

Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies

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ABSTRACT

Objective To assess the relation between the level of habitual salt intake and stroke or total cardiovascular disease outcome.

Design Systematic review and meta-analysis of prospective studies published 1966-2008.

Data sources Medline (1966-2008), Embase (from 1988), AMED (from 1985), CINAHL (from 1982), Psycinfo (from 1985), and the Cochrane Library.

Review methods For each study, relative risks and 95% confidence intervals were extracted and pooled with a random effect model, weighting for the inverse of the variance. Heterogeneity, publication bias, subgroup, and meta-regression analyses were performed. Criteria for inclusion were prospective adult population study, assessment of salt intake as baseline exposure, assessment of either stroke or total cardiovascular disease as outcome, follow-up of at least three years, indication of number of participants exposed and number of events across different salt intake categories.

Results There were 19 independent cohort samples from 13 studies, with 177 025 participants (follow-up 3.5-19 years) and over 11 000 vascular events. Higher salt intake was associated with greater risk of stroke (pooled relative risk 1.23, 95% confidence interval 1.06 to 1.43; $P=0.007$) and cardiovascular disease (1.14, 0.99 to 1.32; $P=0.07$), with no significant evidence of publication bias. For cardiovascular disease, sensitivity analysis showed that the exclusion of a single study led to a pooled estimate of 1.17 (1.02 to 1.34; $P=0.02$). The associations observed were greater the larger the difference in sodium intake and the longer the follow-up.

Conclusions High salt intake is associated with significantly increased risk of stroke and total cardiovascular disease. Because of imprecision in measurement of salt intake, these effect sizes are likely to be underestimated. These results support the role of a substantial population reduction in salt intake for the prevention of cardiovascular disease.

INTRODUCTION

During the past century, the evidence for the risks imposed on human health by excess salt consumption has become compelling. The causal relation between

habitual dietary salt intake and blood pressure has been established through experimental, epidemiological, migration, and intervention studies. Most adult populations around the world have average daily salt intakes higher than 6 g, and for many in eastern Europe and Asia higher than 12 g. International recommendations suggest that average population salt intake should be less than 5-6 g per day. Population based intervention studies and randomised controlled clinical trials have shown that it is possible to achieve significant reductions in blood pressure with reduced salt intake in people with and without hypertension.¹ Based on the effects of high salt intake on blood pressure and on the prominent role of high blood pressure in promoting cardiovascular diseases, it has been suggested that a population-wide reduction in salt intake could substantially reduce the incidence of cardiovascular disease.² On the basis of the results of a meta-analysis of randomised controlled trials of salt reduction,³ it was estimated that a reduction in habitual dietary salt intake of 6 g a day would be associated with reductions in systolic/diastolic blood pressure of 7/4 mm Hg in people with hypertension and 4/2 mm Hg in those without hypertension. At the population level these reductions in blood pressure could predict an average lower rate of 24% for stroke and 18% for coronary heart disease.⁴ Validation of these predictions by a randomised controlled trial of the effects of long term reduction in dietary salt on morbidity and mortality from cardiovascular disease would provide definite proof. At present, a study of this kind is not available and, in fact, it is extremely unlikely that it will ever be performed because of practical difficulties, the long duration required, and high costs. Nevertheless, prospective cohort studies performed in the past three decades that measured the levels of dietary salt intake at baseline and recorded the incidence of vascular events have provided important indirect evidence. Most of these studies found evidence of such relation, although few had enough power to attain statistical significance.

We performed a systematic review and meta-analysis of the prospective studies of habitual dietary salt intake and incidence of stroke and total cardiovascular

disease using strictly predetermined criteria for inclusion or exclusion. We assessed whether or not the overall evidence in prospective studies supports the presence of a relation between levels of dietary salt intake and both stroke and cardiovascular outcomes and calculated an estimate of the risk.

METHODS

Data sources and searches

We performed a systematic search for publications using Medline (1966-2008), Embase (from 1988), AMED (from 1985), CINAHL (from 1982), Psychinfo (from 1985), and the Cochrane Library. Search strategies used subject headings and key words with no language restrictions. Further information was retrieved through a manual search of references from recent reviews and relevant published original studies. We examined reference lists of the relevant reviews, identified studies, and reviewed the cited literature.⁵

Study selection

Two reviewers (LD and N-BK) independently extracted the data. Discrepancies about inclusion of studies and interpretation of data were resolved by arbitration (PS or FPC), and consensus was reached after discussion. In the case of missing data for potentially suitable studies, we contacted authors and asked them to provide the necessary information. To be included in the meta-analysis a published study had to be an original article published from January 1966 to December 2008, be a prospective population study, assess salt intake as baseline exposure, determine either stroke or total cardiovascular disease prospectively as the outcome, follow participants for at least three years, include an adult population, and indicate the number of participants exposed and the rate or number of events in different categories of salt intake.

Of the 3246 publications retrieved, we identified 15 studies that met the inclusion criteria. One was a duplicate analysis of a single cohort previously described by the same authors^{6,7} and another⁸ referred to the same cohort (national health and nutrition examination survey (NHANES) I) analysed by other authors with more stringent criteria.⁹ We therefore included 13 studies in the meta-analysis that provided suitable data on 19 population samples^{6,10-21} (tables 1 and 2).

Data extraction

From the identified studies and respective populations we recorded publication reference, total number of participants, country, sex, age (mean, median, or range), recruitment time, follow-up (years), outcome reported (stroke, cardiovascular disease) and method of outcome assessment, number (rate) of events, method of assessing salt intake, and level of salt intake in different categories.

Categorisation of salt intake differed among studies. Some reported the number of subjects exposed and the rate (number) of events across the distribution of salt intake; others reported differences in the event rate for a 100 mmol/day difference in sodium intake, as in the

studies by He et al⁹ and Tuomilehto et al.¹³ In the last two cases we used the relative risk or hazard ratio reported by the authors for the analysis. In all the cases in which categorisation of the study participants by level of salt intake was 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.

Statistical analysis

We evaluated the quality of the studies included in the meta-analysis with the Downs and Black score system.²¹ We extracted relative risks or hazard ratios from the selected publications and calculated their standard errors from the respective confidence intervals. The value from each study and the corresponding standard error were transformed into their natural logarithms to stabilise the variances and to normalise their distribution. The pooled relative risk (and 95% confidence interval) was estimated with a random effect model, weighting for the inverse of the variance.²² The heterogeneity among studies was tested by Q statistic and quantified by H statistic and I² statistic.²³ The influence of individual studies, from which the meta-analysis estimates are derived, was examined by omitting one study at a time to see the extent to which inferences depend on a particular study or group of studies (sensitivity analysis). Subgroup or meta-regression analyses were used to identify associations between risk of stroke or cardiovascular disease and relevant study characteristics (age and sex of participants, year of publication, duration of follow-up, method of assessment of sodium intake, difference in sodium level, control for baseline blood pressure) as possible sources of heterogeneity. We used funnel plot asymmetry to detect publication bias and applied Egger's regression test to measure any asymmetry.^{24,25} All statistical analyses were performed with MIX software version 1.7²⁶ and Stata software for meta-regression analysis.

RESULTS

Characteristics of the study cohorts

We included in the meta-analysis 13 studies reporting on 19 independent cohorts (table 1). There were 177 025 participants from six different countries (six studies from the United States, two each from Finland and Japan, one each from the Netherlands, Scotland, and Taiwan). Eleven studies recruited both male and female participants, while two studies included only men. Follow-up ranged from 3.5 to 19 years. Four studies reported only stroke events (either total stroke rate or stroke deaths), three only cardiovascular disease (total cardiovascular disease rate or cardiovascular disease deaths), and six reported both. Salt intake was assessed by 24 hour dietary recall (n=4), food frequency questionnaire (n=4), 24 hour urine excretion (n=4), and questionnaire (n=1). In total there were 5346 strokes reported and 5161 total cardiovascular disease events. Of the 11 studies that included both

Table 1 | Characteristics of prospective studies included in meta-analysis of studies on salt intake and stroke and cardiovascular disease (CVD)

Study	Age (years)	Sex	No of people	Outcome(s)	Outcome assessment	Sodium intake assessment	Study quality score
Kagan, 1985, US (Hawaii) ¹⁰	45-68	Men	7895	Total stroke	Physical examination for residual of stroke at baseline, 2 and 6 year follow-up; surveillance of hospital discharges and death certificates reviewed by neurologist	24h dietary recall	14
Hu, 1992, Taiwan ¹¹	≥36	Men and women	8562	Total stroke	Case finding through local hospital referrals and study nurses. Certification by computed tomography	Household survey questionnaire	12
Alderman, 1995, US, occupational ⁶	52; 54	Men; women	1900; 1037	Total CVD, total stroke	Review of hospital charts and death certificates (ICD-9): CVD I410, I430-I434, I436-I438; stroke as above without I410	24h urine collection	12
Tunstall-Pedoe, 1997, Scotland ¹²	40-59	Men; women	5754; 5875	Total CVD	Case notes requested for all hospital episodes of myocardial infarction and other emergency admission for coronary heart disease, then extracted and coded according to MONICA project criteria	24h urine collection	15
He, 1999, US, NHANES I ⁹	25-74	Men; women; non-overweight; overweight	3686; 5799; 6797; 2688	CVD death, total stroke, stroke death	Mortality based on death certificate reports. Incident stroke based on death certificate reports in which underlying cause of death was recorded with ICD-9 code (430-434.9, 436 or 437.0-437.1) or one or more hospital stays with discharges with one of these codes	24h dietary recall	17
Tuomilehto, 2001, Finland ¹³	25-64	Men; women	1173; 1263	CVD death, total stroke	National hospital discharge register ICD-8 and ICD-9, 430-438, and 390-448	24h urine collection	18
Nagata, 2004, Japan ¹⁴	≥35	Men; women	13 355; 15 724	Stroke death	National vital statistics ICD-9 430-448	FFQ	18
Cohen, 2006, US, NHANES II ¹⁵	30-74	Men and women	7154	CVD death, stroke death	Mortality based on death certificate reports ICD-9 430-438	24h dietary recall	18
Geleijnse, 2007, Netherlands ¹⁶	≥55	Men and women	1448	CVD death, total stroke	GPs registries (ICD-10): I20-I25, I46, I49, I50, I60-I67, I70-I74 and R96; I60-I67	FFQ and overnight urine sodium	15
Cook, 2007, US, TOHP I, USA, TOHP II ¹⁷	30-54; 30-54	Men and women; men and women	542; 1873	Total CVD	Notification of non-fatal outcomes in post-trial surveillance, review by physician plus National Death Index	24h urine collection	12
Larsson, 2008, Finland ¹⁸	50-69	Men (smokers)	26,556	Total stroke	Discharge diagnoses and death certificates (ICD-8, 9, and 10)	FFQ	15
Umesawa, 2008, Japan ¹⁹	40-79	Men; women	23 119; 35 611	CVD death, stroke death	National Vital Statistics ICD-9	FFQ 4×3 day dietary records	18
Cohen, 2008, US, NHANES III ²⁰	≥30	Men and women	8699	Total CVD	Vital status and cause of death (ICD-9 and ICD-10)	24h dietary recall	18

FFQ=food frequency questionnaire.

men and women, five reported outcomes separately.^{6,9,13-15} The TOHP study included two different cohorts (I and II)¹⁷ and the study by He and coworkers provided separate findings for men and women or, alternatively, for normal weight and overweight participants.⁹ Overall, data on the relation between salt consumption and stroke were available from 14 cohorts and on the relation between salt intake and cardiovascular disease from 14 cohorts.

The overall study quality, evaluated by the Downs and Black score, averaged 15.5 (range 12-18) on a scale of 19 (table 1).

Salt intake and risk of stroke

Table 2 provides data on the relation between salt intake and risk of stroke in each of the 14 cohorts included in our study. Figure 1 shows the results of the pooled analysis. In the pooled analysis, higher salt intake was associated with greater risk of stroke (relative risk 1.23, 95% confidence interval 1.06 to 1.43; $P=0.007$). There was significant heterogeneity between studies ($P=0.04$; $I^2=61\%$). The funnel plot did not show asymmetry, thus excluding publication bias (Egger's test $P=0.26$; see appendix on [bmj.com](http://www.bmj.com)). As shown in

figure 1 for the individual cohorts included in the analysis, we found a trend towards a direct association between salt intake and risk of stroke in nine cohorts, which was significant in four. We observed a non-significant inverse trend in three cohorts.

Sensitivity analysis showed that the pooled estimate of the effect of salt intake on risk of stroke did not vary substantially with the exclusion of any one study; in particular, the exclusion of the study by Umesawa et al,¹⁹ which accounted for about 40% of all participants in the meta-analysis and nearly 20% of all strokes, resulted in a pooled relative risk of 1.19 (1.03 to 1.39), $P=0.022$.

Salt intake and risk of cardiovascular disease

Table 2 provides data on the association between salt intake and the risk of cardiovascular disease in 14 cohorts. In the pooled analysis, there was an association between higher salt intake and risk of cardiovascular disease (1.14, 0.99 to 1.32; $P=0.07$) (fig 2). The heterogeneity between studies was significant ($P<0.01$; $I^2=80\%$), but the funnel plot did not show asymmetry, thus excluding publication bias (Egger's test: $P=0.39$; see appendix on [bmj.com](http://www.bmj.com)). The

Table 2 | Detailed outcome of studies on salt intake and stroke and cardiovascular disease (CVD)

Study	Comparison	All CVD		All stroke		Factors controlled for in multivariate analysis
		Events	RR (95% CI)	Events	RR (95% CI)	
Kagan, 1985 ¹⁰	Fifth (V v I)	—	—	238	0.92 (0.60 to 1.42)	Age
Hu, 1992 ¹¹	Salty food (yes v no)	—	—	104	1.79 (1.18 to 2.70)	Age
Alderman, 1995 ⁶	Quarter (IV v I) in men	96	0.37 (0.18 to 0.75)	17	0.59 (0.10 to 3.43)	Unadjusted
Alderman, 1995 ⁶	Quarter (IV v I) in women	21	2.29 (0.44 to 11.90)	6	2.10 (1.01 to 4.33)	
Tunstall-Pedoe, 1997 ¹²	Difference in men between fifths	404	1.05 (0.97 to 1.14)	—	—	Age
Tunstall-Pedoe, 1997 ¹²	Difference in women between fifths	177	1.16 (1.01 to 1.33)	—	—	
He, 1999 ⁹	Continuous variable (men, women)	895	1.67 (1.27 to 2.19), 1.54 (1.12 to 2.10)	—	—	Age, sex, race, SBP, cholesterol, BMI, diabetes, diuretic use, education, alcohol, smoking, total energy intake
He, 1999 ⁹	Continuous variable	—	—	430 overweight, 250 normal weight	0.99 (0.81 to 1.20), 1.39 (1.10 to 1.76)	
Tuomilehto, 2001 ¹³	Continuous variable (men)	72	1.38 (1.05 to 1.81)	43	1.00 (0.68 to 1.48)	Age, study year, smoking, total cholesterol, HDL cholesterol, SBP, BMI
Tuomilehto, 2001 ¹³	Continuous variable (women)	15	1.43 (0.74 to 2.79)	41	1.34 (0.87 to 2.06)	
Nagata, 2004 ¹⁴	Thirds (III v I) in men	—	—	137	2.34 (1.23 to 4.47)	Age, marital status, education, BMI, smoking, alcohol, exercise, hypertension, diabetes, intake of protein, total energy, vitamins K and E
Nagata, 2004 ¹⁴	Thirds (III v I) in women	—	—	132	1.70 (0.96 to 3.00)	
Cohen, 2006 ¹⁵	Above v below median sodium intake	541	0.88 (0.74 to 1.05)	79	0.56 (0.28 to 1.11)	Age, sex, race, smoking, alcohol, SBP, BMI, education, exercise, potassium and calories intake, diabetes, cholesterol, anti-hypertensive treatment.
Geleijnse, 2007 ¹⁶	Continuous variable	217	0.77 (0.60 to 0.99)	181	1.08 (0.81 to 1.45)	Age, sex, creatinine and potassium excretion, BMI, smoking, diabetes, diuretic use, education, energy intake, alcohol, calcium, saturated fat.
Cook I, 2007 ¹⁷	Habitual v reduced salt intake	49	2.53 (1.30 to 4.94)	—	—	Age, race, sex, weight loss, baseline weight, sodium excretion
Cook II, 2007 ¹⁷	Habitual v reduced salt intake	151	1.12 (0.78 to 1.59)	—	—	
Larsson, 2008 ¹⁸	Fifths (V v I)	—	—	2702	1.04 (0.93 to 1.17)	Age, supplementation group, smoking, BMI, SBP and DBP, total cholesterol, HDL cholesterol, diabetes, CHD, exercise, alcohol, energy intake
Umesawa, 2008 ¹⁹	Fifth (V v I)	2087	1.42 (1.19 to 1.69)	986	1.55 (1.20 to 2.00)	BMI, smoking, alcohol, hypertension, diabetes, menopause, hormone therapy, exercise, education, mental stress, calcium and potassium intake
Cohen, 2008 ²⁰	Continuous variable	436	0.88 (0.77 to 1.01)	—	—	Age, sex, race, education, added table salt, exercise, alcohol, smoking, diabetes, cancer, SBP, cholesterol, potassium intake, weight, anti-hypertensive treatment

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, HDL=high density lipoprotein, CHD=coronary heart disease.

evaluation of individual studies showed a trend towards a direct association between salt intake and risk of cardiovascular disease in 10 cohorts, with significantly higher relative risk in six. An inverse trend was observed in four cohorts and was significant in one. Sensitivity analysis showed that the exclusion of the only study showing a significant inverse trend⁶ led to a pooled estimate of relative risk of 1.17 (1.02 to 1.34), $P=0.02$ (fig 2). Further exclusion of the study by Umesawa et al,¹⁹ which accounted for over 50% of all participants and about 40% of all cardiovascular disease events led to a pooled relative risk of 1.14 (0.99 to 1.31), $P=0.06$.

Sources of heterogeneity

Age—Meta-regression analyses indicated no association between mean age of study participants and effect of sodium intake on the risk of stroke: $\exp(b)=1.01$

(0.99 to 1.03). Likewise, meta-regression showed no association between age and effect of sodium intake on the risk of cardiovascular disease: $\exp(b)=0.99$ (0.97 to 1.02).

Sex—Three studies reported data for men and women separately for incidence of stroke.^{6,13,14} The pooled estimates from these three studies were 1.30 (0.64 to 2.65; $P=0.47$) and 1.56 (1.14 to 2.13; $P<0.01$), respectively. Three studies reported data for men and women separately for incidence of cardiovascular disease.^{9,12,13} The pooled estimates were 1.31 (0.97 to 1.77; $P=0.08$) and 1.27 (1.05 to 1.55; $P=0.01$), respectively.

Method of assessment of sodium intake—In nine cohorts that used food frequency questionnaires or dietary recall for the evaluation of habitual sodium intake the pooled risk estimate for stroke was 1.25 (1.03 to 1.51; $P=0.02$).^{10-12,14,15,18,19} In five cohorts that used 24 hour

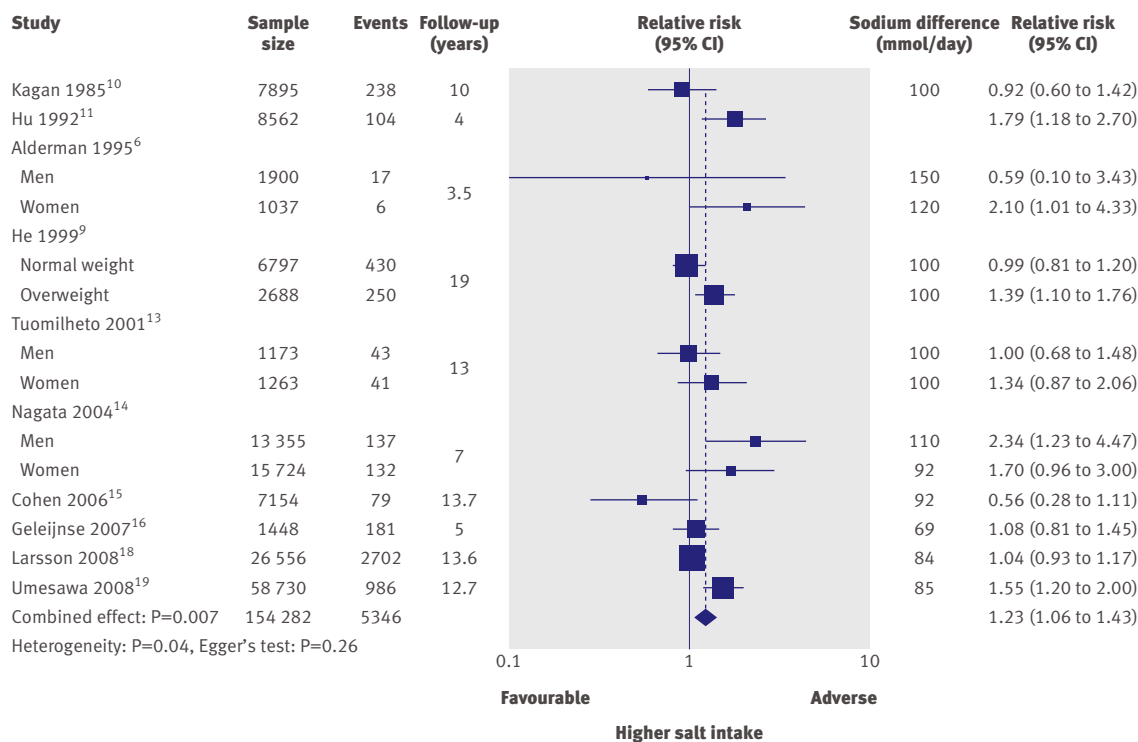


Fig 1 Risk of incident stroke associated with higher compared with lower salt intake in 14 population cohorts from 10 published prospective studies including 154 282 participants and 5346 events

urine collection the pooled risk estimate was 1.16 (0.94 to 1.44; P=0.17).^{6 13 16} In five cohorts that used food frequency questionnaires or dietary recall the pooled estimate for cardiovascular disease was 1.21 (0.92 to 1.59; P=0.17),^{9 15 19 20} and in nine cohorts that used 24 hour urine collection the pooled risk estimate for cardiovascular disease was 1.10 (0.92 to 1.31; P=0.32).^{6 12 13 16 17}

Baseline blood pressure or hypertension status—In the studies that provided relative risk estimates adjusted for baseline blood pressure or hypertension status, the pooled relative risk was 1.22 (1.02 to 1.45; P=0.03) for stroke (nine cohorts) and 1.25 (0.99 to 1.57; P=0.06) for cardiovascular disease (seven cohorts).

Baseline body mass index (BMI) or body weight—In the studies that provided relative risk estimates adjusted for baseline BMI or body weight, the pooled relative risk was 1.20 (1.02 to 1.40; P=0.02) for stroke (10 cohorts) and 1.22 (1.00 to 1.49; P=0.05) for cardiovascular disease (10 cohorts).

Length of follow-up—Meta-regression analysis showed a significant association between duration of follow-up and the effect of sodium on the risk of stroke. The log relative risk was estimated to increase by 0.07 per increase of one year of follow-up: $\exp(b)=1.07$ (1.04 to 1.10). The estimated variance between studies (heterogeneity) was reduced from 0.05 to 0.02. In contrast, however, we found no association between duration of follow-up and effect of sodium on the risk of cardiovascular disease: $\exp(b)=0.98$ (0.95 to 1.02).

Dose-response analysis—Variance weighted least squares regression of the risk of stroke on the study

specific difference between higher and lower categories of sodium intake (differences in sodium intake values reported in table 2) provided evidence of a significant direct association ($\exp(b)=1.06$ (1.03 to 1.10)), indicating a 6% increase in the rate of stroke for every 50 mmol/day difference in sodium intake. There was a similar trend for the risk of cardiovascular disease ($\exp(b)=1.19$ (0.69 to 2.07)), that was not significant.

Time trend (year of publication)—Starting with the first published study¹⁰ we calculated the cumulative pooled relative risk by stepwise addition of the results of the other available studies up to the last one published in July 2008.¹⁹ Figure 3 shows the results of these cumulative meta-analyses. The pooled relative risk for stroke stabilised early in the 1.20-1.30 interval and achieved significance starting in 2001. Similar results were obtained in the analysis of cardiovascular disease, for which the pooled relative risk estimate also stabilised early and close to the final value, achieving significance starting in 1999.

DISCUSSION

This meta-analysis shows unequivocally that higher salt intake is associated with a greater incidence of strokes and total cardiovascular events. Our systematic review identified 13 relevant and suitable studies published from 1996 to 2008. These studies provided evidence from 170 000 people contributing overall more than 10 000 vascular events.

Cardiovascular diseases are the major cause of death among people aged over 60 and second among those aged 15-59. According to the World Health

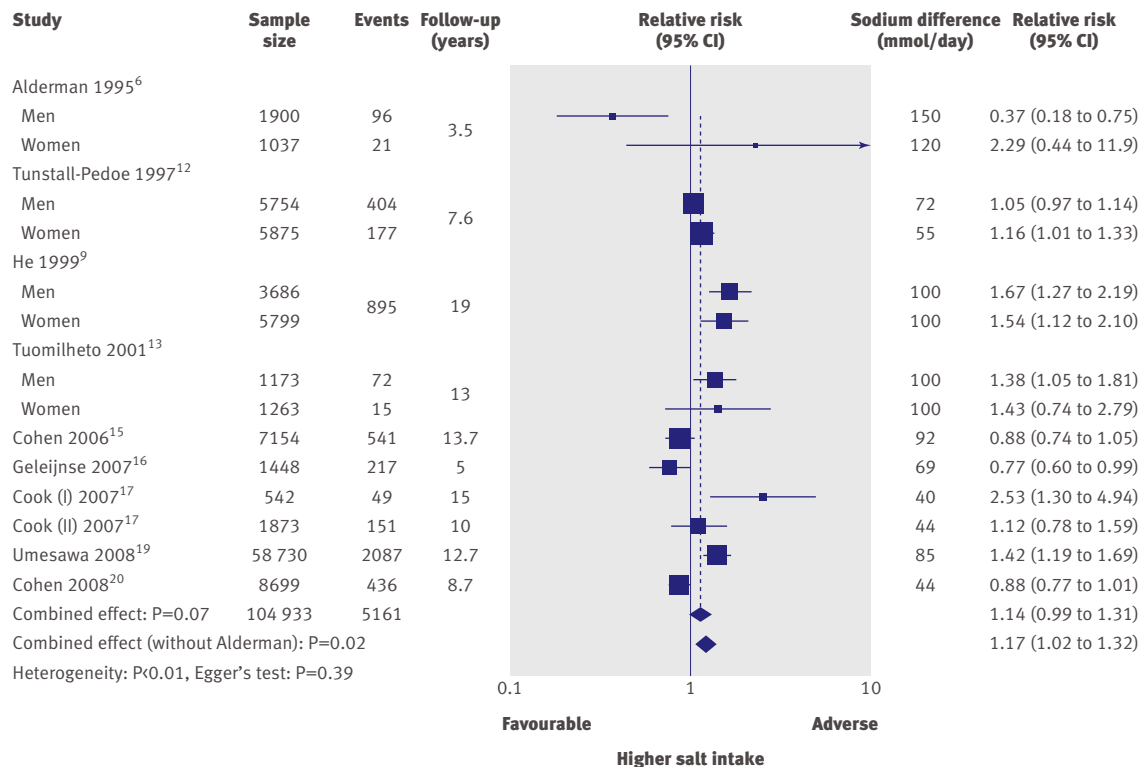


Fig 2 | Risk of incident cardiovascular disease associated with higher compared with lower salt intake in 14 population cohorts from nine published prospective studies including 104 132 participants and 5161 events. Pooled analysis after the exclusion of the study by Alderman et al⁶ (men and women), including 102 086 participants and 5044 events

Organization, 62% of all strokes and 49% of coronary heart disease events are attributable to high blood pressure.²⁷ The direct causal relation between levels of dietary salt intake and blood pressure at the population level has also been recognised.^{1,28,29} Given the graded causal relation between blood pressure and cardiovascular disease, beginning at around 115 mm Hg systolic pressure,³⁰ it is reasonable to expect considerable benefit on the rate of cardiovascular disease from a reduction in salt intake.

Association between salt intake, stroke, and cardiovascular disease

The results of this meta-analysis provide evidence of a direct association between high dietary salt intake and risk of stroke. Despite the considerable heterogeneity between the 14 cohorts available for the analysis, the results are strengthened by the lack of major publication bias and by the observation of a significant association in four individual cohorts included in the analysis, whereas in none was an inverse statistical association apparent. The pooled relative risk indicates a 23% greater risk of stroke for an average difference in sodium intake (weighted for the population size of each study) of 86 mmol (equivalent to about 5 g of salt a day). Sensitivity analysis with the exclusion of a single study, on the basis of its particular weight with regard to both number of participants and events, only moderately reduced the difference in risk (from 23% to 19%), which remained significant.

Likewise, the pooled analysis of the 12 cohorts for which data on cardiovascular disease outcome were available (after the exclusion of a single outlier) showed a direct association between higher salt intake and risk of cardiovascular disease, with a pooled relative risk of 1.17.⁴ A trend in this direction occurred in as many as nine of the 12 cohorts and was significant in six. There was an inverse trend in three cohorts.^{15,16,20} The study by Alderman et al,⁶ showing a relative risk in men of 0.37, has been challenged because of the low number of events recorded and several methodological inadequacies, the most important being the evaluation of habitual salt consumption on the basis of 24 hour urine collection obtained shortly after the study participants had been instructed to reduce their usual level of sodium intake.³¹ The results of sensitivity analysis indicate that the exclusion of this single study from our meta-analysis strengthens the estimate. The additional exclusion of a large Japanese cohort providing a high proportion of participants and events overall¹⁹ only slightly reduced the pooled relative risk estimate (from 1.17 to 1.14) and the level of significance (to 0.06).

Evaluation of main sources of heterogeneity

We used subgroup and meta-regression analyses to assess the influence of several factors on the association between habitual sodium intake and risk of stroke or cardiovascular disease. For both stroke and cardiovascular disease outcomes, separate analyses of the

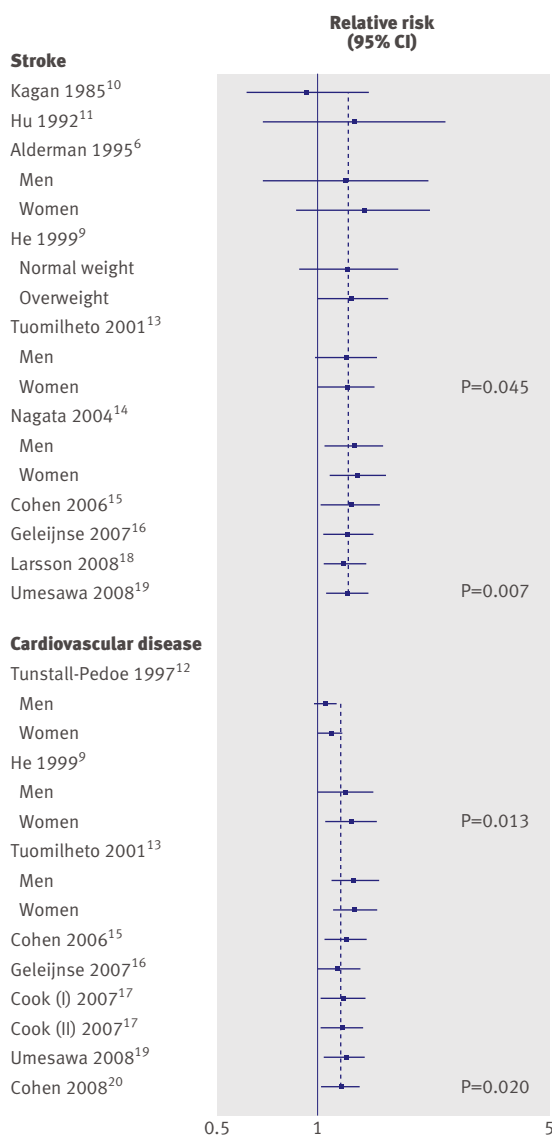


Fig 3 | Cumulative meta-analysis. Evaluation of time trends (year of publication) in relation between habitual sodium intake and risk of stroke or cardiovascular disease

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 habitual sodium intake used in the various studies.

Eight studies provided data adjusted for baseline blood pressure or hypertension status. Separate evaluations of these studies provided relative risk estimates for both stroke and cardiovascular disease similar to those obtained for the total number of studies included in the meta-analysis. This finding seems at variance with the hypothesis that the effect of salt on cardiovascular risk is substantially mediated by its unfavourable action on blood pressure. Adjustment for baseline blood pressure or hypertension status only partially corrects for the overall influence of blood pressure on the study results in as much as it

does not account for changes in blood pressure occurring during the observation period, a problem more relevant the longer the follow-up period. Part of the association observed, however, might be mediated by factors other than blood pressure, and there is evidence in the literature of deleterious effects of high salt intake on left ventricular mass,³²⁻³⁴ arterial stiffness,³⁵ and renal function,³⁶⁻³⁷ which are not totally explained by its effect on blood pressure.

Overweight and obesity are often associated with high blood pressure and are causally involved in the development of hypertension.³⁸ Nine out of 13 studies included in the meta-analysis provided relative risk estimates adjusted for BMI or body weight at entry into the study.⁹⁻¹⁴⁻²¹ Therefore, as for blood pressure, the association between habitual sodium intake and risk of stroke and cardiovascular disease seems partly independent from the influence of excess body weight. Two studies, however, reported a significant interaction between overweight and habitual sodium intake on the risk of cardiovascular events.⁹⁻¹³ This finding is consistent with the description of alterations in renal tubular sodium handling in obese individuals, making them particularly sensitive to the effects of high salt intake.³⁹

Study limitations

The studies included in our meta-analysis were heterogeneous regarding sample size, number of events, and duration of follow-up, with a few cohorts having small numbers. In the calculation of the pooled relative risk we weighted the results of the individual studies for sample size but did not account for the duration of follow-up. Our meta-regression analysis indicated that the longer the follow-up the greater the effect of habitual sodium intake on the risk of stroke but not, apparently, on the risk of total cardiovascular events. Possible explanations for this discrepancy are the higher mean age at occurrence of stroke, which would increase the chances of an event the longer the follow-up, and the closer relation of high blood pressure to stroke compared with other types of vascular events.

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

Categorisation of salt intake was also heterogeneous: some studies stratified the population by categories of sodium intake and compared cardiovascular outcomes across categories, other studies gave a difference in outcome for a given difference (for example, 100 mmol/24 h) in sodium intake or excretion. To standardise our comparison between higher and lower salt consumption we sought to refer to a difference as close as possible to 100 mmol or 6 g a day

WHAT IS ALREADY KNOWN ON THIS TOPIC

Experimental, epidemiological, migration, and intervention studies have shown a causal relation between habitual dietary salt intake and blood pressure

Population based intervention studies and meta-analyses of randomised controlled trials have shown that it is possible to achieve significant reductions in blood pressure with reduced salt intake in both hypertensive and normotensive individuals

WHAT THIS STUDY ADDS

Higher salt intake is associated with significantly greater incidence of strokes and total cardiovascular events, with a dose dependent association

A difference of 5 g a day in habitual salt intake is associated with a 23% difference in the rate of stroke and 17% difference in the rate of total cardiovascular disease

Each year a 5 g reduction in daily salt intake at the population level could avert some one and a quarter million deaths from stroke and almost three million deaths from cardiovascular disease worldwide

between high and low salt intake. Nevertheless, there remained appreciable differences in this respect between studies. We tried to overcome the problem with meta-regression analysis, which provided evidence of a highly significant dose-response relation between the difference in sodium intake and the increase in risk of both stroke and cardiovascular disease.

Implications

The habitual salt intake in most Western countries is close to 10 g a day (and much higher in many Eastern European and Asian countries), and we calculated that the average difference between higher and lower salt intake across the study cohorts included in our meta-analysis was 5 g a day. Given this approach, we believe that, despite the inherent inaccuracies, the results of our meta-analysis are applicable to real life conditions. A reduction of 5 g (about one teaspoon) of salt would bring consumption close to the WHO recommended level (5 g a day at the population level).

According to a recent report of the World Heart Federation there are over 5.5 million deaths a year from stroke throughout the world and close to 17.5 million deaths a year from cardiovascular disease.⁴⁰ Given that the case fatality rates for stroke is estimated at one in three and those for total cardiovascular disease at one in five, a 23% reduction in the rate of stroke and a 17% overall reduction in the rate of cardiovascular disease attributable to a reduction in population salt intake could avert some one and a quarter million deaths from stroke and almost three million deaths from cardiovascular disease each year. Many studies have also shown that a reduction in salt intake is cost effective,⁴¹⁻⁴³ arguing for the more widespread introduction of national programmes to reduce dietary salt consumption. In recent years, a few countries have made some progress towards reduction of habitual salt intake through a voluntary approach¹ or by regulation, as in Finland,⁴² but levels of salt consumption are still far from the WHO recommended targets. There are many reasons for these delays. One barrier to a

more effective implementation of public health policies has been the historical opposition of the food industry,⁴⁴ based on the arguments that the available evidence does not show significant benefits on hard end points at a population level from a moderate reduction in salt intake. Our study now clearly addresses those doubts. Some progress has been made in the past few years by closer collaboration between governments, public health bodies, and some sectors of the industry on a “voluntary” basis, as in the UK, with the reformulation of many food items towards a lower salt content and proposals of improved labelling. These efforts have led to a reduction of 0.9 g a day (or about 10%) in population salt intake in four years (from 9.5 to 8.6 g a day), still far from the recommended 6 g a day initial targets that were set in the UK. While the voluntary approach is the preferred choice for many governments, the “regulatory” approach has advantages,⁴⁵ sometimes being the most efficient, effective, and cost effective way of achieving public health targets.⁴¹⁻⁴³ For population salt intake to approach the recommended targets within a reasonable time frame, an “upstream” approach is now necessary alongside the traditional “downstream” public health approach based on health promotion and behavioural changes.

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- 1 He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens* 2009;23:363-84.
- 2 World Health Organization. Reducing salt intake in populations: report of a WHO forum and technical meeting. WHO, 2007:1-60.
- 3 He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens* 2002;16:761-70.
- 4 He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003;42:1093-9.
- 5 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999;354:1896-900.
- 6 Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;25:1144-52.
- 7 Alderman MH, Sealey JE, Cohen H, Madhavan S and Laragh JH. Urinary sodium excretion and myocardial infarction in hypertensive patients: a prospective cohort study. *Am J Clin Nutr* 1997;65(suppl):682-6S.
- 8 Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the national health and nutrition examination survey (NHANES I). *Lancet* 1998;351:781-5.
- 9 He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA* 1999;282:2027-34.
- 10 Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke* 1985;16:390-6.

- 11 Hu HH, Sheng WY, Chu FL, Lan CF, Chiang BN. Incidence of stroke in Taiwan. *Stroke* 1992;23:1237-41.
- 12 Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. *BMJ* 1997;315:722-9.
- 13 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.
- 14 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.
- 15 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 e7-14.
- 16 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.
- 17 Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007;333:885-8.
- 18 Larsson SC, Virtanen MJ, Mars M, Mannisto 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.
- 19 Umehara 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.
- 20 Cohen HW, Hailpern SM, Alderman MH. Sodium intake and mortality follow-up in the third national health and nutrition examination survey (NHANES III). *J Gen Intern Med* 2008;23:1297-302.
- 21 Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84.
- 22 Dersimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- 23 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 24 Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
- 25 Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000;320:1574-7.
- 26 Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. *BMC Med Res Methodol* 2006;6:50.
- 27 World Health Organization. The world health report 2002—reducing risks promoting healthy life. WHO, 2002.
- 28 Scientific Advisory Committee on Nutrition. Salt and health. Stationery Office, 2003:1-134.
- 29 World Health Organization. Reducing salt intake in populations. Report of a WHO forum and technical meeting. WHO, 2007:1-60.
- 30 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-13.
- 31 Karppanen H, Mervaala E. Sodium intake and mortality. *Lancet* 1998;351:1509.
- 32 Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994;89:1041-50.
- 33 Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake. A determinant of cardiac involvement in essential hypertension. *Circulation* 1988;78:951-6.
- 34 Du Calair G, Ribstein J, Daures JP, Mimran A. Sodium and left ventricular mass in untreated hypertensive and normotensive subjects. *Am J Physiol* 1992;263:H177-81.
- 35 Avolio AP, Clyde KM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. *Arteriosclerosis* 1986;6:166-9.
- 36 Du Calair G, Ribstein J, Mimran A. Dietary sodium and target organ damage in essential hypertension. *Am J Hypertens* 2002;15:222-9.
- 37 Verhave JC, Hillege HL, Burgerhof JG, Janssen WM, Gansevoort RT, Navis GJ, et al. Sodium intake affects urinary albumin excretion especially in overweight subjects. *J Intern Med* 2004;256:324-30.
- 38 National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res* 1998;(suppl 2):51-209S.
- 39 Strazzullo P, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinero E, et al. Altered renal sodium handling in men with abdominal adiposity and insulin resistance: a link to hypertension. *J Hypertens* 2001;19:2157-64.
- 40 World Health Organization. *The world health report 2004—changing history*. WHO, 2004.
- 41 Selmer RM, Kristiansen IS, Haglerod A, Graff-Iversen S, Larson HK, Meyer HE, et al. Cost and health consequences of reducing the population intake of salt. *J Epidemiol Community Health* 2000;54:697-702.
- 42 Murray CJ, Lauer JA, Hutubessy RC, Niessen L, Tomijima N, Rodgers A, et al. Effectiveness and costs of interventions to lower systolic blood pressure and cholesterol: a global and regional analysis on reduction of cardiovascular-disease risk. *Lancet* 2003;361:717-25.
- 43 Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet* 2007;370:2044-53.
- 44 Godlee F. The food industry fights for salt. *BMJ* 1996;312:1239-40.
- 45 Cappuccio FP. Salt and cardiovascular disease. *BMJ* 2007;334:859-60.

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