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Original Article

Sodium intake and chronic kidney disease risk: a meta-analysis of prospective studies

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Abstract: Objective: Epidemiological studies evaluating the association of sodium intake and the risk of chronic kidney disease (CKD) have produced inconsistent results. We therefore conducted a meta-analysis to summarize the evidence from prospective cohort studies to assess the association between them. Methods: We searched the PubMed and Web of knowledge to identify all studies that assessed the association between sodium intake and CKD risk through July 1, 2015. Meta-regression analysis was used to explore potential sources of between-study heterogeneity. Publication bias was estimated using Egger's regression asymmetry test. Results: Six related prospective cohort articles met our selection criteria and contained a total of 1716 CKD cases and 6006 participants. Our meta-analysis results revealed that dietary sodium intake could increase the CKD risk [Summary relative risk (RR) = 1.10, 95% CI = 1.01-1.19, $P<0.05$]. The association was significant in the European populations [Summary RR = 1.10, 95% CI = 1.01-1.21], but not in the American populations and other populations. When we conducted the subgroup analysis by follow-up duration (<10 years and ≥10 years), significant association was found only in the ≥10 years follow-up, but not in the <10 years follow-up. *Conclusions*: In conclusions, findings from this study indicated that dietary sodium intake is associated with increased risk of CKD.

Keywords: Sodium intake, chronic kidney disease, meta-analysis

Introduction

Chronic Kidney Disease (CKD) defined as estimated glomerular filtration rate (GFR) <60 mL/minute/1.73 m^2 or estimated GFR ≥60 ml/min/1.73 m^2 with albuminuria. Experimental data suggests that sodium intake may be an important risk factor for CKD. Measures of sodium intake included 24 hour urine, food frequency questionnaire, and dietary recall or timed urine samples. 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 [1-3]. 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 [4]. Major consequences of these changes in renal hemodynamics are an increase in urinary protein excretion and progression of CKD [5]. Up to now, many original studies were conducted to assess the associations between dietary sodium intake and CKD risk; whether higher dietary sodium intake could increase the CKD risk was still unclear. Hence, we conducted a meta-analysis to clarify these conflicting results and assess the association between them.

Materials and methods

Literature search and study selection

The databases of PubMed and Web of knowledge were searched electronically (last updated search in July 1, 2015) for published studies reporting a relationships between sodium

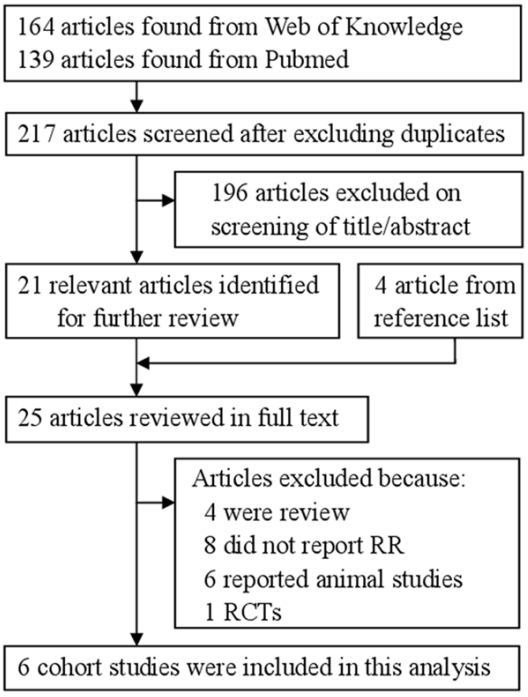

Figure 1. Flowchart of meta-analysis for exclusion/inclusion of studies.

intake and CKD risk. The following keywords and search terms were used: 'sodium' OR 'salt' AND 'chronic kidney disease' OR 'glomerular filtration rate (GFR)' AND 'cohort' OR 'prospective' with written in the English language. Eligible texts were retrieved from the above data. In addition, we reviewed references of relevant articles.

Eligible studies should meet the following criteria: (1) human study, (2) prospective cohort study, (3) the exposure was sodium intake, (4) the outcomes was CKD, (5) multivariate-adjusted relative risk (RR) with 95% confidence interval (CI) was provided (or data available to calculate them).

Exclusion criteria included: (1) animal study, (2) repeated or overlapped publications, (3) review.

Data extraction

We used a standardized data extraction form to collect the data. The following information was extracted from each of the included studies: the first author's last name, publication year, country where the study was performed, measures of sodium intake, duration of follow-up for prospective studies, sample size and number of cases, variables adjusted for in the analysis, RR (OR) estimates with corresponding 95% confidence intervals (CI) for sodium intake and statistical adjustment for the main confounding or mediating factors. Two independent authors conducted all of the above procedures, and any disagreements were resolved by discussion.

Quality assessment

The quality of studies was examined and controlled in accordance with checklists of Preferred Reporting Items for Systematic reviews and Meta-Analyses for randomized trials (PRISMA) [6]. To determine the quality score of included studies, two reviewers independently performed the quality assessment by using the Newcastle-Ottawa Scale, which is a validated scale for non-randomized studies in meta-analyses [7]. The Newcastle-Ottawa Scale is a nine-point scale that allocates points. We assigned scores of 0-3, 4-6, and 7-9 for low, moderate, and high quality of studies, respectively.

Statistical analysis

The estimated RR and the corresponding 95% CI were used to assess the association between sodium intake and the risk of CKD. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [8]. Homogeneity testing was performed with the Q and I^2 statistics [9], and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively [10]. Meta-regression analysis was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [11]. Additionally, the subgroup analyses were conducted to identify the between-study heterogeneity between the sodium intake and CKD risk. The Egger regression asymmetry test [12] was used to assess the evidence of the publication bias. Sensitivity analysis was used to investigate the influence of a single study on the overall effect estimate by omitting one study at a time during repeated analyses [13]. In the present study, *P*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata 10.0 (Stata Corp, College Station, Texas, USA).

Table 1. Characteristics of the included studies

Study, year	Country	Study design	Defined of CKD	Cases	Age	Measures of sodium intake	Quality score	Highest vs. lowest RR (95% CI)
Thomas et al. 2011	Finland	Prospective	Estimated GFR and log albumin excretion rate	217	39±12	24 hour urine sodium	8	2.15 (1.49-3.11)
Fan et al. 2014	United States	Prospective	Estimated by GFR and level of proteinuria	159	51.7±12.4	24 hour urine sodium	7	0.97 (0.82-1.16)
Humalda et al. 2014	Netherlands	Prospective	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	75	50.7±10.5	24 hour urine sodium	8	1.37 (0.96-1.96)
McQuarrie et al. 2014	United Kingdom	Prospective	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	154	51.1±16.8	24 hour urine sodium	8	1.03 (0.99-1.06)
Nerbass et al. 2014	Brazil	Prospective	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	1039	72.9±9.0	24 hour urine sodium	7	1.35 (1.02-1.79)
Ortega et al. 2014	Spain	Prospective	CKD defined as estimated GFR <60 mL/minute/1.73 m^2	72	68±15	24 hour urine sodium	7	1.04 (1.01-1.09)

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

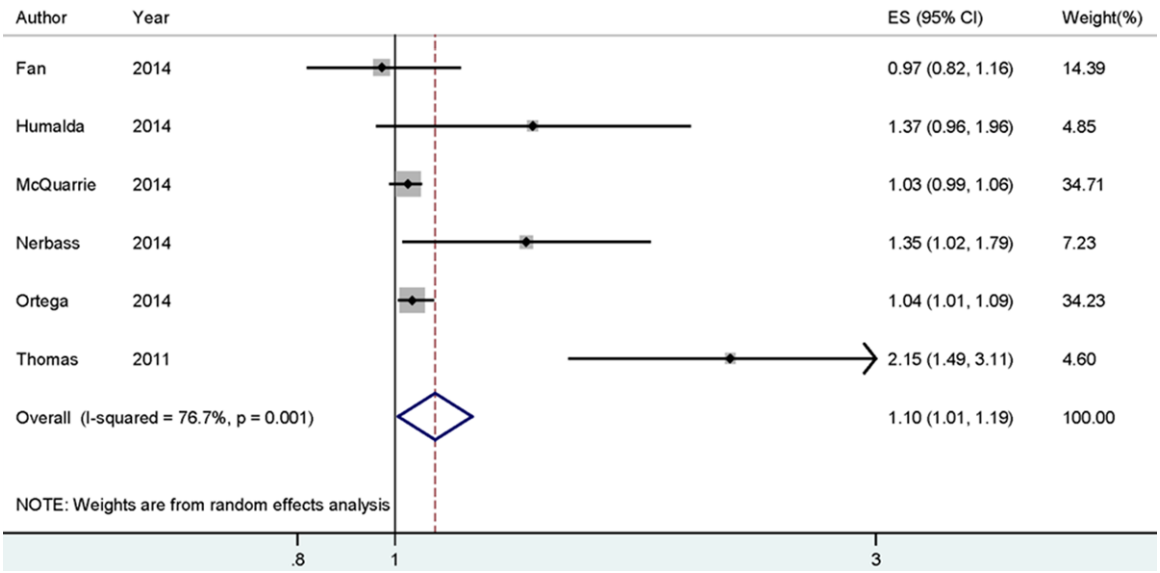

Figure 2. The forest plot of the relationship between dietary sodium intake and CKD risk.

Table 2. The subgroup analyses of the association between sodium intake and CKD risk

Subgroups	No. (cases)	No. studies	Risk estimate (95% CI)	Heterogeneity test I^2 (%)	Heterogeneity test *P*-value
All studies	1716	6	1.10 (1.01-1.19)	76.7	0.001
Follow-up duration					
<10 years	1427	4	1.08 (0.95-1.23)	53.2	0.093
≥10 years	289	2	1.46 (1.11-1.97)	93.2	0.000
Geographic locations					
America	1198	2	1.12 (0.81-1.54)	74.0	0.050
Europe	518	4	1.10 (1.01-1.21)	82.9	0.001

Results

Literature search and study characteristics

Figure 1 presents the study inclusion process. A total of 139 articles from PubMed and 164 articles from Web of knowledge were initially retrieved. From the retrieved studies, 86 studies were excluded because of duplicates. There are 196 articles were further excluded after review the title or abstract. Four articles are searched from reference list. Furthermore, 4 review articles, 8 articles lacking of RR and 95% CI, 6 reported animal studies, 1RCTs were further excluded. At the end, 6 prospective cohort articles [14-19] comprising 1716 CKD cases and 6006 participants were included in our meta-analysis. **Table 1** presents the general data and characteristics for the included studies.

Meta-analysis of findings

Data from 6 prospective articles were analyzed in a random-effects model to assess the relationship between dietary sodium intake and CKD risk. The combined results suggested that higher sodium intake could increase the risk of CKD (Summary RR = 1.10, 95% CI = 1.01-1.19, $P<0.05$). Significant heterogeneity was found among these studies (I^2 = 76.7%, P = 0.001). **Figure 2** presents the results of this analysis.

In subgroup analyses for geographic locations, the association of dietary sodium intake and CKD risk was found only in European populations [summary RR = 1.10, 95% CI = 1.01-1.21], but not in the American populations [summary RR = 1.12, 95% CI = 0.81-1.54]. When we conducted the subgroup analysis by follow-up duration (<10 years and ≥10 years), significant association was found only in the ≥10 years follow-up, but not in the <10 years follow-up. **Table 2** presents the results of the subgroup analyses.

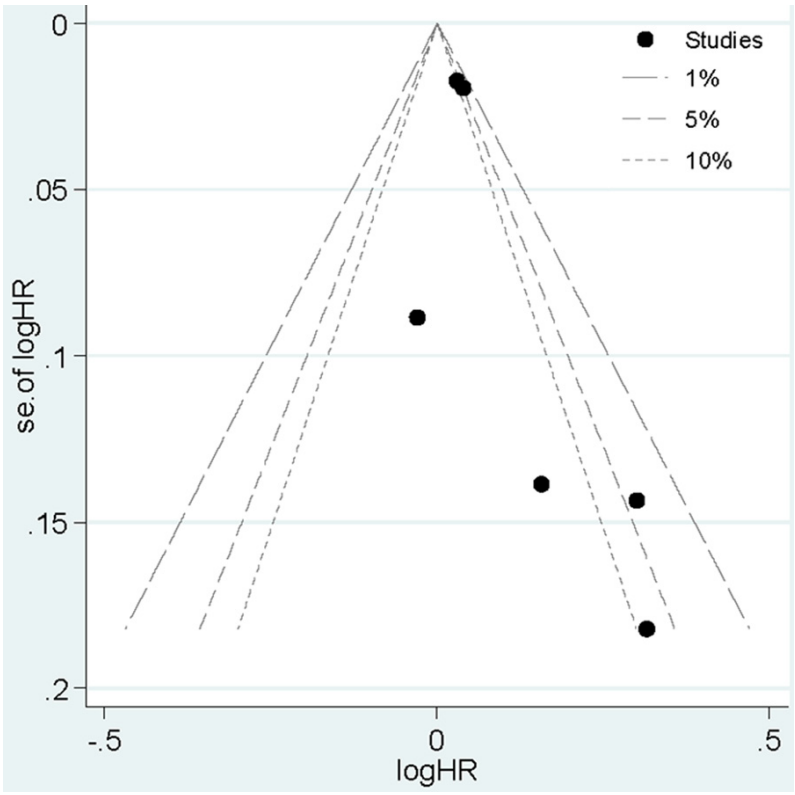

Figure 3. Funnel plot for the analysis of publication bias between dietary sodium intake and CKD risk.

Sensitivity analysis showed that when one of the included studies was omitted, the combined RR was not changed significantly.

According to the Egger's regression asymmetry test and funnel plot (**Figure 3**), no evidence of publication bias (P = 0.195) was found.

Discussion

Our study illustrated that higher dietary sodium intake may increase the CKD risk. The association was also significant European populations, but not in the American populations and other populations. Significant association was also found in the duration follow-up of ≥10 years, but not in the <10 years follow-up.

However, our pooled results showed strong heterogeneity among the studies. The paper had reported that between-study heterogeneity is common in the meta-analysis [20]. We then used meta-regression with the covariates of publication years, follow-up duration and geographic locations to explore the causes of heterogeneity. No significant finds was found in the above analysis. Furthermore, subgroup analyses with follow-up duration and geographic locations were conducted to explore the source of the between-study heterogeneity. However, evidence of heterogeneity was found in both the subgroup analyses.

A major strength of this study was the large number of participants included from prospective studies, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. And prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case-control studies. Second, no publication bias was found, indicating that our results are stable. However, there were some limitations should be concerned in this meta-analysis. First, some original studies did not adjust for potentially relevant confounders. Any of these factors could lead to bias in the results. Second, four studies were conducted from Europe and 2 studies from America. And the association was only significant in the European populations, but not in the American populations. Due to the limitation results, more studies originating in America countries and other countries are required to investigate the association between sodium intake and CKD risk. Third, 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 [21]. Fourth, the association was only significant in the duration follow-up of ≥10 years, but not in the <10 years. Therefore, further studies should have a longer follow-up duration in the future article. Finally, the statistical heterogeneity that appeared in our pooled analysis and subgroup analyses would also have a small effect on the reliability of our results.

In conclusions, findings from this study indicated that dietary sodium intake is associated with increased risk of CKD.

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Disclosure of conflict of interest

None.

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