META-ANALYSIS

High Salt Intake and Stroke: Meta-analysis of the Epidemiologic Evidence

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Hemorrhagic stroke; High salt intake; Ischemic stroke; Meta-analysis; Stroke.

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Received 23 February 2012; accepted 21 March 2012.

SUMMARY

Research on the potential impact of high salt intake on health has grown rapidly over the last decades. Recent studies have suggested that high salt intake could also be associated with adverse effects on cardiovascular system. The review evaluated the current level of epidemiologic evidence on the association between the level of habitual salt intake and stroke outcome. We also suggest further research direction. There were 21 independent samples from 12 studies, with 225,693 participants (follow-up, 3–19 years) and 8135 stroke events. High salt intake was associated with risk of stroke event (pooled odd ratio [OR], 1.34; 95% confidence interval [CI], 1.19–1.51), stroke death (1.40; 1.21–1.63) and stroke onset (1.11; 1.00–1.24), ischemic stroke death (2.15; 1.57–2.95), not associated with risk of ischemic stroke onset (1.07, 0.95–1.2), with no significant evidence of publication bias. High salt intake is associated with significantly increased risk of stroke event. Further research should be directed toward clarifying and quantifying these possible effects and generating testable hypotheses on plausible biologic mechanisms.

doi: 10.1111/j.1755-5949.2012.00355.x

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Introduction

During the past century, the evidence for the risks imposed on human health by excess salt consumption has become compelling. There is widespread evidence that long-term (years) effects of high salt intake on the risk of cardio-cerebral-vascular disease in the past decades [1–18], and relevant meta-analysis between high salt intake and health effects [19]. Most of these studies found evidence of the association between high salt diet and the risk of stroke [4–15], but results are inconsistent. Ikehara et al. [4] and Umesawa et al. [9] studies found that there were significant association between high salt intake and the death as a result of stroke (OR 1.22; 95% CI, 1.00–1.49 for women and 1.55; 1.21–2.00 for men and women). Finding from Kono et al. [5] study shows high salt intake is related to stroke recurrence (1.98, 1.02–4.22), and that from Liang et al. [7] and Ellekjaer et al. [15] studies shows no significant association between high salt intake and ischemic stroke onset.

Past investigations of high salt intake, the stroke event outcome measure primarily focused on overall mortality or morbidity index used such routinely collected data as death counts or death rates, hospitalization or emergency room visit rates, in some investiga-

tions, categories of stroke diagnoses were selected as outcome measures. Few studies investigated presented an analysis on the association between high salt diet and stroke events.

Considerable consistency across studies has been observed for many health effects, for example, stroke death, onset or recurrence, particularly for those linked with high salt diet, although the biologic mechanisms of the health effects are unclear.

Methods**Search Strategy for Identification of Study**

We identified papers through electronic searches of medical and biologic databases (Chinese Biomedical Database, CBM, 1978–January 2012; Medline 1966–January 2012; Embase 1980–January 2012; CAB Health 1973–January 2012; Science Citation Index, Web of Science 1981–January 2012; Conference Papers Index via Cambridge Scientific Abstracts databases 1982–January 2012, using a comprehensive list of stroke/stroke disease/and salt/salt intake/high salt diet keywords and phrases). We also searched web-based resources (available with the electronic version of these articles at <http://www.ncbi.nlm.nih.gov/pubmed/>), scanned

reference lists (of review articles and published studies), and consulted with key experts in the field. Identified publications were scanned by one of the authors.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) non-accidental exposure to directly measured sodium; (2) be a prospective population study, assess salt intake as baseline exposure, and determine stroke event prospectively as the outcome; (3) an adult population, and indicate the number of participants exposed and the rate or number of events in the different categories of salt intake; (4) to be original article published from January 1989 to January 2012 in the English language or Chinese language; and (5) follow participants for at least 3 years.

Exclusion criteria were as follows: (1) the outcome related to occupational or accidental exposure; (2) animals served as subjects; (3) the original article did not involve the exposure–response relationship between high salt intake and stroke; (4) repeated report; (5) reviews, letters, and comments; (6) low-quality article; and (7) results presented only as abstracts.

Data Extraction

Papers meeting the inclusion criteria were formally reviewed by pairs of reviewers using a data extraction form based on the previous reviews. This form was piloted before starting the data extraction process. From the identified studies, we recorded publication reference, age (mean, median or range), total number of participants, gender, method of assessing salt intake, study design, statistical techniques, country, outcome reported (stroke, ischemic stroke, or hemorrhagic stroke), number of events, method of outcome (death, onset, recurrence, or incidence) assessment, follow-up (years), level of salt intake in different categories, confounding factors, and results.

Table 1 presents the summary of the study design for each study; Table 2 presents the results of the study for each study. There are multiple entries for publications that reported results for more than one outcome. Results were referenced back to the specific publication (rather than to the study) from which they were produced. When possible, effect estimates (odds and risk ratios, mean change) are recalculated as the expected change in outcome for an increase in salt intake levels by 100 mmol/day. This scale is not comparable across studies measuring different salt intake, but its use facilitates comparison among studies using the same salt intake measurements. It was not appropriate to combine the results in a formal meta-analysis because the study methods vary so widely.

Exposure Measurements

Categorization of salt intake differed among studies. Some reported the number of subjects exposed and the number (rate) of events across the distribution of salt intake; others reported differences in the event rate for a 100mmol/day difference in sodium. In the last three cases, we used the relative risk and hazard ratio reported by authors for the analysis. In all the cases in which categorization of the study participants by level of salt intake was

Table 1 Characteristics of studies included in meta-analysis of studies on salt intake and stroke

First author	Age (year)	Events	Sex	Sodium intake assessment	Design	Statistical analysis	Country
Ikehara et al. [4]	40–79	35515; 49275	Men and Women	Questionnaire	Prospective cohort study	Cox proportional hazard models	Japan
Liang et al. [7]	Mean of 69	838	Men and women	Questionnaire	A case–control study	Logistic regression	China
Kono et al. [5]	Mean of 64	102	Men and women	A self-monitoring device	Prospective cohort study	Cox proportional hazard models	Japan
Larsson et al. [8]	50–69	26556	Men	Questionnaire	Prospective ATBC Study	Cox proportional hazard models	Finland
Umesawa et al. [9]	40–79	58730	Men and women	Questionnaire	Prospective cohort study	Cox proportional hazard models	Japan
Geleijnse et al. [10]	≥ 55	1448	Men and women	Questionnaire and overnight urine sodium	A case–cohort analysis	Cox proportional hazard models	Netherlands
Nagata et al. [11]	≥ 35	13355; 15724	Men and Women	Questionnaire	Prospective cohort study	Cox proportional hazard models	Japan
Tuomilehto et al. [13]	25–64	1173; 1263	Men and Women	24-h urinary sodium excretion	Prospective study	Cox proportional hazard models	Finland
He et al. [12]	25–74	2688; 6797	Men and women	24-h dietary recall	Prospective cohort study	Cox proportional hazard models	US
Alderman et al. [14]	52–54	2937	Men and women	24-h urinary sodium excretion	Prospective cohort study	Cox proportional hazard models	US
Ellekjaer et al. [15]	Mean 69	730	Men and women	Questionnaire	A case–control study	Logistic regression	Norceland
Hu et al. [6]	≥ 36	8562	Men and women	Questionnaire	Prospective study	The Mantel-Haenszel procedure	Taiwan

Table 2 Detailed data of studies included in meta-analysis

First author/year of publication	Sex	Cases	Sodium difference (mmol/day)	Follow-up(years)	Outcome	OR (95% CI)	Controlled factors
Ikehara 2012 (1) ^a	Men	1023	12	16.4	Total stroke death	1.21 (0.99, 1.49)	Age, BMI, diabetes, smoking, education, sport, walking, mental stress, alcohol, and fresh fish intake.
Ikehara 2012 (2) ^a	Women	947	13	16.4	Total stroke death	1.22 (1.00, 1.49)	
Liang 2011	Men and women	374	27	5	Ischemic stroke onset	1.30 (0.73, 2.32)	Weekly energy intake; sex; and age.
Kono 2011	Men and women	89	183	3	Stroke recurrence	1.98 (1.02, 4.22)	Sex, disease, age, height, weight, BP, lipid, glucose, HbA1c, smoking, alcohol, exercise, waist, ankle-brachial pressure index, and physical activity.
Larsson 2008	Male smokers	2702	84	13.6	Ischemic stroke onset	1.04 (0.92, 1.18)	Age, supplementation, cigarettes, BMI, BP, cholesterol, diabetes and CHD, physical activity.
Umesawa 2008 (1) ^a	Men and women	986	85	12.7	Total stroke death	1.55 (1.21, 2.00)	BMI, smoking, alcohol, hypertension, diabetes, menopause, hormone, exercise, education, mental stress, calcium and potassium intake
Umesawa 2008 (2) ^a	Men and women	510	85	12.7	Ischemic stroke death	2.04 (1.41, 2.94)	
Geleijnse 2007	Men and women	181	69	5	Total stroke death	1.08 (0.80, 1.46)	Age, sex, 24-h urinary creatinine excretion, BMI, smoking, diabetes, diuretics, education, energy, alcohol, 3calcium, saturated fat intake.
Nagata 2004 (1) ^a	Men	137	110	7	Total stroke death	2.33 (1.23, 4.45)	Age, energy, education, BMI, smoking, exercise, hypertension and intake of protein, potassium, alcohol and vitamin E, diabetes, marital status.
Nagata 2004 (2) ^a	Men	137	110	7	Ischemic stroke death	3.22 (1.22, 8.53)	
Nagata 2004 (3) ^a	Men	137	110	7	Hemorrhagic stroke death	2.27 (0.85, 6.02)	
Nagata 2004 (4) ^a	Women	132	92	7	Total stroke death	1.70 (0.96, 3.02)	
Nagata 2004 (5) ^a	Women	132	92	7	Ischemic stroke	2.10 (0.96, 4.64)	
Nagata 2004 (6) ^a	Women	132	92	7	Hemorrhagic stroke death	1.28 (0.49, 3.37)	
Tuomilehto 2001 (1) ^a	Men	43	100	7	Total stroke incidence	1.00 (0.68, 1.47)	Age, education smoking, serum total and HDL cholesterol, systolic blood pressure, and BMI
Tuomilehto 2001 (2) ^a	Women	41	100		Total stroke incidence	1.34 (0.87, 2.07)	
He 1999 (1) ^a	Overweight	430	100	19	Total stroke death	0.99 (0.81, 1.20)	Age, sex, race, SBP, BMI, diabetes, diuretic use, physical activity, cholesterol, alcohol consumption, education
He 1999 (2) ^a	Normal	250	100	19	Total stroke death	1.39 (1.10, 1.76)	
Alderman 1995	Men and women	23	140	3.5	Total stroke	1.20 (0.30, 4.00)	Unadjusted
Ellekaer 1992	Men and women	163		3	Ischemic stroke onset	0.92 (0.26, 3.31)	Physical activity
Hu 1992	Men and women	104		4	Total stroke incidence	1.79 (1.18, 2.71)	Age

BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein.

^aRank indicates the different findings in the same paper.

available, we calculated the relative risk of higher versus lower salt intake by comparing the event rate in the two categories with a difference in average salt intake closest to 100 mmol of sodium or about 6 g of salt a day.

Stroke Outcomes

Daily counts of stroke event (non-trauma deaths [minus accidents and homicides], attack) were aggregated. Using the International Classification of Disease, tenth Revision (ICD-10) [20], total daily counts of stroke events (ICD-10 codes: I60–I69 or ICD-9: 430–438) were determined.

Study Design

Systematic review and meta-analysis of prospective or case-control study published from 1966 to 2012.

Quality of the Studies

Study quality was described by the extent to which the design, conduct, and analysis minimized selection, measurement, and confounding biases. The following methodological domains have

been suggested to describe the quality of observational studies: study design, comparability of subjects, exposure measurement, outcome measurement, statistical analysis, and funding or sponsorship. The main variations among the reviewed studies were in (1) study design (prospective vs. case-control); (2) exposure measurement (follow-up time used; validity and reliability of the measurement method; comparability of measurement across the study groups; and spatial or compositional heterogeneity among the examined districts); (3) adjustment for key confounders (in particular, age, smoking, BMI and so on); and (4) statistical analysis (appropriateness and whether multiple comparisons were taken into consideration in the interpretation of the results). Key points in relation to these criteria are given in Table 1 and taken into account in the narrative summary.

Statistical Analysis

Pooled ORs of high salt intake with 95% confidence intervals (CI) for stroke events in meta-analyses were obtained by using the fixed-or random-effects model, heterogeneity among the risk estimates were tested using Q and I^2 statistics. When the result of the Q -test and I^2 statistics showed evidence for heterogeneity ($P \leq 0.05$ and $I^2 > 50\%$), we used a random effect analysis,

Figure 1 Forest plots of meta-analysis on salt intake and stroke event. (A) The effect of salt intake to stroke event. (B) The effect of salt intake to ischemic stroke event. (C) The effect of salt intake to stroke event for men. (D) The effect of salt intake to stroke event for women.

Figure 2 Funnel plots of meta-analysis on salt intake and stroke event. (A) The effect of salt intake to stroke event. (B) The effect of salt intake to ischemic stroke event. (C) The effect of salt intake to stroke event for male. (D) The effect of salt intake to stroke event for female.

following the method of DerSimonian and Laird [21]. Otherwise, a fixed-effects analysis was conducted using the Mantel-Haenszel method [22]. We also produced forest plots to show ORs from each of the individual studies included in the meta-analyses and the estimation of the pooled OR. The sizes of the markers of each OR in the plots represent the relative weight each study contributed to the pooled estimation. Publication bias was assessed by funnel plots or Begger's test and a weighted Egger test [23]. We also performed sensitivity analyses, whereby each study was omitted in turn, recalculating the pooled estimates under extreme conditions. All analyses were performed using software STATA version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the Study

The meta-analysis included 12 studies reporting on 21 independent estimates (Table 1). There were 225,693 participants from 6 different countries (4 studies from Japan; 2 each from Finland, United States, and China; and 1 each from Netherlands and

Norseland). Eleven studies recruited both male and female participants, while 1 included only men. Follow-up ranged from 3 to 19 years. Three studies reported only total stroke death, three only ischemic stroke onset, two only total stroke incidence, one only stroke recurrence, one only stroke death (total stroke death, ischemic stroke death, and hemorrhagic stroke death). Salt intake was assessed by 24-h dietary recall ($n = 1$), 24-h urine excretion ($n = 2$), food frequency questionnaire ($n = 7$), a self-monitoring device ($n = 1$), both questionnaire and overnight urine sodium level ($n = 1$). In total, there were 8135 stroke events reported. Of the 11 studies that included both men and women, 3 reported outcomes separately. He *et al.*'s study provided separate findings for normal weight and overweight participants. Overall, data on the relationship between salt consumption and stroke were available from 21 estimates.

Salt Intake and Risk of Stroke Event

Table 2 provides data on the relation between salt intake and risk of stroke in each of 21 estimates included in the study. Figure 1(A) shows the results of the pooled analysis. In the pooled

Table 3 Sensitivity analysis the associations between high salt intake and stroke events

		Model	OR (95% CI)	Q	P
High salt intake and stroke events	Total	Random effects Model	1.34 (1.19–1.51)	42.37	0.002
	Ikehara 2012 (1) ^a excluded	Random effects Model	1.37 (1.20, 1.56)	42.36	0.002
	Ikehara 2012 (2) ^a excluded	Random effects Model	1.37 (1.20, 1.56)	42.37	0.002
	Liang 2011 excluded	Random effects Model	1.35 (1.19, 1.52)	42.32	0.002
	Kono 2011 excluded	Random effects Model	1.33 (1.18, 1.50)	40.57	0.003
	Larsson 2008 excluded	Random effects Model	1.38 (1.22, 1.56)	33.41	0.022
	Umesawa 2008 (1) ^a excluded	Random effects Model	1.32 (1.17, 1.50)	38.65	0.005
	Umesawa 2008 (2) ^a excluded	Random effects Model	1.29 (1.16, 1.49)	34.62	0.016
	Geleijnse 2007 excluded	Random effects Model	1.37 (1.21, 1.55)	41.69	0.002
	Nagata 2004 (1) ^a excluded	Random effects Model	1.32 (1.17, 1.48)	38.45	0.005
	Nagata 2004 (2) ^a excluded	Random effects Model	1.32 (1.18, 1.48)	38.53	0.005
	Nagata 2004 (3) ^a excluded	Random effects Model	1.33 (1.18, 1.50)	40.82	0.003
	Nagata 2004 (4) ^a excluded	Random effects Model	1.33 (1.18, 1.50)	41.07	0.002
	Nagata 2004 (5) ^a excluded	Random effects Model	1.33 (1.18, 1.50)	40.54	0.003
	Nagata 2004 (6) ^a excluded	Random effects Model	1.35 (1.19, 1.52)	42.36	0.002
	Tuomilehto 2001 (1) ^a excluded	Random effects Model	1.37 (1.21, 1.55)	41.30	0.002
	Tuomilehto 2001 (2) ^a excluded	Random effects Model	1.35 (1.19, 1.52)	41.19	0.002
	He 1999 (1) ^a excluded	Random effects Model	1.38 (1.22, 1.56)	37.42	0.007
	He 1999 (2) ^a excluded	Random effects Model	1.34 (1.18, 1.52)	41.10	0.002
	Alderman 1995 excluded	Random effects Model	1.35 (1.19, 1.52)	42.37	0.002
	Ellekjaer 1992 excluded	Random effects Model	1.35 (1.20, 1.52)	42.18	0.002
	Hu 1992 excluded	Random effects Model	1.32 (1.17, 1.49)	39.03	0.004
High salt intake and ischemic stroke event	Total	Random effect Model	1.60 (1.11, 2.31)	20.89	0.002
	Liang 2011 excluded	Random effect Model	1.68 (1.09, 2.60)	20.75	0.001
	Kono 2011 excluded	Random effect Model	1.55 (1.04, 2.32)	18.70	0.002
	Larsson 2008 excluded	Fixed effect Model	1.87 (1.45, 2.41)	4.24	0.516
	Ellekjaer 1992 excluded	Random effect Model	1.67 (1.13, 2.48)	20.75	0.001
	Umesawa 2008 (2) ^a excluded	Random effect Model	1.48 (1.01, 2.14)	11.08	0.050
	Nagata 2004 (2) ^a excluded	Random effect Model	1.49 (1.03, 2.14)	16.64	0.005
	Nagata 2004 (5) ^a excluded	Random effect Model	1.54 (1.04, 2.29)	18.70	0.002
High salt intake and stroke for male	Total	Random effects Model	1.30 (1.02–1.65)	13.76	0.017
	Ikehara 2012 (1) ^a excluded	Random effects Model	1.47 (0.99, 2.19)	13.03	0.011
	Larsson 2008 excluded	Random effects Model	1.52 (1.06, 2.19)	9.97	0.041
	Nagata 2004 (1) ^a excluded	Fixed effects Model	1.10 (0.99, 1.22)	8.64	0.071
	Nagata 2004 (2) ^a excluded	Fixed effects Model	1.11 (1.10, 1.22)	9.18	0.057
	Nagata 2004 (3) ^a excluded	Random effects Model	1.25 (0.98, 1.59)	11.74	0.019
	Tuomilehto 2001 (1) ^a excluded	Random effects Model	1.42 (1.05, 1.91)	13.41	0.009
High salt intake and stroke for female	Total	Fixed effects Model	1.31 (1.11–1.54)	2.61	0.614
	Ikehara 2012 (2) ^a excluded	Fixed effects Model	1.52 (1.13, 2.05)	1.24	0.742
	Nagata 2004 (4) ^a excluded	Fixed effects Model	1.27 (1.07, 1.52)	1.78	0.619
	Nagata 2004 (5) ^a excluded	Fixed effects Model	1.28 (1.05, 1.51)	1.21	0.751
	Nagata 2004 (6) ^a excluded	Fixed effects Model	1.31 (1.10, 1.55)	2.67	0.445
	Tuomilehto 2001 (2) ^a excluded	Fixed effects Model	1.30 (1.09, 1.56)	2.66	0.448

^aRank indicates the different findings in the same paper.

analysis, high salt intake was associated with risk of stroke (OR, 1.34; 95% CI, 1.19–1.51). There was significant heterogeneity among studies ($Q = 42.37$, $P = 0.002$; $I^2 = 63.7\%$). The funnel plot did not show asymmetry, thus excluding publication bias (Begger's test $z_c = 1.18$, $P = 0.239$; Egger's test $t = 0.08$, $P = 0.094$). As shown in Figure 2(A) for the individual estimates included in the analysis, we found a trend toward a direction association between salt intake and risk of stroke in 19 estimates, which was significant in 7. We observed a non-significant inverse trend in 2 estimates. Sensitivity analysis showed the pooled estimate of the effect of salt intake on the risk of stroke did not vary

substantially with the exclusion of any one study, as shown in Table 3.

Table 2 provides data on the relation between salt intake and risk of ischemic stroke event in each of 7 estimates included in the study. Figure 1(B) shows the results of the pooled analysis. In the pooled analysis, high salt intake was associated with risk of stroke (OR, 1.60; 95% CI, 1.11–2.31). There was significant heterogeneity among studies ($Q = 20.89$, $P = 0.002$; $I^2 = 71.3\%$). The funnel plot did not show asymmetry, thus excluding publication bias (Begger's test $z_c = 0.00$, $P = 1.000$; Egger's test $t = -0.38$, $P = 0.717$). As shown in Figure 2(B) for the individual estimates

Figure 3 Forrest plots of meta-analysis on salt intake and stroke death or attack. **(A)** The effect of salt intake to stroke death. **(B)** The effect of salt intake to ischemic stroke death. **(C)** The effect of salt intake to stroke attack. **(D)** The effect of salt intake to ischemic stroke attack.

included in the analysis, we found a trend toward a direction of association between salt intake and risk of stroke in 7 estimates, which was significant in 3. We observed a non-significant inverse trend in one estimates. Sensitivity analyses that showed the pooled estimate of the effect of salt intake on the risk of ischemic stroke event were robust, as shown in Table 3.

There were 6 estimates, and 5 estimates reported data for men and women separately for stroke event. The pooled estimates from these estimates were 1.30 (1.02–1.65) and 1.31 (1.11–1.54), as shown in Figure 1(C,D), respectively. Heterogeneity tests showed evidence for heterogeneity and homogeneity among studies for men and women ($Q = 13.76$, $P = 0.017$, $I^2 = 63.7\%$; $Q = 2.67$, $P = 0.614$, $I^2 = 0$); the funnel plots were shown in Figure 2(C,D), respectively. Sensitivity analysis showed the pooled estimate of the effect of salt intake on the risk of women stroke event did not vary substantially with the exclusion of any one study, but the results for men were not robust to the inclusion of Umesawa study, as shown in Table 3.

Salt Intake and Risk of Stroke Death

Table 2 provides data on the association between salt intake and the risk of stroke death in 13 cohorts. In the pooled analysis, there was an association between high salt intake and risk of stroke death (OR, 1.40; 95% CI, 1.21–1.63), as shown in Figure 3(A). The heterogeneity among studies was significant ($Q = 27.68$, $P = 0.006$; $I^2 = 56.7\%$), but the funnel plot did not show asymmetry, thus excluding publication bias ($z_c = 1.77$, $P = 0.077$;

$t = -0.09$, $P = 0.927$), as shown in Figure 4(A). The evaluation of individual estimates showed a trend toward a direct association between salt intake and risk of stroke death in 12 estimates, with significantly higher relative risk in 5. An inverse trend was observed in one estimate but was not significant. Sensitivity analysis showed that the result was robust, as shown in Table 4.

Table 2 provides data on the association between salt intake and the risk of ischemic stroke death in 3 cohorts. In the pooled analysis, there was an association between high salt intake and risk of ischemic stroke death (OR 2.15, 95% CI 1.57–2.95), as shown Figure 3(B). The homogeneity among studies was not significant ($Q = 0.74$, $P = 0.689$; $I^2 = 0$), but the funnel plot did not show asymmetry, thus excluding publication bias ($z_c = 1.04$, $P = 0.296$; $t = 2.42$, $P = 0.250$), as shown in Figure 4(B). The evaluation of individual estimates showed a trend toward a direct association between salt intake and risk of ischemic stroke death in 3 estimates, with significantly higher relative risk in 2. An inverse trend was observed in none. Sensitivity analysis showed that the result was robust, as shown in Table 4.

Salt Intake and Risk of Stroke Attack

Table 2 provides data on the association between salt intake and the risk of stroke attack in 7 estimates. In the pooled analysis, there was an association between high salt intake and risk of stroke attack (OR, 1.11; 95% CI, 1.00–1.24), as shown in Figure 3(C). The homogeneity among studies was not significant ($Q = 10.05$, $P = 0.122$; $I^2 = 40.3\%$), but the funnel plot did not

Figure 4 Funnel plots of meta-analysis on salt intake and stroke death or attack. **(A)** The effect of salt intake to stroke death. **(B)** The effect of salt intake to ischemic stroke death. **(C)** The effect of salt intake to stroke attack. **(D)** The effect of salt intake to ischemic stroke attack.

show asymmetry, thus excluding publication bias ($z_c = 0.60$, $P = 0.548$; $t = -0.23$, $P = 0.827$), as shown in Figure 4(C). The evaluation of individual estimates showed a trend toward a direct association between salt intake and risk of stroke attack in 6 estimates, with significantly higher relative risk in 2. An inverse trend was observed in one estimate but was not significant. Sensitivity analysis showed that the exclusion of the only estimate showing an inverse trend but not significant, as shown in Table 4.

Table 2 provides data on the association between salt intake and the risk of ischemic stroke attack in 4 cohorts. In the pooled analysis, there was no association between salt intake and risk of ischemic stroke attack (OR, 1.07; 95% CI, 0.95–1.20), as shown in Figure 3(D). The homogeneity among studies was not significant ($Q = 3.58$, $P = 0.311$; $I^2 = 16.1\%$), but the funnel plot did not show asymmetry, thus excluding publication bias ($z_c = 0.34$, $P = 0.734$; $t = -0.12$, $P = 0.914$), as shown in Figure 4(D). The evaluation of individual estimates showed a trend toward a direct association between salt intake and risk of ischemic stroke attack in 3 estimates, with significantly higher relative risk in 1. We observed a non-significant inverse trend in 1 estimate. Sensitivity analysis showed that the result was robust, as shown in Table 4.

Discussion

Stroke remains one of the most devastating of all neurological conditions, which caused an estimated 5.7 million deaths in 2005, and 8.7% of these deaths were in low-income and middle-income

countries [16]. Worldwide it accounts for approximately 5.5 million deaths annually, with 44 million disability-adjusted life-years lost. As a disease of aging, the prevalence of stroke is expected to increase significantly around the world in the years ahead as the global population older than 65 years of age continues to increase by approximately 9 million people per year [17]. Stroke is a severely neglected condition in lower-income regions [18]. There are many risk factors of stroke, for example, systolic blood pressure, body-mass index, smoking, and environment and so on [24–26]; the high salt intake-stroke relationships were also being investigated widely [27–29]. However, according to stroke outcome category (death or attack) and diagnosis category (ischemic stroke/hemorrhagic stroke), few studies on the high salt intake-stroke relationships had been investigated systematically.

The systematic review identified 12 relevant and suitable studies published from 1992 to 2012. These studies provided evidence from 225,693 participants contributing overall more than 8000 stroke events.

Stroke events were defined as rapidly developing signs of focal (or global) disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death) with no apparent nonvascular cause. The definition included patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. Typically, the first 2 types were gone by the name of hemorrhagic stroke, and the last was known as ischemic stroke. On the basis of the status within 28 days of onset, stroke events were subdivided into first

Table 4 Sensitivity analysis on the associations between high salt intake and stroke death/onset

		Model	OR (95% CI)	Q	P
High salt intake and stroke death	Total	Random effects Model	1.40 (1.21, 1.63)	27.68	0.006
	Ikehara 2012 (1) ^a excluded	Random effects Model	1.45 (1.22, 1.73)	27.18	0.004
	Ikehara 2012 (2) ^a excluded	Random effects Model	1.45 (1.22, 1.73)	27.27	0.004
	Umesawa 2008 (1) ^a excluded	Random effects Model	1.39 (1.18, 1.64)	25.46	0.008
	Umesawa 2008 (2) ^a excluded	Random effects Model	1.34 (1.16, 1.54)	21.47	0.029
	Geleijnse 2007 excluded	Random effects Model	1.45 (1.23, 1.71)	26.17	0.006
	Nagata 2004 (1) ^a excluded	Random effects Model	1.37 (1.18, 1.58)	24.42	0.011
	Nagata 2004 (2) ^a excluded	Random effects Model	1.37 (1.19, 1.58)	24.29	0.012
	Nagata 2004 (3) ^a excluded	Random effects Model	1.39 (1.19, 1.62)	26.41	0.006
	Nagata 2004 (4) ^a excluded	Random effects Model	1.39 (1.19, 1.63)	26.80	0.005
	Nagata 2004 (5) ^a excluded	Random effects Model	1.38 (1.19, 1.63)	26.22	0.006
	Nagata 2004 (6) ^a excluded	Random effects Model	1.41 (1.21, 1.65)	27.69	0.004
	He 1999 (1) ^a excluded	Fixed effects Model	1.38 (1.25, 1.51)	18.86	0.064
	He 1999 (2) ^a excluded	Random effects Model	1.42 (1.20, 1.68)	27.28	0.004
High salt intake and stroke onset	Total	Fixed effects Model	1.11 (1.00, 1.24)	10.05	0.122
	Liang 2011 excluded	Fixed effects Model	1.11 (0.99, 1.24)	9.77	0.082
	Kono 2011 excluded	Fixed effects Model	1.10 (0.99, 1.23)	7.48	0.187
	Larsson 2008 excluded	Fixed effects Model	1.35 (1.10, 1.66)	5.58	0.349
	Tuomilehto 2001 (1) ^a excluded	Fixed effects Model	1.12 (1.01, 1.26)	9.72	0.083
	Tuomilehto 2001 (2) ^a excluded	Fixed effects Model	1.10 (0.99, 1.23)	9.31	0.093
	Ellekjaer 1992 excluded	Fixed effects Model	1.12 (1.00, 1.24)	9.96	0.076
	Hu 1992 excluded	Fixed effects Model	1.08 (0.97, 1.20)	4.71	0.452
	Total	Fixed effects Model	1.07 (0.95, 1.20)	3.58	0.311
High salt intake and ischemic stroke onset	Liang 2011 excluded	Fixed effects Model	1.06 (0.94, 1.20)	3.11	0.211
	Kono 2011 excluded	Fixed effects Model	1.05 (0.93, 1.18)	0.59	0.745
	Larsson 2008 excluded	Fixed effects Model	1.45 (0.95, 2.22)	1.37	0.505
	Ellekjaer 1992 excluded	Fixed effects Model	1.07 (0.95, 1.21)	3.52	0.175
	Total	Fixed effects Model	2.15 (1.57, 2.95)	0.74	0.689
High salt intake and ischemic stroke death	Umesawa 2008 (2) ^a excluded	Fixed effects Model	2.49 (1.35, 4.59)	0.45	0.503
	Nagata 2004 (2) ^a excluded	Fixed effects Model	2.05 (1.47, 2.86)	0.00	0.948
	Nagata 2004 (5) ^a excluded	Fixed effects Model	2.16 (1.53, 3.05)	0.74	0.389
	Total	Fixed effects Model	2.15 (1.57, 2.95)	0.74	0.689

^aRank indicates the different findings in the same paper.

or recurrent and into fatal or nonfatal. Stroke attack refers to all strokes (both first and recurrent) within 28 days [30].

According to the World Health Organization, 62% of all strokes are attributable to high blood pressure [31]. The direct relation between levels of dietary salt intake and blood pressure has been established through experimental, epidemiological, migration, and intervention studies. However, the relation between salt intake and stroke events was devoid of system study. Up to now, according to our inclusion criteria in the study, there was the sole study involved the association between salt intake and hemorrhagic stroke death, none involved hemorrhagic stroke attack. Many studies focus on the effect of salt intake to total stroke events or ischemic stroke events.

We used subgroup to assess the influence of gender on the association between high salt intake and risk of stroke. For stroke event outcome, separate analyses of the male and female cohorts suggest that the associations are consistent and not significantly different between the sexes. Similar results were obtained with respect to the method of assessment of salt intake used in the various studies.

Meta-analyses suggest unequivocally that high salt intake was related to statistically significant increases in risk of death as a result of stroke events, especially ischemic stroke events,

and high salt intake to ischemic stroke death, which was not inconsistent with hemorrhagic stroke that was the finding from sole study by Nagata *et al.* [11]. Strazzullo *et al.* [19] concluded that high salt intake was associated with risk of stroke (a pooled relative risk of 1.23, 1.06–1.43) based on 14 cohorts, which is slightly lower than our meta-analysis estimates of 1.34 (1.19–1.51) based on 21 estimates of 12 studies. Meta-analyses show that high salt intake statistically significant increases in risk of stroke attack, but found no statistically significant increases in the risk of ischemic stroke attack in relation to high salt intake. We lacked a sufficient number of studies to calculate hemorrhagic stroke estimate for Nana study only. Whether there is any association between high salt intake and hemorrhagic stroke merits to further study. This review and its meta-analysis raise important issues that may guide both the design and presentation of future studies.

Large heterogeneity in estimated high salt intake-stroke event risk estimates was observed across studies. We found some suggestive evidence that type-specific factor (e.g., ischemic stroke and hemorrhagic stroke) can explain some of the heterogeneity. However, the fact that analyses of the same country data (e.g., Japan) by different researchers resulted in markedly different

estimates suggests a large influence of model specification on the results. An analysis of multiple cities using several alternative model specifications would provide information on the extent of model uncertainty.

Most adult populations around the world have average daily salt intakes higher than 6 g/day, and for many in Eastern Europe and Asia higher than 12 g/day. International recommendations suggest that average population salt intake should be <5–6 g/day [31].

Six studies provided data adjusted for hypertension status or baseline blood pressure.

Overweight and obesity are often associated with high blood pressure and causally involved in the development of hypertension. Eight of 12 studies included in the meta-analysis provided relative risk estimates adjusted for BMI or body weight at entry into the study. All 12 of these studies lacked adjustment particulate matter; however, we found that particulate matters were related to stroke attack.

Clearly, our meta-analysis has many limitations. Although we attempted to capture the crucial dimensions of methodological heterogeneity, there are many factors either difficult to quantify or unreported by the authors that could influence effect estimates. The studies included in the meta-analysis were heterogeneous regarding sample size, study design, number of events, and duration of follow-up, with a few cohorts having small numbers. In the calculation of the pooled estimate, we weighted the results of the individual studies for sample size but did not account for the duration of follow-up.

Another limitation is the fact that the estimate of the baseline population salt intake in each study was based on a single measurement (whether through 24-h urine collection or dietary assessment). We were therefore unable to correct for the bias. Because of the large day-to-day variability within people in salt consumption and the consequent effect imposed on the average estimate of exposure, our estimates of risk are probably underestimated.

Finally, categorization of salt intake was also heterogeneous: Some studies gave us difference in outcome for a given difference (e.g., 100 mmol/24 h) in sodium intake or excretion; other studies stratified the population by categories of sodium intake and compared stroke outcomes across categories. To standardize our comparison between higher and lower salt consumption, we sought to refer a difference as close as possible to 100 mmol or 6 g a day between high and low salt intakes. Nevertheless, there remained appreciable difference in this respect among studies. How to overcome the problem was the merit to further study.

Despite these limitations, we can draw some conclusions that are useful for public policy. First, there are high salt intake–stroke relationships, especially ischemic stroke. Second, few studies on high salt intake–stroke by diagnosis category have been investigated. Third, the robustness of the high salt intake–stroke relationship, even when controlling for key confounders and effects modifiers, indicates that inclusion of high salt intake–stroke in future regulatory impact analyses may be warranted, although further investigation is need into particulate matter (PM) confounding and the personal exposure–ambient concentration relationship. Future studies should explicate PM or other personal exposure surrogates into the estimation of an appropriate high salt intake–stroke relationship.

Acknowledgments

This research was supported by Zhejiang University Student Research Training Program (SRTF) (2012) and Zhejiang Province Experimental Teaching Demonstration Center Construction Projects (2010).

Conflict of Interest

The authors declare no conflict of interest.

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