Sodium Intake and Risk of Death From Stroke in Japanese Men and Women

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Background and Purpose—Despite the evidence for a positive association of dietary salt and blood pressure, the few prospective studies that have assessed the association between dietary salt and stroke have reported inconsistent results. The purpose of this study was to examine the relation between sodium intake and death from stroke in a population-based cohort of Japanese men and women.

Methods—In 1992, usual diet including sodium intake was determined in 13 355 men and 15 724 women in Takayama City, Gifu, with the use of a validated food frequency questionnaire.

Results—There were 269 stroke deaths (137 men and 132 women) between baseline and 1999. In men, the highest compared with the lowest tertile of sodium intake was significantly positively associated with death from total stroke after controlling for covariates (hazard ratio [HR]), 2.33; 95% CI, 1.23 to 4.45). Significantly positive associations were also observed between sodium intake and death from ischemic stroke (HR, 3.22; 95% CI, 1.22 to 8.53) as well as death from intracerebral hemorrhage (HR, 3.85; 95% CI, 1.16 to 12.7). A positive association between sodium intake and death from stroke in women was suggested, although the associations for total stroke and ischemic stroke were of borderline significance (HR, 1.70; 95% CI, 0.96 to 3.02 and HR, 2.10; 95% CI, 0.96 to 4.62, respectively).

Conclusions—These prospective data support the hypothesis that dietary salt increases the risk of death from stroke. **(*Stroke*. 2004;35:1543-1547.)**

Key Words: diet ■ sodium ■ stroke ■ epidemiology

Several epidemiological and clinical studies have demonstrated that a low or reduced intake of salt is associated with lower blood pressure.[1] Because blood pressure is a major contributor to stroke, it would be reasonable to expect that dietary salt could increase the risk of stroke. Etiological studies investigating the relation between salt intake and stroke have generally produced positive associations.[2,3] There has been a suggestion that high salt intake may exert an adverse effect on the risk of stroke independent of blood pressure.[4] However, data from prospective cohort studies on salt intake and stroke are few and the results have been inconsistent.[5–7] To further evaluate the potential effect of salt intake on stroke, we examined the association of sodium intake with death from stroke in a cohort study of Japanese men and women (the Takayama Study).

Subjects and Methods

The Takayama Study is a population-based cohort study conducted in Takayama City, Gifu, Japan. The methodology of the study design has been described previously.[8] Eligible participants were all the nonhospitalized residents of Takayama, aged 35 years and older. In 1992, 14 427 men and 17 125 women completed a baseline self-administered questionnaire that included questions on demographic characteristics, smoking and drinking habits, diet, exercise, and medical and reproductive histories, yielding a participation rate of 85.3% after excluding incomplete or unreliable responses to the dietary questionnaire (criteria shown in [8]). Dietary history was assessed using a 169-item semiquantitative food frequency questionnaire. For each food, participants were asked to indicate the average frequency with which food was consumed in the previous year and specified the usual serving size. Use of table salt was also asked. Intake of sodium and other foods and nutrients were estimated from frequency of intake and portion size using the *Standard Tables of Food Composition in Japan*, published by the Science and Technology Agency of Japan.[9] The validity of this questionnaire was assessed by comparison with other dietary assessment methods, including 3-day diet record, 4 diet recalls over 1 year, and 12 daily diet records over 1 year. Detailed information on the questionnaire, including validity and reproducibility tests, has been described elsewhere.[10] However, we subsequently revised our method of estimating sodium intake based on the use of seasonings. We included independent items for use of soy sauce, sauce, vinegar, and ketchup in the questionnaire, but the use of these seasonings had been also taken account of when we estimated nutrient intakes from dishes and menus. Therefore, such an overlap was corrected. The validity test results were updated according to the revision of the Japanese food composition data. The Spearman correlation coefficients comparing the estimates of sodium intake between the questionnaire and 12 daily diet records over 1 year were 0.53 in men and 0.54 in women. Corresponding figures for total energy, protein, vitamin E, and potassium were 0.45, 0.47, 0.44, and 0.50, respectively, in men and 0.53, 0.54, 0.36, and 0.67, respectively, in women.

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TABLE 1. Baseline Characteristics of Study Subjects According to Tertile of Sodium Intake

	Men Tertile of Sodium Intake*				Women Tertile of Sodium Intake			
Basic Characteristics	Low	Middle	High	*P*	Low	Middle	High	*P*
Sodium intake, mg/d	4082	5699	7194	<0.001	3970	5180	6478	<0.001
Age, y	51.0	53.2	57.7	<0.001	53.3	54.3	57.8	<0.001
Body mass index, kg/m^2	22.6	22.5	22.5	0.08	21.9	22.0	22.1	0.003
Alcohol intake, mL/day	50.2	42.1	33.6	<0.001	9.7	7.9	5.6	<0.001
Exercise, METs† h/wk	28.0	27.2	25.9	0.02	18.0	19.7	18.8	0.15
Energy intake, kJ/d	10 703	11 230	10 836	0.41	8954	8954	8753	0.009
Protein intake, g/d	79.3	96.1	104.4	<0.001	73.7	82.3	88.7	<0.001
Vitamin E intake, mg/d	8.4	11.0	13.0	<0.001	8.7	10.7	12.2	<0.001
Potassium intake, mg/d	2756	3507	4217	<0.001	2817	3377	4061	<0.001
Married, %	90.5	92.1	91.8	0.02	75.1	75.9	74.6	0.32
Years of education ≥15 y, %	10.7	11.9	11.9	<0.001	4.6	5.4	4.1	<0.001
Current smokers, %	59.2	55.4	50.4	<0.001	16.0	12.7	10.6	<0.001
Former smokers, %	25.1	28.4	31.2	<0.001	4.6	4.2	4.3	0.35
Hypertension, %	17.6	18.1	21.0	<0.001	15.8	17.0	19.3	<0.001
Diabetes, %	4.6	5.5	7.7	<0.001	2.0	2.5	3.6	<0.001

Values are means (crude) or percentages. *P* values are for linear trend for continuous variables.
*Based on energy-adjusted value.
†Metabolic equivalent.

Exercise was assessed by asking the average hours per week spent performing various kinds of activities during the past year. The details are described elsewhere.[11]

Registration of death is required under the Family Registration Law in Japan and is implemented throughout the country. Deaths and their causes occurring in Takayama City during the follow-up period (1992 to 1999) were confirmed with data from National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare obtains information on deaths and codes the causes of death using the International Classification of Diseases (ICD). The specified endpoint of this study was death from stroke (ICD-9 codes 430 to 448 and ICD-10 codes I60-I69). Stroke was classified as subarachnoid hemorrhage (ICD-9 codes 430 and ICD-10 codes I60 and I69.0), intracerebral hemorrhage (ICD-9 codes 431 and ICD-10 codes I61 and I69.1), ischemic strokes (ICD-9 codes 434 and ICD-10 codes I63 and I69.3), and stroke of undetermined type. Permission to review the data regarding dates and causes of deaths was obtained from the Management and Coordination Agency, Japan. Information concerning subjects who moved away from Takayama City during the course of the study was obtained from the residential registers. During the study period, 666 (4.6%) men and 506 (3.0%) women moved out of Takayama City. This study was approved by the local institutional review board.

For this analysis, we excluded subjects who reported having stroke (255 men and 154 women), ischemic heart disease (636 men and 707 women), or cancer (181 men and 540 women). Hence, the analytic population at baseline consisted of 29 099 (13 355 men and 15 724 women).

The associations of sodium intake with death from stroke were examined using Cox proportional hazard models. For each subject, person-years of follow-up were calculated from the study entry (September 1, 1992) to the date of death from stroke and any other cause, the date on which the person moved out of Takayama City, or the end of the study (December 31, 1999), whichever came first. Intakes of foods and nutrients including sodium were adjusted for total energy after log-transformation by using the residual method proposed by Willett.[12] Energy-adjusted sodium intake were categorized by tertile based on the distribution among the study population at baseline. The hazard ratios (HRs) and their 95% CIs for death from stroke for each category of sodium intake were computed in comparison with the lowest intake category. Selection of potential confounders was based primarily on priori consideration of their association with both sodium intake and stroke as well as the change in risk estimates before and after adjustment. Variables adjusted for in the multivariate included age, level of education, marital status, body mass index, smoking status, alcohol consumption, histories of diabetes and hypertension, and energy-adjusted intake of protein, potassium, and vitamin E. Additional adjustment for menopausal status, use of aspirin or hormone replacement therapy, and other dietary intakes such as fat, fish oil, soy, dietary fiber, folate, calcium, carotene, vitamins B6, B12, and C, which have been reported to be associated with risk of stroke, did not substantially alter the results; therefore, these variables were not included in the final model. Statistic testing for linear trend was performed on continuous variables using the median value of the categories. All the statistical analyses were performed using SAS programs.[13] Because early symptoms related to stroke could result in change in dietary habits, we repeated the analyses described after excluding deaths from stroke (n=24 in men and n=36 in women) occurring during the first 2 years of follow-up.

Results

Baseline characteristics of the study population according to levels of sodium intake are given in Table 1. Participants with the highest intake of sodium tended to be older, less likely to be smokers, more likely to consume the nutrients listed, and more likely to have hypertension and diabetes.

A total of 269 cohort members (137 men and 132 women) died from stroke during the 7-year follow-up. These strokes included 43 subarachnoid hemorrhages, 59 intracerebral hemorrhages, and 137 ischemic strokes. Table 2 shows the HRs of total stroke and subtypes of stroke according to sodium intake. In men, sodium intake had a marginally significant positive association with death from total stroke after controlling for nondietary variables. However, after additional adjustment for dietary variables, this association attained

TABLE 2. Hazard Ratios and 95% Confidence Intervals of Mortality From Total Stroke and Subtype According to Sodium Intake

	Men Tertile of Sodium Intake*			*P* Trend	Women Tertile of Sodium Intake			*P* Trend
	Low	Middle	High		Low	Middle	High	
Median intake,* mg/d	4070	5209	6613		3799	4801	5930	
N of person-years	30 670	30 779	29 587		36 719	36 874	36 530	
Total stroke, N of deaths	23	40	74		40	39	53	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.23 (0.74–2.06)	1.45 (0.90–2.33)	0.12	1.00	0.94 (0.61–1.46)	0.94 (0.62–1.42)	0.77
Adjusted for nondietary variables†	1.00	1.33 (0.78–2.19)	1.58 (0.97–2.55)	0.06	1.00	0.99 (0.64–1.55)	1.00 (0.66–1.51)	0.99
Multivariate adjusted‡	1.00	1.60 (0.92–2.80)	2.33 (1.23–4.45)	0.009	1.00	1.33 (0.80–2.21)	1.70 (0.96–3.02)	0.07
Hemorrhagic stroke, N of deaths	13	19	23		16	15	16	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.25 (0.62–2.54)	1.24 (0.62–2.50)	0.57	1.00	0.88 (0.44–1.78)	0.75 (0.37–1.49)	0.41
Adjusted for nondietary variables†	1.00	1.31 (0.65–2.67)	1.32 (0.65–2.69)	0.46	1.00	0.95 (0.47–1.66)	0.82 (0.41–1.66)	0.58
Multivariate adjusted‡	1.00	1.76 (0.79–3.91)	2.27 (0.85–6.02)	0.11	1.00	1.25 (0.56–2.82)	1.28 (0.49–3.37)	0.62
Subarachnoid hemorrhage, N of deaths	5	6	6		9	8	9	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.06 (0.32–3.51)	0.92 (0.27–3.12)	0.88	1.00	0.85 (0.33–2.20)	0.84 (0.33–2.14)	0.72
Adjusted for nondietary variables†	1.00	1.10 (0.34–3.64)	0.94 (0.28–3.20)	0.91	1.00	0.97 (0.37–2.53)	0.95 (0.37–2.44)	0.92
Multivariate-adjusted‡	1.00	1.01 (0.27–3.82)	0.77 (0.14–4.27)	0.76	1.00	1.39 (0.47–4.13)	1.73 (0.48–6.27)	0.40
Intracerebral hemorrhage, N of deaths	8	13	17		7	7	7	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.37 (0.57–3.32)	1.44 (0.61–3.40)	0.43	1.00	0.98 (0.34–2.78)	0.71 (0.25–2.01)	0.51
Adjusted for nondietary variables†	1.00	1.47 (0.61–3.58)	1.59 (0.66–3.83)	0.31	1.00	0.99 (0.34–2.83)	0.71 (0.25–2.03)	0.51
Multivariate-adjusted‡	1.00	2.41 (0.89–6.56)	3.85 (1.16–12.7)	0.03	1.00	1.21 (0.36–4.05)	0.92 (0.22–3.89)	0.89
Ischemic stroke, N of deaths	8	19	43		21	15	31	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.49 (0.65–3.41)	1.86 (0.87–3.99)	0.10	1.00	0.72 (0.37–1.39)	1.06 (0.61–1.84)	0.77
Adjusted for nondietary variables†	1.00	1.67 (0.73–3.83)	2.06 (0.96–4.45)	0.06	1.00	0.76(0.39–1.48)	1.10 (0.63–1.93)	0.68
Multivariate-adjusted‡	1.00	2.07 (0.86–5.00)	3.22 (1.22–8.53)	0.02	1.00	1.09 (0.51–2.32)	2.10 (0.96–4.62)	0.05

*Adjusted for total energy.

†Adjusted for age, total energy, marital status, years of education, body mass index, smoking status, alcohol intake, exercise, and histories of hypertension and diabetes.

‡Adjusted for age, total energy, marital status, years of education, body mass index, smoking status, alcohol intake, exercise, histories of hypertension and diabetes, and intake of protein, potassium, and vitamin E.

HR indicates hazard ratio; CI, confidence interval.

statistical significance. Sodium intake was also significantly positively associated with intracerebral hemorrhage and ischemic stroke. In the multivariate models, protein intake contributed greatly as a confounder; after controlling for nondietary variable and protein intake, the HRs of total stroke, intracerebral hemorrhage, and ischemic stroke for the highest tertile of sodium intake were 2.26 (95% CI, 1.25 to 4.08), 3.62 (95% CI, 1.21 to 10.8), and 2.80 (95% CI, 1.14 to 6.91), respectively.

In women, the associations of sodium intake with total stroke and ischemic stroke were of borderline significance after controlling for dietary variables. Actually, adjustment for potassium intake had great impacts on HR estimates; after controlling for nondietary variable and potassium intake, the HRs of total stroke and ischemic stroke for the highest tertile of sodium intake were 1.69 (95% CI, 0.98 to 2.91) and 2.19 (95% CI, 1.04 to 4.61), respectively.

Obese persons are thought to be more sensitive to the effects of sodium on blood pressure than nonobese persons.[14] Reanalyses restricting the subjects to those with a body mass index of ≥23 revealed that the associations were somewhat strengthened; the HRs of total stroke for the highest tertile of sodium intake were 4.84 (95% CI, 1.10 to 21.3, $P=0.04$ for trend) in men and 2.26 (95% CI, 0.67 to 7.57, $P=0.17$ for trend) in women after controlling for the covariates.

We repeated the analyses after excluding the deaths from stroke that occurred during the first 2 years. The results were similar in men (for the highest compared with the lowest tertile of sodium intake, HR, 2.40; 95% CI, 1.16 to 4.94; $P=0.02$ for trend). In women, somewhat strengthened asso-

ciation of sodium intake with total stroke (HR, 1.98; 95% CI, 1.02 to 3.84, $P=0.04$ for trend) was observed.

Discussion

We found a 2.4-fold increased risk of death from stroke associated with high sodium intake in men. In women, the association of sodium intake with stroke mortality was weaker and of marginal significance. Considering that the exclusion of cases during the first 2 years strengthened the HRs in women, the observed weaker association in women may be partially explained by the fact that women were more likely to have reduced sodium intake than men because of early symptoms leading to stroke death. Sodium intake was significantly positively associated with death from 2 major types of stroke, intracerebral hemorrhage and ischemic stroke in men. However, there was no association between sodium intake and intracerebral hemorrhage in women. The discrepancy for our findings between men and women may be caused by the difference in distributions of subtypes of intracerebral hemorrhage and ischemic stroke. Intracerebral hemorrhage and ischemic stroke are heterogenous stroke types and their etiopathologies are poorly understood.[15] The subtypes of each major type may have different etiologies. Although we could not obtain information concerning subtype, recent brain and vessel imaging techniques have prompted a need for a reevaluation of the standard procedure for defining subtypes of stroke.[16] The small number of cases in the present study also precluded drawing conclusions concerning dietary sodium and type of stroke.

To our knowledge, there have been 3 prospective studies of dietary sodium in relation to the risk of stroke.[5–7] The present study is the first prospective investigation of this topic in the Japanese population living in Japan. The strengths of the present study include the prospective design, use of a general population, relatively low proportion of loss of follow-up, and adjustment for various potential confounders.

A significantly positive association between sodium intake and stroke was reported in overweight adults in the US (relative risk [RR], 2.2 for the highest quintile of sodium-to-energy ratio).[6] However, the remaining 2 studies found no significant positive association. In a cohort of people of Japanese ancestry living in Hawaii, no relation was found between sodium intake and stroke incidence.[5] In a study of Finnish men and women, urinary sodium excretion was significantly positively associated with mortality from cardiovascular disease but not with mortality from stroke (RR=1.3 in men).[7] In another prospective study that examined the relationship of dietary sodium to cardiovascular disease as a whole,[17] dietary sodium intake was significantly inversely associated with mortality from cardiovascular disease in the participants in the National Health and Nutrition Examination Survey.

Most of the subjects in the present study were not obese, but the observed magnitude of association between sodium intake and stroke mortality was similar to that reported in the study among overweight US adults (with a body mass index of ≥27.8). We could not include blood cholesterol level as a covariate, which may have resulted in an overestimation of the risk. However, in our previous study of a subsample from this cohort,[18] salt intake was not associated with serum cholesterol level. In addition, 2 of the 3 prospective studies on dietary salt and stroke[6,7] showed that adjustments for nondietary risk factors, including blood cholesterol, had little effect on the HRs associated with dietary sodium. (The effect of adjustment was not referred to in the other study.[5]) In our study, adjustments for dietary variables strengthened the association between sodium intake and stroke mortality. The lack of a significant positive association in some of the previous studies[5,7] may be caused by the confounding effects of dietary variables. Still, we cannot eliminate the possibility that sodium intake is a marker for other unmeasured factors related to stroke. It is also possible that a positive association can be detected in a population with a relatively high intake of sodium, such as this Japanese population.

In the present study, adjustment for a history of hypertension did not substantially alter the magnitude of the association between sodium intake and stroke mortality. This result suggests that dietary sodium may be associated with the risk of stroke independently of the effect of hypertension. High salt intake can increase vascular oxidative stress in a rat model, possibly by reducing nitric oxide bioavailability.[19] This oxidative stress may be directly associated with vascular damage leading to stroke. Structural changes of the cerebral arteries or the carotid artery have been reported in spontaneous hypertensive rats with a high-salt diet without any change in blood pressure,[20,21] suggesting the potential deleterious effects of sodium intake excluding blood pressure. Because of the lack of data on blood pressure from each participant, we cannot deny the possibility that the effect of dietary sodium on the risk of stroke is mediated by blood pressure levels. It is also possible that some people on a high-salt diet developed hypertension during the follow-up. However, adjustment for blood pressure did not alter the association between dietary salt and stroke in previous studies.[6,7]

The use of mortality data instead of incidence data is also one of the limitations of the present study. We could not distinguish the effect of dietary sodium on incidence, survival, or both. Although the widespread use of computed tomography scans in Japanese local hospitals since the 1980s has probably made a death certificate data sufficiently accurate for diagnosis of stroke and differentiation of major stroke types,[22] we have no available data concerning the sensitivity and specificity of these diagnoses. However, it is unlikely that misclassification of the diagnoses is dependent on sodium intake.

We did not measure urinary sodium excretion. Urinary sodium is a good marker of short-term, but not long-term, sodium intake.[23] Some previous studies on dietary sodium and stroke or cardiovascular disease included urinary sodium measurements, but none of them repeated 24-hour urine collection.[7,24] The other studies were based on a single 24-hour dietary recall. The food frequency questionnaire, like all methods of dietary assessment, is subject to measurement error. However, in the present study, the questionnaire has been validated in comparison with daily 12 diet records over 1 year and estimates well the dietary intake of sodium.

Our findings provide support for dietary guidelines that advocate the reduction of salt intake for protection from

cardiovascular disease. Given the aforementioned limitations, our results cannot be considered definitive. Nevertheless, our findings do contribute additional significant evidence regarding this important public health issue.

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