Clinical Nutrition 38 (2019) 1092–1100

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Dietary sodium, sodium-to-potassium ratio, and risk of stroke: A systematic review and nonlinear dose-response meta-analysis

Ahmad Jayedi [a], Farnoosh Ghomashi [b], Mahdieh Sadat Zargar [c], Sakineh Shab-Bidar [b, *]

[a] Food (salt) Safety Research Center, Semnan University of Medical Sciences, Semnan, Iran
[b] Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
[c] Nursing Care Research Center, Semnan University of Medical Sciences, Semnan, Iran

ARTICLE INFO

Article history:
Received 4 January 2018
Accepted 24 May 2018

Keywords:
Cardiovascular disease
Dietary sodium
Hypertension
Meta-analysis
Stroke

SUMMARY

Background & aims: The association of high sodium intake with risk of stroke has been accepted. But considering the proposed J/U-shaped association between sodium intake and risk of all-cause mortality, the shape of the dose-response relationship has not been determined yet. This study aimed to test the dose-response association of dietary sodium and sodium-to-potassium ratio with risk of stroke in adults aged 18 years or older.

Methods: We performed a systematic search using PubMed and Scopus, from database inception up to October 2017. Prospective and retrospective observational studies reporting risk estimates of stroke for three or more quantitative categories of dietary sodium or sodium-to-potassium ratio were included. Studies that reported results as continuous were also included. Two independent authors extracted the information and assessed the quality of included studies. Pooled relative risk (RR) was calculated using a random-effects model. Publication bias was tested. Sensitivity and subgroup analyses were done.

Results: Of initial 20,412 studies identified, 14 prospective cohort studies, one case-cohort study, and one case-control study (total n = 261,732) with 10,150 cases of stroke were included. The Pooled RRs of stroke were 1.06 (95%CI: 1.02, 1.10; $I^2 = 60\%$, n = 14 studies) for a 1 gr/d increment in dietary sodium intake, and 1.22 (95%CI: 1.04, 1.41; $I^2 = 60\%$, n = 5 studies) for a one-unit increment in dietary sodium-to-potassium ratio (mmol/mmol). The risk of stroke increased linearly with increasing dietary sodium intake, and also along with the increase in dietary sodium-to-potassium ratio. No evidence of a J/U-shaped association was found in the analyses of total stroke, stroke incidence, and stroke mortality. High sodium intake was associated with a somewhat worse prognosis among Asian countries as compared to westerns.

Conclusion: Higher sodium intake and higher dietary sodium-to-potassium ratio were associated with a higher risk of stroke. Reducing dietary sodium-to-potassium ratio can be considered as a supplementary approach in parallel with the decrease in sodium intake in order to decrease stroke risk. The interpretation of the results is limited by observational nature of studies examined.

1. Introduction

Prevalence of stroke and stroke-associated deaths and disabilities has been increased substantially in recent decades [1]. The global prevalence of hemorrhagic and ischemic stroke among younger adults aged 20–64 years increased almost 2-fold between 1990 and 2013 [1]. Hypertension (HTN), has been proposed to be the main risk factor of stroke [2]; in a way that about 54%–62% of all cases of stroke are attributable to HTN [3,4]. It has been proposed that higher sodium consumption, both directly by increasing blood pressure levels; and indirectly through several mechanism such as oxidative stress, endothelial dysfunction, and left ventricular hypertrophy; is associated with a greater risk of stroke [3]. Furthermore, previous meta-analyses have indicated that the salt-stroke association is stronger than other cardiovascular diseases (CVDs) [5,6], possibly due to the greater association between high blood

Abbreviations: CVD, Cardiovascular diseases; HTN, Hypertension; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; FFQ, Food frequency questionnaire.

* Corresponding author. Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, P. O. Box 14155/6117, Tehran, Iran. Fax: +98 21 88955979.
E-mail address: s_shabbidar@tums.ac.ir (S. Shab-Bidar).

https://doi.org/10.1016/j.clnu.2018.05.017
0261-5614/

pressure and stroke risk as compared to other CVDs [7]. It is projected that reducing sodium intake by 1200 mg/day decreases the annual number of new cases of stroke by 32,000 to 66,000 in the US [8].

Several meta-analyses of randomized controlled trials have indicated that reducing sodium intake can diminish blood pressure levels [9,10], and therefore, it has been concluded that reducing sodium intake can decrease the risk of CVDs. However, some indications of a nonlinear association were found in observational studies, in which both low and high sodium intake were associated with higher risk of all-cause mortality and CVD events, in a J-shaped or U-shaped fashion [11,12]. A recent meta-analysis of 25 cohort studies suggested that, as compared to low sodium intake (<2.7 g/day), a moderate sodium intake (2.7–5 g/day) was associated with a 9% lower risk of all-cause mortality, and a 10% lower risk of CVD events [5]. Regarding stroke risk, they did not observe such a decreased risk, but shape of the dose-response relationship was not determined. Considering the fact that major current guidelines recommend different cut points for reducing sodium intake: <1500 mg/d by American Heart Association [3], <2000 mg/d by WHO [13], and <2300 mg/d by the U.S. Department of Agriculture [14]; the possible changes in the risk within intake of <2700 mg/day have not been determined yet. Thus, it seems that the nonlinear dose-response meta-analysis may be an appropriate approach to establish the association of different levels of sodium intake with risk of stroke.

In contrast to sodium, higher potassium intake, mainly through its lowering effects on blood pressure [15], is associated with a lower risk of stroke [16]. Thus, it seems that higher sodium and lower potassium intakes may have synergistic effects on the risk of CVDs. In accordance with this hypothesis, some investigations have suggested that, in comparison to higher sodium intake, higher dietary sodium-to-potassium ratio may be more strongly associated with risk of CVD mortality [17,18]. To our knowledge, no systematic review has assessed the association of dietary sodium-to-potassium ratio and risk of any cardiovascular disease. Therefore, the objective of this study was to test the dose-response association of dietary sodium and sodium-to-potassium ratio with risk of stroke in adults aged 18 years or older, with the use of prospective and retrospective observational studies.

2. Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to write the present systematic review and report the results [19]. We also followed the 12-item PRISMA extension to write the Abstract [20].

2.1. Search strategy

A systematic literature search was conducted with the use of PubMed and Scopus, with studies published from 1966 up to October, 2017. The search included combinations of keywords relevant to sodium intake, stroke, and study design (Supplementary Table 1). The reference lists of all related articles and reviews were also manually searched. The search was restricted to only articles published in English.

2.2. Eligibility and study selection

Two independent authors (AJ, MSZ) reviewed the titles and abstracts of all studies identified. Prospective and retrospective cohort, nested case control, case-cohort, case-control, or prospective reports within interventional studies were obtained and included in this review if they:*1*) conducted among adults aged 18 years or older; *2*) measured and reported baseline sodium intake or dietary sodium-to-potassium ratio as exposure and in at least three quantitative categories; *3*) reported the outcome of interest as stroke incidence or mortality or total stroke at follow-up; *4*) reported adjusted risk estimates (relative risk (RR) or hazard ratio or odds ratio) and the corresponding 95% confidence intervals (CIs) of stroke for each category of dietary sodium or sodium-to-potassium ratio; and *5*) reported the number of cases and participants/personyears or non-cases in each category of dietary sodium or sodium-to-potassium ratio. Studies that reported results per unit increment in dietary sodium or sodium-to-potassium ratio were also included. We excluded: *1*) cross-sectional studies to avoid reverse causation bias; *2*) studies with only two categories of exposures; *3*) studies conducted among patients with specific diseases such as kidney disease; and *4*) studies with un-adjusted risk estimates.

2.3. Data extraction and assessment for study quality

Two independent authors (AJ, FG) reviewed the full texts of selected eligible studies, and extracted the following information: first author's name, publication year, study design, study name, location, follow-up duration, mean age and/or age range, gender, dietary assessment method, covariates adjusted in the multivariate analysis, exposure levels, number of participants/cases and the reported risk estimates and the 95% CIs of stroke across categories of dietary sodium or sodium-to-potassium ratio. The models with the most covariates adjustment were selected and included in the meta-analysis. The same two authors independently assessed the quality of included studies using a 9-point Newcastle-Ottawa Scale [21]. There were no quality criterias for study inclusion in the present meta-analysis. Any discrepancies were resolved through discussion under supervision a third author (SS-b).

2.4. Data synthesis and statistical analysis

The relative risk (RR) and 95% CI was considered the effect size of all studies. The reported hazard ratios or odds ratios in the primary studies were considered as equal as RR. We measured the linear dose-response relation using the generalized least squares trend estimation, according to the methods developed by Greenland and Longnecker [22,23]. The method needs distribution of cases and personyears or non-cases across categories of dietary sodium and sodium-to-potassium ratio, median value and adjusted RR with its 95% CI for each category of exposures. If the reference category was not the lowest one, we recalculated risk estimates assuming the lowest category as reference [24]. If in a given study number of personyears in each category has not been reported, we estimated distribution of personyears across categories according to method developed by Aune et al [25]. In the analysis of sodium-to-potassium ratio, one study categorized participants into four categories as follows: low sodium/high potassium (ref), low sodium/low potassium, high sodium/high potassium, and high sodium/low potassium (highest category) [26]; and we estimated the median points of dietary sodium-to-potassium ratio in each category according to the method described in Supplementary Table 2. In the NHEANES I study [27], sodium intake was categorized according to quartiles of sodium-to-energy ratio (mmol/7452 kJ), in which 7452 kJ was the average daily energy intake in the whole study population. However, because that daily energy intake differed significantly across quartiles of dietary sodium intake, we recalculated median of sodium intake in each category assuming the median of energy intake in that category as the average daily energy intake. If studies reported results separately for men and women or other subgroups, we combined the subgroup-specific

estimates using a fixed-effects model to generate an overall estimate so that each study was only represented once in the main analysis. To test the potential effect of each study on pooled effect size, influence analysis was done with one study removed at a time. Subgroup analyses were conducted on the basis of some of the study and participants characteristics. Between-study heterogeneity was explored using Cochrane's Q test of heterogeneity and I^2 statistic ($P < 0.05$) [28]. Publication bias was assessed using funnel plots asymmetry, and tested by Egger's asymmetry test [29] and Begg's test [30] ($P < 0.10$). The pooled RR and 95%CIs were calculated for a 1 mg/d increment in dietary sodium intake, and a one-unit increment in dietary sodium-to-potassium ratio (mmol/mmol). For studies that reported the results for a one mg/mg increment in dietary sodium-to-potassium ratio, we used the scaling factor of 0.59 to translate a 1 mg/mg increment risk estimate to a 1 mmol/mmol RR (1 mmol sodium = 23 mg, and 1 mmol potassium = 39 mg, and therefore, a 1 mmol/mmol sodium-to-potassium ratio = 0.59 mg/mg).

Potential nonlinear association was examined by modeling dietary sodium and sodium-to-potassium ratio levels using restricted cubic splines with three knots at fixed percentiles (10, 50 and 95%) of the distribution [31]. A P-value for nonlinearity of the meta-analysis was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. In the analysis of sodium-to-potassium ratio, for studies that reported the doses as mg/mg, we used the scaling factor of 1.69 to transform the doses to mmol/mmol. All analyses were conducted with Stata software, version 13 (Stata Corp, College Station, Texas, USA). A P value < 0.05 was considered statistically significant.

3. Results

The systematic search identified 25,277 articles. Of these, 4865 were duplicates and another 20,346 articles were not relevant on the basis of screening of the title and abstract. Of the remaining 66 articles, another 50 articles were eliminated by full-test assessing. Detailed reasons for study exclusion are provided in Fig. 1. Eventually, 16 studies with a total of 261,732 participants and 10,150 cases of stroke were included in the present meta-analysis [26,27,32–45]. Six studies were conducted in the US [27,32,33,35,36,45], four studies were from Europe [34,37,39,44], five were from Asia [26,38,40,42,43], and one study was a prospective evaluation within the two large international controlled trials [41]. Two studies included only men [36,37], and the rest included both sexes. One study was a case-control study [38], one had a case-cohort design [34], two studies were prospective evaluations within interventional studies [37,41], and the remainders were prospective cohort studies (median follow-up duration: 4.7–28 years). All of the studies were at high quality (≥7 scores). Eight studies used a food frequency questionnaire (FFQ) to assess dietary intakes [26,32,35,37,38,40,43,45], three studies used a single 24-h dietary recall [27,33,36], three studies measured urinary excretion [34,41,44], one study used 3-day weighing dietary records [42], and one study conducted dietary history interview [39]. Two different studies reported the results of the Northern Manhattan Study on dietary sodium and dietary sodium-to-potassium ratio, and were separately included in the relevant analyses [33,45]. Two studies reported age-adjusted risk estimates [36,42], and the remainders reported multivariate risk estimates, in which results were adjusted for much of the confounding variables including body mass index (n = 14 studies), physical activity (n = 11 studies), educational level (n = 8 studies), alcohol consumption (n = 10 studies), energy intake (n = 11 studies), blood pressure (n = 12 studies), and history of diabetes or CVDs (n = 12 studies). Fourteen studies were included in the analysis of sodium intake, and five studies were included in the analysis of dietary sodium-to-potassium ratio. The general characteristics of the studies are provided in Table 1 and the number of participants/cases and reported risk estimates of stroke across categories of dietary sodium and sodium-to-potassium ratio in each study are presented in Supplementary Tables 3 and 4, respectively.

3.1. Dietary sodium intake and risk of stroke

Fourteen studies (total n = 253,449) with 9877 cases of stroke were included in the analysis of sodium intake [26,27,32–41,43,44].

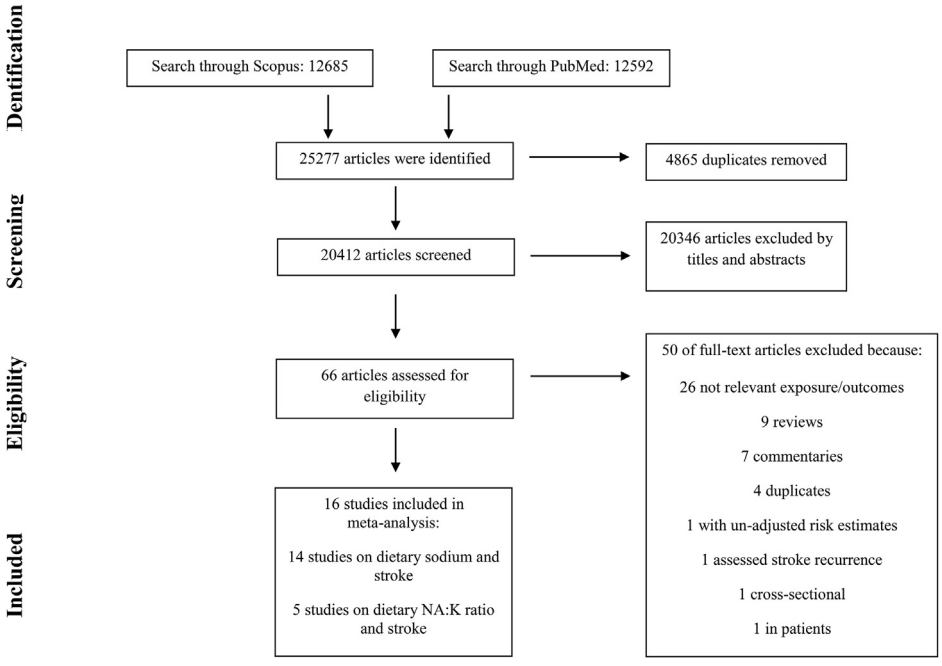

Fig. 1. Literature search and study selection process for inclusion in the meta-analysis of dietary sodium, sodium-to-potassium ratio and risk of stroke.

Table 1
General characteristics of included studies in meta-analysis of dietary sodium, sodium-to-potassium ratio and risk of stroke.

Author, year, study, country	Study design	Follow-up (years)	participants	Mean age/age range (year)	Sex	Cases	Sodium intake assessment	Study quality	Covariates
Umesawa [26], 2008 JACC, Japan	Prospective cohort	12.7	58,730	56	W/M	Stroke death: 986	FFQ	8	Age, BMI, smoking status, ethanol intake, history of HTN, history of DM, menopause, hormone replacement therapy, time spent on sports activity, walking time, educational status, perceived mental stress, and calcium intake.
He [27], 1999 NHANES I, US	Prospective cohort	19	9485	48	W/M	Stroke incidence: 680 Stroke mortality: 210	Single 24-hour dietary recall	9	Stratified by birth cohort, and adjusted for age, sex, race, SBP, serum cholesterol, BMI, history of DM, diuretics use, physical activity, level of education, alcohol use, cigarette smoking, and total energy intake.
Cohen [32], 2006 NHANES II, US	Prospective cohort	13.7	7154	48	W/M	Cerebrovascular disease death: 79	Single 24-hour dietary recall	8	Age, sex, race, smoking, alcohol use, SBP, anti-hypertensive treatment, BMI, educational level, physical activity, dietary potassium, DM, serum cholesterol, and energy intake.
Gardener [33], 2012 Northern Manhattan Study, US	Prospective cohort	10	2657	69	W/M	Stroke incidence: 235	FFQ	8	Age, sex, race/ethnicity, education, alcohol use, smoking, physical activity, total calories, total fat, saturated fat, carbohydrates, protein, DM, hypercholesterolemia, HTN, previous cardiac disease, and BMI.
Geleijnse [34], 2007 The Rotterdam Study, Netherland	Case-cohort	5.5	1448	69	W/M	Stroke incidence: 181	Single overnight urine sample	8	Age, sex, 24-h urinary creatinine excretion, BMI, smoking status, DM, use of diuretics, educational level, daily intake of total energy, alcohol, calcium, saturated fat and 24-h urinary potassium excretion.
Judd [35], 2013 REGARDS, US	Prospective cohort	4.9	21,374	≥45	W/M	Stroke incidence: 363	FFQ	7	Age, race, sex, energy, BMI, HTN, DM, history of heart disease, dyslipidemia, smoking, income, education, and bias in retrieving medical records.
Kagan [36], 1985 The Hawaiian study cohort, US	Prospective cohort	10	7895	54	M	Stroke incidence: 238	Single 24-hour dietary recall	7	Age
Larsson [37], 2008 ATBC Study, Finland	Prospective cohort	13.6	26,556	50–69	M	Cerebral infarctions incidence: 2702	FFQ	8	Age, supplementation, cigarettes, BMI, SBP, DBP, total cholesterol, HDL, DM, CHD, physical activity, and intake of alcohol and energy.
Liang [38], 2011 Guangdong case-control study, China	Case-control	–	464 controls	69	W/M	Ischemic stroke: 374	FFQ	7	Age, weekly intake of iron, sodium, potassium, calcium, and magnesium, weekly energy intake, sex, BMI, education level, physical activity, smoking status, alcohol drinking, and presence of HTN, hyperlipidemia, or DM.
Montonen [39], 2009 Finnish Mobile Clinic Health Examination Survey, Finland	Prospective cohort	28	3958	52	W/M	Cerebrovascular disease incidence: 659	Dietary history interview	7	Age, sex, energy intake, smoking, BMI, physical activity, geographic area, HTN, occupation, DM, use of post-menopausal hormones, serum cholesterol, and consumptions of butter, vegetables, fruits and berries.
Nagata [40], 2004 Takayama Study, Japan	Prospective cohort	7	29,079	55	W/M	Stroke death: 269	FFQ	8	Age, total energy, marital status, years of education, BMI, smoking status, alcohol intake, exercise, histories of HTN and DM, and intake of protein, potassium, and vitamin E.
O'Donnell [41], 2011 ONTARGET and TRANSCEND trials, Multinational	Prospective cohort	4.7	4729	67	W/M	Stroke incidence: 1282	24-h urinary sodium excretion	8	Age, sex, race/ethnicity, prior history of stroke or myocardial infarction, creatinine, BMI, HTN, DM, atrial fibrillation, smoking, LDL, HDL, treatment allocation, fruit and vegetable consumption, level of exercise, baseline BP and change in SBP from baseline to last follow-up, and urinary potassium.
Okayama [42], 2016 NIPPON DATA80, Japan	Prospective cohort	24	8283	49	W/M	Stroke death: 273	3-day weighing dietary record	7	Age
Takachi [42], 2010 JPHC, Japan	Prospective cohort	7.7	77,500	57	W/M	Stroke incidence: 1745	FFQ	8	Age, sex, BMI, smoking status, alcohol consumption, physical activity, and intakes of energy, potassium, and calcium.
Tuomilehto [44], 2001 North Karelia, Kuopio, and Turku-Liomaa study, Finland	Prospective cohort	1982/ 1987–1995	2420	46	W/M	Stroke incidence: 84	24-h urinary sodium excretion	8	Age, sex, study year, smoking, serum total and HDL cholesterol, SBP, and BMI.
Willey [45], 2017 Northern Manhattan Study, US	Prospective cohort	12	2570	69	W/M	Stroke incidence: 274	FFQ	8	Age, sex, high-school completion, race ethnicity, total calories, Mediterranean diet score, alcohol use, physical activity, smoking, eGFR, BMI, HTN, DM hypercholesterolemia, and sodium intake.

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; HDL, high density lipoprotein; HTN, hypertension; JACC, Japan Collaborative Cohort study; JPHC, Japan Public Health Center-based Prospective Study; M, men; NHANES, National Health and Nutrition Examination Survey; NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged; SBP, systolic blood pressure; ONTARGET, Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; W, women.

The pooled RR of stroke for a 1 gr/d increment in dietary sodium intake was 1.06 (95%CI: 1.02, 1.10), with high heterogeneity, $I^2 = 60.4\%$, $P_{heterogeneity} = 0.002$ (Fig. 2).

3.2. Sensitivity analysis, subgroup analysis and publication bias

In the sensitivity analysis, the pooled RR ranged from 1.04 (95% CI: 1.01, 1.06) with the exclusion of the Japan Collaborative Cohort Study [26], to 1.07 (95%CI: 1.02, 1.11) with the exclusion of the ONTARGET and TRANSCEND trials [41] (Supplementary Table 5), and the first study explained much of the heterogeneity, $I^2 = 34.5\%$, $P_{heterogeneity} = 0.11$. A subgroup analysis by study location showed a significant positive association only among Asian studies, but not among the US and European studies. A significant positive association persisted even after adjustment for baseline blood pressure, body mass index, smoking, physical activity, and intakes of alcohol, energy, and potassium. The subgroup analyses yielded geographical location, follow-up duration, number of cases, dietary assessment method, and adjustment for main confounders as the potential sources of the heterogeneity (Table 2).

The pooled RRs were 1.03 (95%CI: 1.01, 1.05; $I^2 = 22.1\%$, $P_{heterogeneity} = 0.23$; n = 11 studies), 1.15 (95%CI: 0.98, 1.31; $I^2 = 74.7\%$, $P_{heterogeneity} = 0.008$; n = 4 studies), and 1.14 (95%CI: 1.00, 1.27; $I^2 = 82.5\%$, $P_{heterogeneity} = 0.001$; n = 4 studies) for stroke incidence, stroke mortality, and ischemic stroke, respectively. In the analysis of stroke mortality, when the NHANES II study was excluded [32], the pooled RR altered to 1.20 (95%CI: 1.02, 1.38; $I^2 = 75.7\%$, $P_{heterogeneity} = 0.02$; n = 3 studies). No evidence of publication bias was found with Egger's test ($P = 0.11$) and Begg's test ($P = 0.27$), but the funnel plot showed some indications of asymmetry (Supplementary Fig. 1).

Ten studies reported sufficient information for inclusion in the nonlinear dose-response meta-analysis [26,27,33,36–41,43], and the result showed no evidence of departure from linearity in the main analysis (P for nonlinearity = 0.23, n = 10 studies) (Fig. 3). Nearly similar result with the main analysis was found in the analysis of stroke incidence (P for nonlinearity = 0.06, n = 8 studies) [27,33,36–39,41,43], whereas the analysis of stroke mortality showed a steeper increase in the risk with increasing sodium intake (P for nonlinearity = 0.95, n = 3 studies) [26,27,40]. The analysis of Asian studies demonstrated a steeper increase in the risk in comparison to western studies (Fig. 3).

3.3. Dietary sodium-to-potassium ratio and risk of stroke

Five studies with a total of 92,405 participants and 2077 cases of stroke were included in the analysis of dietary sodium-to-potassium ratio [26,34,35,42,45]. A one-unit increment in dietary sodium-to-potassium ratio (mmol/mmol) was associated with a 22% higher risk of stroke (Pooled RR: 1.22, 95%CI: 1.04, 1.41), with moderate-to-high evidence of heterogeneity, $I^2 = 60\%$, $P_{heterogeneity} = 0.04$ (Fig. 4). In the sensitivity analysis, the pooled RR ranged between 1.17 and 1.28 with the exclusion of each study in turn (Supplementary Table 6). The pooled RR of ischemic stroke for a one-unit increment in sodium-to-potassium ratio was 1.35 (95% CI: 1.14, 1.56; $I^2 = 0\%$, $P_{heterogeneity} = 0.53$; n = 3 studies).

Three studies were eligible for inclusion in the nonlinear dose-response meta-analysis [26,35,42], and meta-analysis showed that there was a linear association between dietary sodium-to-potassium ratio and risk of stroke (P for nonlinearity = 0.08) (Fig. 3).

4. Discussion

The present study provides new summarized evidence regarding the association of sodium intake and risk of stroke, and indicates that higher sodium consumption (by 6%), as well as higher dietary sodium-to-potassium ratio (by 22%) are associated with a higher risk of stroke. A nonlinear dose-response meta-analysis suggested that the risk of stroke increased linearly in the both analyses. No evidence of a U-shaped or J-shaped association was found in the analyses of total stroke, stroke incidence, and stroke mortality.

In the analysis of sodium intake, a subgroup analysis by region demonstrated a significant positive association only among Asian studies as compared to western studies, possibly due to the higher salt consumption, and higher rate of stroke mortality in Asian societies as compared to western countries [46]. Additionally, the number of participants was substantially higher in Asian subgroup than in western (173,668 *vs* 79,781), making it possible to show greater effect size. A subgroup analysis by assessment method

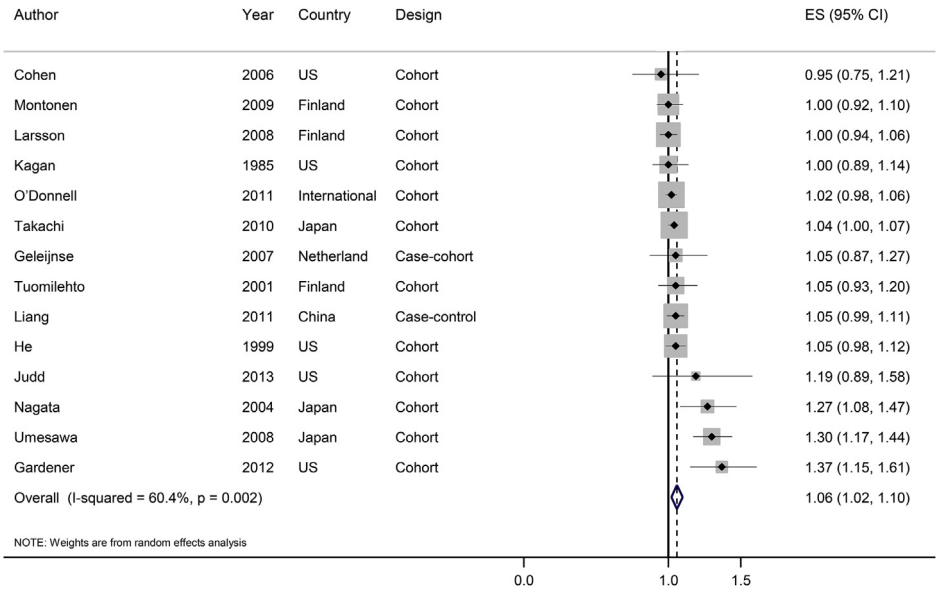

Fig. 2. Relative risk of stroke for a 1 gr/d increment in sodium intake.

Table 2
Relative risk of stroke for a 1 gr/d increment in sodium intake.

Comparison		n	Pooled RRs	I^2 (%), $P_{heterogeneity}$ [a]	$P_{between}$ [b]
All studies		14	1.06 (1.02–1.10)	62.7, 0.001	–
Sex					
Men		3	1.05 (0.91–1.19)	55.9, 0.10	–
Women		2	1.18 (1.00–1.36)	0.0, 0.50	
Region					
US		5	1.08 (0.97–1.19)	57.2, 0.05	0.18
Europe		4	1.01 (0.96–1.05)	0.0, 0.88	
Asia		4	1.13 (1.03–1.23)	83.3, <0.0001	
Follow-up duration					
< 13 years		10	1.09 (1.04–1.14)	69.2, 0.001	0.15
> 13 years		4	1.01 (0.97–1.05)	0.0, 0.66	
Number of cases					
< 500		9	1.07 (1.01–1.12)	45.3, 0.07	0.33
> 500		5	1.05 (0.99–1.12)	76.9, 0.002	
Assessment of intake					
Dietary assessment		11	1.07 (1.02–1.12)	68.3, <0.0001	0.30
Urinary excretion		3	1.02 (0.99–1.06)	0.0, 0.88	
Weight					
Nonoverweight		2	1.15 (0.85–1.45)	91.9, <0.0001	–
Overweight		2	1.17 (1.05–1.28)	0.0, 0.45	
Adjustments					
Smoking status	Yes	13	1.06 (1.02–1.10)	63.0, 0.001	0.52
	No	1	1.00 (0.89–1.14)	–	
Blood pressure or HTN	Yes	11	1.08 (1.02–1.13)	69.2, <0.0001	0.84
	No	3	1.04 (1.00–1.07)	0.0, 0.83	
Physical activity	Yes	10	1.07 (1.02–1.11)	71.6, <0.0001	0.93
	No	4	1.04 (0.96–1.12)	0.0, 0.77	
Body mass index	Yes	13	1.06 (1.02–1.10)	63.0, 0.001	0.52
	No	1	1.00 (0.89–1.14)	–	
Educational levels	Yes	8	1.14 (1.05–1.23)	80.8, 0.001	0.005
	No	6	1.02 (1.00–1.05)	0.0, 0.85	
Alcohol intake	Yes	10	1.08 (1.03–1.14)	69.2, 0.001	0.12
	No	4	1.02 (0.98–1.05)	0.0, 0.75	
Energy intake	Yes	10	1.05 (1.01–1.09)	47.8, 0.04	0.97
	No	4	1.09 (0.97–1.20)	80.8, 0.001	
Potassium intake	Yes	6	1.04 (1.01–1.07)	28.1, 0.22	0.64
	No	8	1.09 (1.01–1.16)	72.7, 0.001	

Abbreviations: HTN, hypertension; FFQ, food frequency questionnaire.
[a] *P*-heterogeneity within subgroups with the use of a random-effects model.
[b] *P*-heterogeneity between subgroups with the use of a fixed-effects model.

yielded a significant positive association only among studies used FFQ or dietary recall or record as compared to those studies measured urinary sodium excretion, despite the fact that, as compared to urinary excretion, dietary assessment methods tend to underestimate sodium intake [47]. The large-scale cohort studies generally use FFQ to assess sodium intake, and as a result, this inconsistent finding may partly be due to the substantial higher number of participants in the subgroup with dietary assessment method (244,852 *vs* 8,597, respectively).

A nonlinear dose-response meta-analysis demonstrated that there was no evidence of a nonlinear dose-response association between dietary sodium and sodium-to-potassium ratio with risk of stroke. As above mentioned, some investigations demonstrated a J/U-shaped association between sodium intake with risk of all-cause and CVD mortality and morbidity [5,11,12,48]. However, our outcome is limited to stroke. Thus, our conclusion regarding the absence of a J/U-shaped association cannot be generalized to other CVD events. In addition, we observed a marginally significant dose-dependent association in the analysis of sodium intake and stroke incidence (P for nonlinearity = 0.06). This finding is very similar with that of western studies, and this may be due to the fact that six out of eight studies included in the analysis of stroke incidence were from western countries. The analysis of western countries demonstrated that the risk of stroke did not change within intake of 0–5 gr/day, and then increased linearly, with risk increasing significantly at an intake of about 6 gr/day. The analysis of western countries indicated that change in dietary sodium intake within intake of 0–6 gr/day did not materially increase the risk of stroke, whereas the analysis of Asian studies indicated that even a small increase in dietary sodium intake is associated with a higher risk.

In the analysis of stroke mortality, the risk increased with an evidently steeper trend in comparison to stroke incidence, especially at low and moderate intakes (<5 gr/d). Generally, because of the fewer number of cases, the risk of stroke mortality is expected to be less than stroke incidence. [27], This inconsistent finding may be partially because that two of three studies included in the analysis of stroke mortality were conducted in Japan, a country with higher sodium intake and higher rate of stroke mortality as compared to western countries [26,46]. Additionally, included studies in the analysis of stroke mortality were large-scale prospective cohort studies. Thus, it is reasonable to show stronger effect size.

Reducing sodium consumption is expected to decrease the risk of CVD events. A recent meta-analysis of five randomised trials suggested a nonsignificant trend toward a lower CVD risk with decreasing sodium intake [49]. The national-based interventional policies in some countries also yielded successful results, in which reducing sodium content of foods in the national level resulted in a substantial decrement in population sodium intake, and simultaneously, a substantial decrement in the rate of CVD events [50,51]. However, due to the wide distribution of sodium in different foods, especially fast foods, food additives, seasonings, and condiments; and also due to the great correlation between sodium and energy intakes, it may be hard to comply efficiently with low-sodium diets, especially in long term [52]. Current sodium and potassium intakes among the US populations are estimated to be 2300–4500 mg/d and 2400–3200 mg/d, respectively [53], suggesting a possible dietary sodium-to-potassium ratio of more than one. A prospective evaluation within the third NHANES study indicated that higher dietary sodium-to-potassium ratio was associated with significant higher risk of all-cause and CVD mortality [18]. Thus, it seems that reducing dietary sodium-to-potassium ratio can be considered as a supplementary approach along with the decrease in dietary sodium intake. A recent meta-analysis of fifteen randomized controlled trials indicated that potassium supplementation could decrease blood pressure in both patients with and without HTN [54]. The authors also found a significant correlation between urinary sodium-to-potassium ratio and blood pressure level. Another recent meta-analysis of 16 cohort studies showed that high *vs* low potassium intake was associated with a 13% significant lower risk of stroke in the blood pressure-adjusted analysis [55], which suggested a possible blood pressure–independent effect of potassium intake on stroke risk. Dietary potassium may inhibit formation of free radicals [56], and has been shown to have protective effects against the development of vascular damage induced by salt loading, partially by suppression of the production of reactive oxygen species [57]. Another meta-analysis of 33 randomized controlled trials indicated that blood pressure-lowering effects of potassium supplementation were more evident among those with higher dietary sodium intakes [58]. It seems that higher potassium intake could mitigate unfavorable effects of high sodium consumption, and has a possible mediatory effect on salt-CVD association [59]. However, well-designed controlled trials are needed to test the possible effects of reducing dietary sodium-to-potassium ratio on the blood pressure levels, and possibly on the risk of stroke and other CVD events.

4.1. Strength and limitations

The present study was the first try to show the nonlinear dose-response association of dietary sodium intake and risk of stroke. We

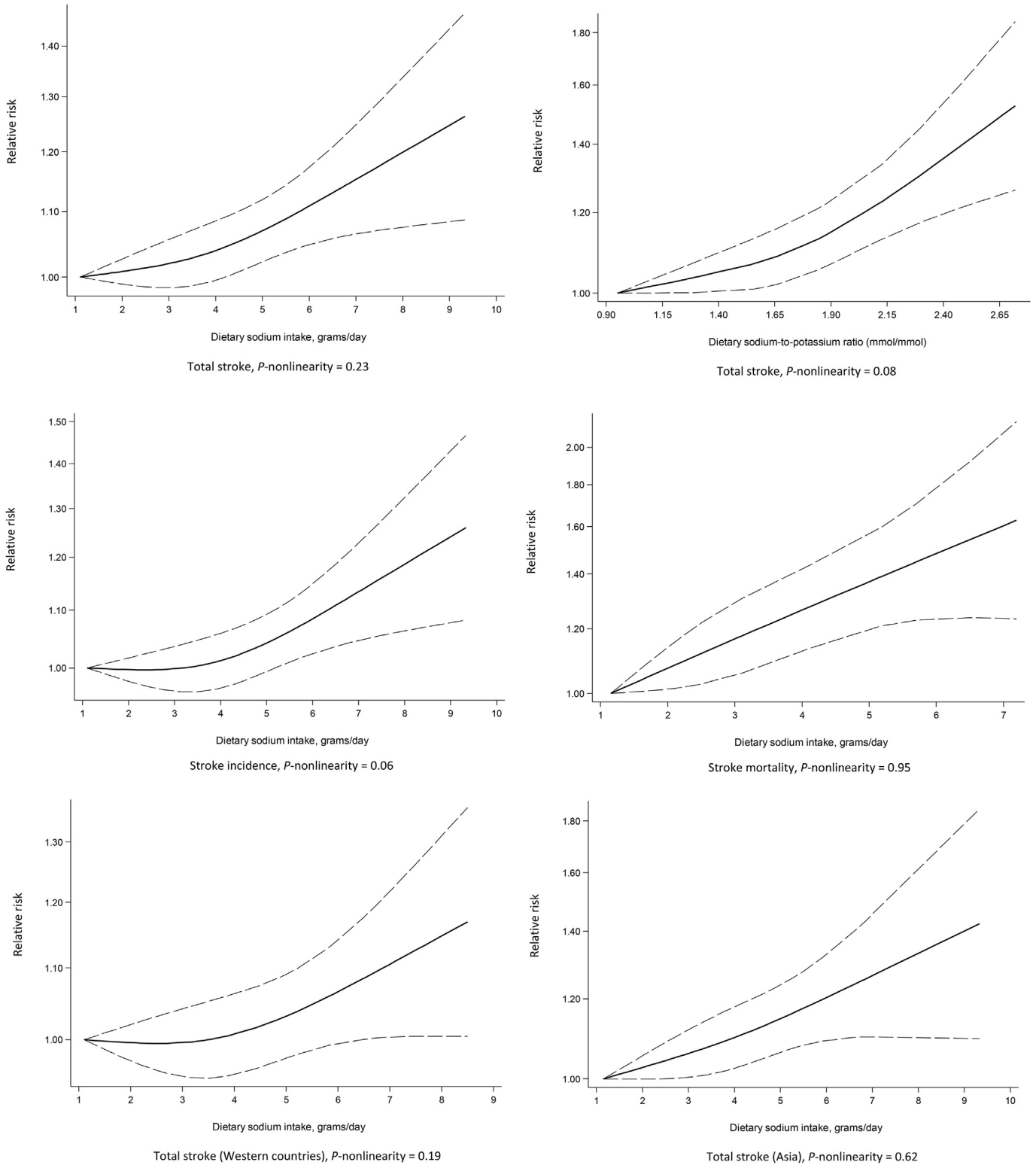

Fig. 3. Dose-response association of sodium intake and dietary sodium-to-potassium ratio with risk of stroke.

appropriately could show the association of different levels of dietary sodium intake with risk of stroke, with several subgroup and sensitivity analyses. Furthermore, for the first time, we could show the shape of the dose-response association of dietary sodium-to-potassium ratio with risk of stroke.

Our work also was accompanied by several important limitations. Our main limitation may be the observational nature of studies examined, making it hard to conclude a causal relationship from the results. Some important inherent limitations of observational studies assessing salt-CVD association are as follows: not randomly classification of participants across categories of sodium intake, the possible cofounding effects of other factors associated with sodium consumption, not equal distribution of comorbidities across categories of sodium intake, and poor measurement of

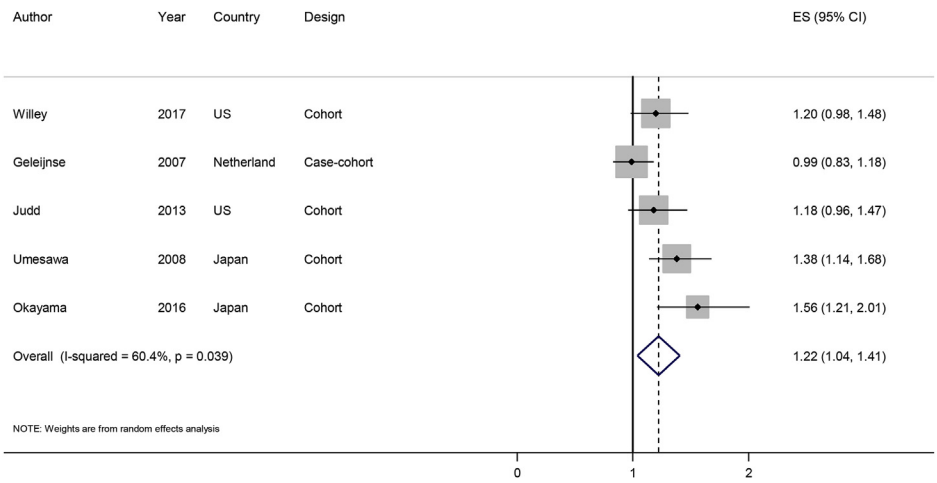

Fig. 4. Relative risk of stroke for a one-unit increment in dietary sodium-to-potassium ratio (mmol/mmol).

dietary sodium and other effective variables in some studies [60,61]. Second, the primary studies did not address within-individual variations in sodium intake over the follow-up period, as well as day-to-day variance in 24-hour urinary sodium excretion [61], which might result in measurement error. Third, our results were accompanied by high heterogeneity in the analysis of dietary sodium. However, subgroup analyses suggested region, follow-up duration, number of cases, dietary assessment method, and adjustment for main confounders as the potential sources of the heterogeneity. Additionally, ten of fourteen studies reported effect size above 1, and only one study reported effect size below 1. Thus, the observed heterogeneity may be largely attributable to differences in the effect size of the studies examined, rather than inconsistencies in the direction of the association. Fourth, although there was no evidence of publication bias with Egger's test and Begg's test, but the funnel plot seemed to be asymmetric. Thus, our results may have been affected by publication bias. Finally, in the analysis of sodium-to-potassium ratio, the weights of the two studies implemented in Japan are by far bigger compared with other studies. Considering that significant associations between dietary sodium-to-potassium ratio and risk of stroke were highlighted mainly in the two large-scale Japanese prospective cohort studies, this could probably determine the final significant pooled effects. This seems quite an important limitation of the present meta-analysis and raises concerns about the generalization of the results.

5. Conclusion

The present meta-analysis suggests that both higher dietary sodium and higher dietary sodium-to-potassium ratio are associated with a higher risk of stroke. Therefore, reducing dietary sodium-to-potassium ratio can be considered as a supplementary approach along with the decrease in dietary sodium intake. Well-controlled trials are needed to assess the possible effects of reducing dietary sodium-to-potassium ratio on blood pressure levels, as well as on the risk of stroke and other CVD events.

Statement of authorship

(AJ) designed research, screened articles, extracted data, analyzed data and wrote paper (MSZ) conducted systematic search, screened articles, and wrote paper (FG) extracted data and wrote paper (SS-b) designed research, analyzed data, wrote paper and had primary responsibility for final content. All authors have read and approved the final manuscript.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Human and animal rights

Not applicable.

Conflicts of interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.05.017.

References

[1] Krishnamurthi RV, Moran AE, Feigin VL, Barker-Collo S, Norrving B, Mensah GA, et al. Stroke prevalence, mortality and disability-adjusted life years in adults aged 20-64 years in 1990-2013: data from the global burden of disease 2013 study. Neuroepidemiology 2015;45:190–202.
[2] Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2012 update. Circulation 2012;125:e2–220.
[3] Appel LJ, Frohlich ED, Hall JE, Pearson TA, Sacco RL, Seals DR, et al. The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke. Circulation 2011;123:1138–43.
[4] Organization WH. The world health report 2002: reducing risks, promoting healthy life. World Health Organization; 2002.
[5] Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low-and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 2014;27:1129–37.
[6] Strazzullo P, D'Elia L, Kandala N-B, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339.b4567.
[7] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–23.
[8] Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;362:590–9.
[9] Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013;346. f1326.

[10] He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ 2013;346. f1325.
[11] Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail 2014;16:394–402.
[12] O'donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014;2014:612–23.
[13] Organization WH. WHO Guideline: sodium intake for adults and children. Geneva: World Health Organization; 2012.
[14] Department of Health and Human Services, Department of Agriculture. Dietary guidelines for Americans 2015–2020. 82015. (http://health.gov/dietaryguidelines/2015/guidelines).
[15] Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 2013;346. f1378.
[16] D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease a meta-analysis of prospective studies. J Am Coll Cardiol 2011;57:1210–9.
[17] Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings. Public health and medical care implications. Hypertension 1989;14:570–7.
[18] Yang Q, Liu T, Kuklina EV, Flanders WD, Hong Y, Gillespie C, et al. Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2011;171:1183–91.
[19] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[20] Beller EM, Glasziou PP, Altman DG, Hopewell S, Bastian H, Chalmers I, et al. PRISMA for Abstracts: reporting systematic reviews in journal and conference abstracts. PLoS Med 2013;10:e1001419.
[21] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[22] Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993:218–28.
[23] Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. STATA J 2006;6:40.
[24] Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008;27:954–70.
[25] Aune D, Greenwood D, Chan D, Vieira R, Vieira A, Navarro Rosenblatt D, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose–response meta-analysis of prospective studies. Ann Oncol 2011;23:843–52.
[26] Umesawa M, Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, et al. Relations between dietary sodium and potassium intakes and mortality from cardiovascular disease: the Japan Collaborative Cohort Study for Evaluation of Cancer Risks. Am J Clin Nutr 2008;88:195–202.
[27] He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. J Am Med Assoc 1999;282:2027–34.
[28] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ Br Med J (Clin Res Ed) 2003;327:557.
[29] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[30] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[31] Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2011;175:66–73.
[32] Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. Am J Med 2006;119. 275. e277–275. e214.
[33] Gardener H, Rundek T, Wright CB, Elkind MS, Sacco RL. Dietary sodium and risk of stroke in the Northern Manhattan study. Stroke 2012;43:1200–5.
[34] Geleijnse JM, Witteman JC, Stijnen T, Kloos MW, Hofman A, Grobbee DE. Sodium and potassium intake and risk of cardiovascular events and all-cause mortality: the Rotterdam Study. Eur J Epidemiol 2007;22:763–70.
[35] Judd SE, Aaron KJ, Letter AJ, Muntner P, Jenny NS, Campbell RC, et al. High sodium: potassium intake ratio increases the risk for all-cause mortality: the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. J Nutr Sci 2013;2.
[36] Kagan A, Popper J, Rhoads G, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. Stroke 1985;16:390–6.
[37] Larsson SC, Virtanen MJ, Mars M, Männistö S, Pietinen P, Albanes D, et al. Magnesium, calcium, potassium, and sodium intakes and risk of stroke in male smokers. Arch Intern Med 2008;168:459–65.
[38] Liang W, Lee AH, Binns CW. Dietary intake of minerals and the risk of ischemic stroke in Guangdong Province, China, 2007-2008. Prev Chronic Dis 2011;8.
[39] Montonen J, Järvinen R, Reunanen A, Knekt P. Fish consumption and the incidence of cerebrovascular disease. Br J Nutr 2009;102:750–6.
[40] Nagata C, Takatsuka N, Shimizu N, Shimizu H. Sodium intake and risk of death from stroke in Japanese men and women. Stroke 2004;35:1543–7.
[41] O'donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. J Am Med Assoc 2011;306:2229–38.
[42] Okayama A, Okuda N, Miura K, Okamura T, Hayakawa T, Akasaka H, et al. Dietary sodium-to-potassium ratio as a risk factor for stroke, cardiovascular disease and all-cause mortality in Japan: the NIPPON DATA80 cohort study. BMJ open 2016;6:e011632.
[43] Takachi R, Inoue M, Shimazu T, Sasazuki S, Ishihara J, Sawada N, et al. Consumption of sodium and salted foods in relation to cancer and cardiovascular disease: the Japan Public Health Center–based Prospective Study. Am J Clin Nutr 2010;91:456–64.
[44] Tuomilehto J, Jousilahti P, Rastenyte D, Moltchanov V, Tanskanen A, Pietinen P, et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. Lancet 2001;357:848–51.
[45] Willey J, Gardener H, Cespedes S, Cheung YK, Sacco RL, Elkind MS. Dietary sodium to potassium ratio and risk of stroke in a multiethnic urban population: the northern manhattan study. Stroke 2017 Nov;48(11):2979–83. https://doi.org/10.1161/STROKEAHA.117.017963. Epub 2017 Oct 10.
[46] Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas A-M, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. Stroke 1995;26:361–7.
[47] Cogswell ME, Maalouf J, Elliott P, Loria CM, Patel S, Bowman BA. Use of urine biomarkers to assess sodium intake: challenges and opportunities. Annu Rev Nutr 2015;35:349–87.
[48] Alderman MH, Cohen HW. Dietary sodium intake and cardiovascular mortality: controversy resolved?. Oxford University Press; 2012.
[49] Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database Syst Rev 2011 Jul 6;7. https://doi.org/10.1002/14651858.CD009217. CD009217.
[50] He FJ, Pombo-Rodrigues S, MacGregor GA. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. BMJ open 2014;4:e004549.
[51] Udagawa K, Miyoshi M, Yoshiike N. Mid-term evaluation of "Health Japan 21": focus area for the nutrition and diet. Asia Pac J Clin Nutr 2008;17(Suppl 2):445–52.
[52] Drewnowski A, Maillot M, Rehm C. Reducing the sodium-potassium ratio in the US diet: a challenge for public health. Am J Clin Nutr 2012;96:439–44.
[53] US Department of Agriculture UDoHaHS. Dietary guidelines for Americans, 2010. 7th ed. Washington, DC: US Government Printing Office; 2010.
[54] Binia A, Jaeger J, Hu Y, Singh A, Zimmermann D. Daily potassium intake and sodium-to-potassium ratio in the reduction of blood pressure: a meta-analysis of randomized controlled trials. J Hypertens 2015;33:1509–20.
[55] Vinceti M, Filippini T, Crippa A, de Sesmaisons A, Wise LA, Orsini N. Meta-analysis of potassium intake and the risk of stroke. J Am Heart Assoc 2016;5.
[56] McCabe RD, Bakarich MA, Srivastava K, Young DB. Potassium inhibits free radical formation. Hypertension 1994;24:77–82.
[57] Kido M, Ando K, Onozato ML, Tojo A, Yoshikawa M, Ogita T, et al. Protective effect of dietary potassium against vascular injury in salt-sensitive hypertension. Hypertension 2008;51:225–31.
[58] Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, et al. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 1997;277:1624–32.
[59] Kanbay M, Bayram Y, Solak Y, Sanders PW. Dietary potassium: a key mediator of the cardiovascular response to dietary sodium chloride. J Am Soc Hypertens 2013;7:395–400.
[60] Cobb LK, Anderson CA, Elliott P, Hu FB, Liu K, Neaton JD, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes. Circulation 2014 Mar 11;129(10):1173–86. https://doi.org/10.1161/CIR.0000000000000015.
[61] Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk—measurement matters. N Engl J Med 2016;375:580.