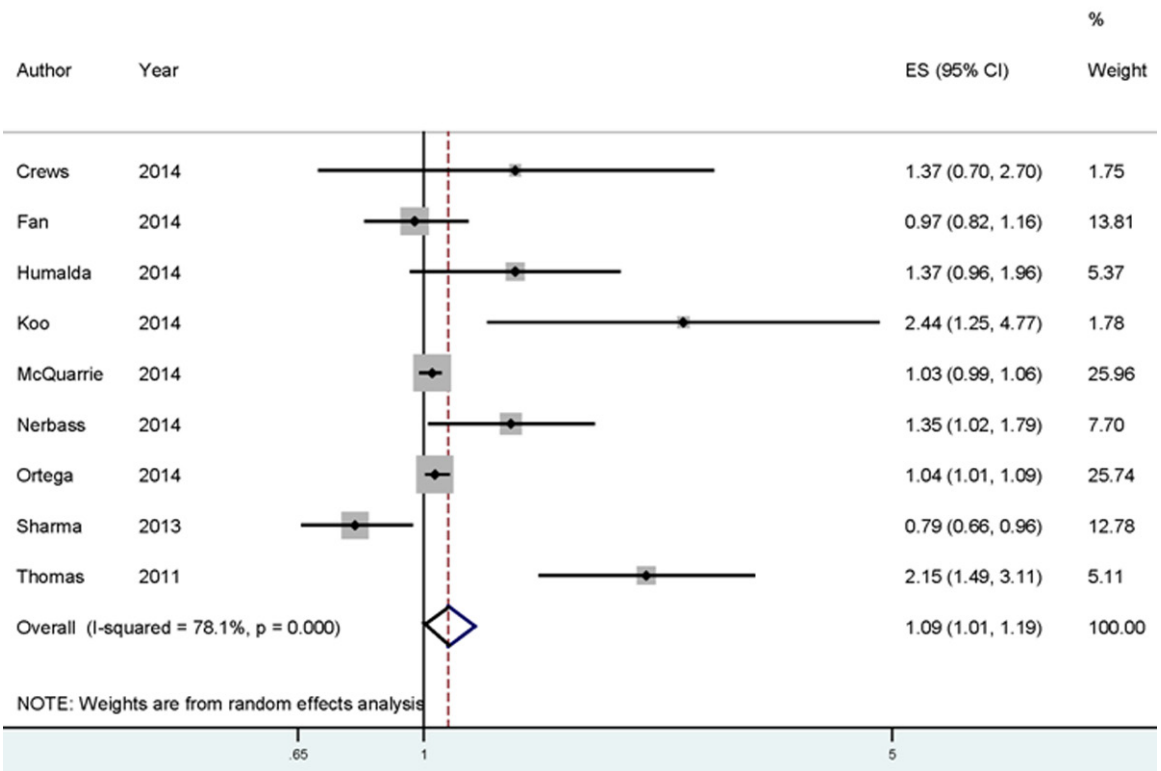

Figure 2. The forest plot between sodium intake and CKD risk. White diamond denotes the pooled RR. Black squares indicate the RR in each study, with square sizes inversely proportional to the standard error of the RR. Horizontal lines represent 95% CI.

95% CI of the combined analysis. All the statistical analyses were performed with STATA version 10.0 (Stata Corporation, College Station, TX, USA). Two-tailed P≤0.05 was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 547 articles from Pubmed and 758 from the Web of Knowledge, and 45 articles were reviewed in full after reviewing the title/abstract. Thirty-six of these 45 articles were subsequently excluded from the meta-analysis for various reasons. Hence, 9 articles [17-25] (6 prospective studies, 3 cross-sectional study) involving 5638 CKD cases were included in this meta-analysis. The detailed steps of our literature search are shown in **Figure 1**. The characteristics of these studies are presented in **Table 1**. Three studies come from United States, 1 from Netherlands, 1 from United Kingdom, 1 from Brazil, 1 from Spain, 1 from Finland and 1 from Korea.

High versus low analyses.

Data from 9 studies including 5638 CKD cases were used in this meta-analysis. Four studies reported that sodium intake could increase the risk of CKD, while no significant association was reported in 4 studies. However, 1 study reported that sodium intake is a protective factor for CKD. Pooled results suggested that highest sodium intake level versus lowest level was significantly associated with the risk of CKD [summary RR = 1.088, 95% CI = 1.009-1.193, I^2 = 78.1%] (**Figure 2**).

In stratified analysis by study design, the association was also found in the prospective studies [summary RR = 1.096, 95% CI = 1.007-1.192], but not in the cross-sectional studies. In subgroup analyses for geographic locations, highest sodium intake level versus lowest level was significantly associated with the risk of CKD in Europe [summary RR = 1.097, 95% CI = 1.009-1.205], but not in the America. The details results are summarized in **Table 2**.

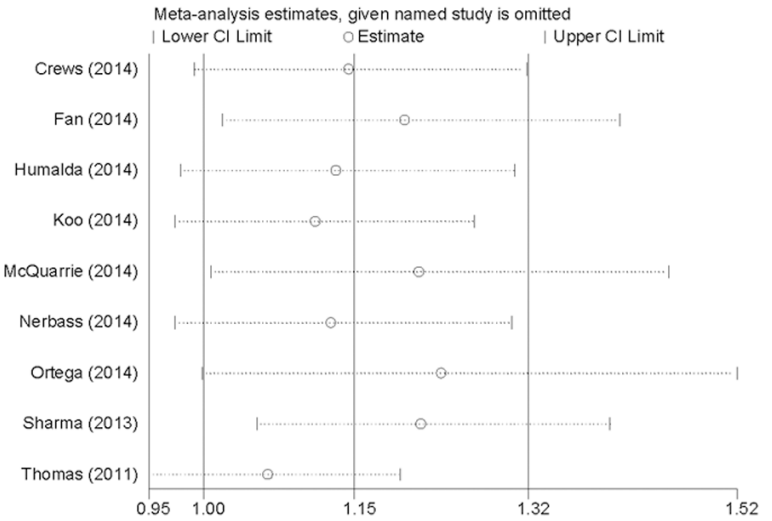

Figure 3. Analysis of influence of individual study on the pooled estimate in sodium intake and CKD risk. Open circle, the pooled OR, given named study is omitted. Horizontal lines represent the 95% CIs.

Sources of heterogeneity and meta-regression

We found evidence of heterogeneity (I^2 = 78.1%, $P_{heterogeneity}$ = 0.000) in the pooled results. In order to explore the high between-study heterogeneity in several analysis, univariate meta-regression with the covariates of publication year, location where the study was conducted, study design (cross-sectional or prospective), measures of sodium intake and number of cases was performed. No covariate had a significant impact on between-study heterogeneity in the above-mentioned analysis.

Influence analysis and publication bias

No individual study had excessive influence on the association of sodium intake and CKD risk for influence analysis (**Figure 3**). No evidence of significant publication bias between sodium intake and CKD risk was found by Egger's test (P = 0.164).

Discussion

Finding from this meta-analysis suggested that the higher intake of sodium could increase the risk of CKD. The associations were also found in subgroups of Europe and prospective studies for sodium intake and CKD risk.

Experimental data suggests that sodium intake may be an important risk factor for CKD. Sodium may be nephrotoxic directly by increasing oxidative stress and indirectly by increasing blood pressure and attenuating the effects of renin-angiotensin-aldosterone system (RAAS) blockers. Several studies have shown increased oxidative stress in the renal cortex and vascular beds in response to increased dietary salt intake [26-28]. These same experimental models also showed a benefit of sodium restriction on progression of CKD. High sodium consumption has also been shown to result in decreased renal blood flow and increased glomerular pressure, GFR and filtration fraction [29]. Major consequences of these changes in renal hemodynamics are an increase in urinary protein excretion and progression of CKD [30]. In our study, we found that a high sodium diet was associated with increased the risk of CKD. These findings were expected as we hypothesized that a high sodium diet would be associated with a higher risk of CKD.

Between-study heterogeneity is common in meta-analysis because of diversity in design quality, population stratification, characteristics of the sample, publication year, variation of the covariates, etc. [31]. For sodium intake with the risk of CKD, high between-study heterogeneity was found in the pooled results. Thus, meta-regression we used to explore the causes of heterogeneity for covariates. However, no covariate had significant impact on between-study heterogeneity for the above mentioned covariates. Considering the pooled meta-analysis was fraught with the problem of heterogeneity, subgroup analyses by the type of study design, location where the study and measures of sodium intake was conducted were performed to explore the source of heterogeneity. However, the between-study heterogeneity persisted in some subgroups, suggesting the presence of other unknown confounding factors. CKD is a complex etiology and pathophysiology disease generated by the combined effects of genes and environment factors. Thus, other genetic and environment variables, as well as their possible interaction, may well be potential contributors to the heterogeneity observed.

As a meta-analysis of published studies, our findings showed some advantages. The study includes large number of cases and participants, allowing a much greater possibility of reaching reasonable conclusions between sodium intake and CKD risk. However, there were some limitations in this meta-analysis. First, as a meta-analysis of observational studies, we cannot rule out that individual studies may have failed to control for potential confounders, which may introduce bias in an unpredictable direction. Second, measurement errors are important in the assessment of dietary intake, which can lead to overestimation of the range of intake and underestimation of the magnitude of the relationship between dietary intake and CKD risk [32]. Third, one study using 24 hour recall and evaluated in quartiles for measures of sodium intake. Also, this study found an inverse association between sodium intake and CKD risk. Overstated association may be expected from the 24 hour recall studies because of recall or selection bias. Seven of 9 studies measured the sodium intake using 24 hour urine sodium. And the association was significant between sodium intake and CKD risk for measures of 24 hour urine sodium. Fourth, for the subgroups of geographic locations, the association was only significant in the Europe, but not in the America. And only one study come from Korea. Due to this limitation, the results are applicable to the Europe, but cannot be extended to populations elsewhere. More studies originating in other countries are required to investigate the association between sodium intake and CKD risk. Fifth, although we combined the results with highest category of sodium intake versus lowest category, we did not do a dose-response analysis because of the limited data in the reported articles. Finally, between-study heterogeneity was found in some analysis in this meta-analysis, but the between-study heterogeneity was not successfully explained by the subgroup analysis and meta-regression. However, other genetic and environment variables, as well as their possible interaction may be potential contributors to this disease-effect unconformity.

In summary, results from this meta-analysis suggested that the higher intake of sodium might increase the risk of CKD, especially in Europe.

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Disclosure of conflict of interest

None.

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