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Original Article

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Seaweed Intake and Risk of Cardiovascular Disease: The Circulatory Risk in Communities Study (CIRCS)

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Aim: Seaweed contains soluble dietary fibers, potassium, and flavonoids and was recently reported to be inversely associated with the risk of coronary heart disease and mortality from stroke. However, epidemiological evidence on this issue has remained scarce.

Methods: At the baseline survey of four Japanese communities between 1984 and 2000, we enrolled 6,169 men and women aged 40–79 years who had no history of cardiovascular disease. We assessed their seaweed intake using the data from a 24 h dietary recall survey and categorized the intake into four groups (0, 1–5.5, 5.5–15, and ≥ 15 g/day). We used sex-specific Cox proportional hazards models to examine the association between seaweed intake and risk of cardiovascular disease (stroke, stroke subtypes, and coronary heart disease).

Results: During the 130,248 person-year follow-up, 523 cases of cardiovascular disease occurred: 369 cases of stroke and 154 cases of coronary heart disease. Seaweed intake levels were inversely associated with the risk of total stroke and cerebral infarction among men but not among women. Adjustment for cardiovascular risk factors did not change the associations: the hazard ratios (95% confidence intervals; *P* for trend) for the highest versus lowest categories of seaweed intake were 0.63 (0.42–0.94; 0.01) for total stroke and 0.59 (0.36–0.97; 0.03) for cerebral infarction. No associations were observed between seaweed intake and risks of intraparenchymal hemorrhage, subarachnoid hemorrhage, or coronary heart disease among men or women.

Conclusions: We found an inverse association between seaweed intake and risk of total stroke, especially that from cerebral infarction, among Japanese men.

Key words: Epidemiology, Stroke, Risk factor, Cohort study, Japan

Introduction

Seaweed is not commonly eaten in most Western countries but is often consumed in East Asian countries[1)], where it is a traditional food and has been believed to be beneficial for health. A cohort study in Japan reported that Japanese dietary patterns characterized by a high contribution of soybeans, fish, vegetables, seaweed, mushrooms, and fruits[2)] were inversely associated with risk of death from cardiovascular disease[3-6)].

Seaweed is rich in dietary fiber, vitamins, and

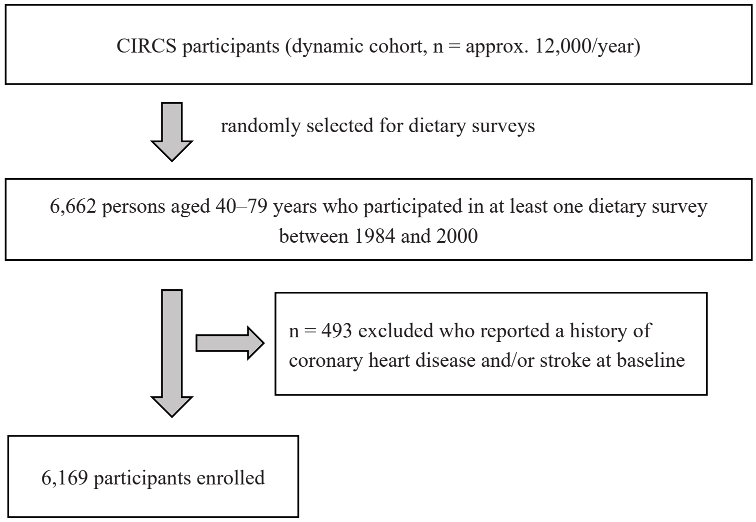

Fig. 1. Flowchart of study participants of the present study

minerals[7, 8]. These components affect blood pressure[9-13], serum lipids[14-16], fatty acid[17], blood glucose[14, 18, 19], and body weight[20, 21], which are known risk factors for cardiovascular disease. As such, seaweeds have been suggested to have various beneficial effects on cardiovascular disease. However, only two cohort studies have examined the association between seaweed intake and risks of mortality[22] and of incidence[23] from cardiovascular disease. Both studies concluded that seaweed intake may be beneficial for preventing cardiovascular disease; however, a part of the findings on sex and outcome differed between them[22, 23]. Thus, we sought to examine the association between seaweed intake and risk of incidence of cardiovascular disease in different populations from those in the previous two studies, under the Circulatory Risk in Communities Study (CIRCS), a large community-based cohort study in Japan.

Methods

Study Cohort

CIRCS is an ongoing community-based epidemiological study using dynamic prospective cohorts involving approximately 12,000 persons every year in five Japanese municipalities; the details of the study have been described elsewhere[24, 25]. The present study includes 6,169 residents aged 40– 79 years who participated in at least one dietary survey between 1984 and 2000 in four CIRCS communities (Ikawa, Yao, Noichi, and Kyowa) and who have no history of coronary heart disease and/or stroke at baseline. **Fig. 1** shows the study flowchart for patients' selection.

Baseline Examination and Assessment of Nutrient Intake

Trained study physicians or nurses measured blood pressure using standard mercury sphygmomanometers with standardized methods[25]. Height without shoes and weight in light clothing were measured. Face-to-face interviews were conducted to determine drinking and smoking status and use of antihypertensive, cholesterol-lowering, or antidiabetic medication. Blood samples were collected without fasting requirement from the participants; approximately 15% of the participants were in a fasting state. Serum total cholesterol, triglyceride, and glucose were measured. The details of the methods in baseline examination were described elsewhere[26]. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg or as the use of antihypertensive medication. Diabetes mellitus was defined as a fasting serum glucose of ≥ 126 mg/dL or a nonfasting serum glucose of ≥ 200 mg/dL or as the use of antidiabetic medication.

We adopted the 24 h dietary recall method to collect the dietary data. In this method, the

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participants were interviewed by trained dietitians or nutritionists about everything they had eaten within 24 h. Actual-sized food models, pictures of food materials and dishes, and/or real foods and dishes were used to help the recall and estimate the amount of the foods. Nutrient intakes were calculated based on the estimated amount using the Standard Tables of Food Composition in Japan, 2015 (seventh revised edition)[27].

We examined the reproducibility of seaweed intake in the 24 h dietary recall survey among the 1,866 participants who had responded to two 24 h dietary recall surveys. The surveys were undertaken 4.3 years apart on average. We categorized seaweed intake into four groups for the first and second surveys and compared the two surveys for group concordance. The quadratic weighted kappa coefficient of the seaweed intake of the two groups in the two surveys was 0.24. In addition, Spearman's rank correlation coefficient between the groups of seaweed intake was 0.14.

Follow-up and Determination of Ischemic Cardiovascular Disease

Follow-up lasted until the end of 2012 for Noichi, until the end of 2015 for Kyowa, and until the end of 2016 for Ikawa and Minami-Takayasu and was terminated at the first incident of coronary heart disease or stroke, moving out of the original community, or death. The median follow-up was 22 years for stroke or coronary heart disease.

The details of the endpoint determination have been described in previous CIRCS reports[26, 28]. For all the residents, cardiovascular disease endpoints were ascertained from the death certificates, national insurance claims, reports by local physicians, reports by public health nurses and health volunteers, and annual cardiovascular risk surveys. To confirm the diagnosis, all living patients were telephoned, visited, or invited to take part in risk factor surveys, or a medical history was obtained from their families. In addition, the medical records in the local clinics and hospitals were reviewed. In the cases of death, the histories were obtained from the patients' families and/or attending physicians, and the medical records were reviewed.

The criteria for coronary heart disease, i.e., definite and probable myocardial infarctions, definite angina pectoris, and sudden cardiac death within 1 h of onset, were modified from those of the World Health Organization Expert Committee[29]. The criterion for incident stroke was a focal neurologic disorder with rapid onset and persisting for at least 24 h or until death. Stroke cases were further classified as intraparenchymal hemorrhage, subarachnoid hemorrhage, ischemic stroke (lacunar, large-artery occlusive, or embolic stroke), or stroke of undetermined type primarily using computed tomography (CT)/magnetic resonance imaging (MRI) findings[30]. CT and/or MRI imaging findings were available for 97% of the stroke cases. The final diagnosis of coronary heart disease or stroke was performed by a panel of two to four physicians participating in this study who were blinded to the data from the risk factor survey.

Statistical Analyses

For the analyses, we categorized seaweed intake into four groups. We sorted a group whose seaweed intake was zero from the participants who had consumed seaweed, and then, we divided those into tertiles. As a result, the four groups of seaweed intake were as follows: intake of 0 g (n=2,478), between 1 and 5.5 g (n=1,244), between 5.5 and 15 g (n=1,214), and more than 15 g (n=1,233) per day. The analysis of covariance was used to test for differences in age-adjusted means and prevalence of baseline characteristics in terms of seaweed intake. Person-years were calculated as the sum of the individual follow-up times until the occurrence of incident coronary heart disease, stroke, death, or emigration, or the end of follow-up. We used Cox proportional hazards models to calculate the sex-specific and age-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for total stroke, cerebral infarction, intraparenchymal hemorrhage, subarachnoid hemorrhage, and coronary heart disease using the risk for persons, with the group of no seaweed intake as the reference (model 1). A test for the trend of association between seaweed intake and cardiovascular disease was also conducted using the median value of seaweed intake for each category. We further adjusted for age; body mass index (quartiles); smoking status (never, past, or current smoker); drinking status (never, past, or current drinker); total energy intake; and dietary intakes of vegetables, fruits, fish, meat, soy, and sodium (continuous) (model 2). To test the potential mediating effects, we further adjusted for hypertension (dichotomous), serum total cholesterol (quartiles), cholesterol-lowering medication use (dichotomous), and diabetes mellitus (dichotomous). Nutrient residual models were not applied in any foods/nutrients since seaweed contains little energy. The nutrient residual models did not alter the main results.

We used SAS version 9.4 software (SAS Institute) for all statistical analyses. All probability values for statistical tests were two-tailed, and P values below 0.05 were considered significant.

Ethical Considerations

The CIRCS protocol was approved by the ethics committees of the Osaka Center for Cancer and Cardiovascular Disease Prevention (R2-Rinri-4), Osaka University (14285-7), and of the University of Tsukuba (66-8). Informed consent was obtained verbally before the dietary surveys, and an opt-out option was provided to all the participants.

Results

Seaweed intake was positively associated with total energy intake and dietary intakes of soy, total fiber, and sodium for both sexes **(Table 1)**. Seaweed intake was positively associated with age, cholesterol-lowering medication use, and dietary intake of fish only among men; conversely, it was associated with dietary intakes of vegetables and fruits only among women. Seaweed intake was not associated with body mass index, smoking status, and drinking status in either sex.

During a median 22 year follow-up totaling 130,248 person-years, we confirmed a total of 523 cases of total cardiovascular diseases (330 men) including 369 total strokes (205 men), 234 cerebral infarctions (145 men), 85 intraparenchymal hemorrhages (45 men), 45 subarachnoid hemorrhages (12 men), and 154 coronary heart disease events (105 men). As shown in **Table 2**, seaweed intake levels were inversely associated with the risk of total stroke, especially cerebral infarction, among men. Adjustment for cardiovascular risk factors did not change the association: the HRs (95% CIs; *P* for trend) for the highest versus lowest category of seaweed intake were 0.63 (0.42–0.94; 0.01) for total stroke and 0.59 (0.36–0.97; 0.03) for cerebral infarction. No significant associations with seaweed intake were observed for coronary heart disease among men and women: the HRs were 1.10 (0.63–1.92; 0.56) among men and 0.57 (0.25–1.32; 0.19) among women (model 2). Furthermore, no significant associations were observed for intraparenchymal and subarachnoid hemorrhages in either sex. After further adjustment for potential mediators, these associations were not materially altered for any outcomes for both men and women; for example, the HRs were 0.63 (0.42–0.95; 0.02) for total stroke and 0.59 (0.36–0.98; 0.04) for cerebral infarction (data not shown in the Tables).

Discussion

In this large, long-term prospective cohort study of middle-aged Japanese individuals, we observed that seaweed intake was inversely associated with the risk of total stroke, especially cerebral infarction, among men but not among women. This is the first study to find an inverse association of seaweed intake with risk of incident total stroke and cerebral infarction.

Recently, two large Japanese cohort studies reported an association between seaweed intake and risk of or mortality from cardiovascular disease. The Japan Public Health Center (JPHC) Study, involving 86,113 men and women aged 40– 69 years during the baseline period (1990–1994), showed that the frequency of seaweed intake was inversely associated with the risk of incident coronary heart disease among men and women but not of stroke[23]. By contrast, another recent report from the Japan Collaborative Cohort (JACC) Study, involving 96,215 men and women aged 40– 79 years during the baseline period (1988–1990), showed that the frequency of seaweed intake based on a food frequency questionnaire was inversely associated with mortality from total stroke, cerebral infarction, and total cardiovascular disease among women but not among men[22]. In that study, seaweed intake was not associated with mortality from coronary heart disease in either sex.

Our results are partly concordant with those of the JACC Study, although we did not find any associations among women. The reasons for the discrepancies between our study and these previous ones are unknown. However, possible reasons are differences in the methods in the dietary survey (food frequency questionnaire in the JPHC and the JACC vs 24 h dietary records in the CIRCS); categories of seaweed intake (frequency in a week: four categories in the JPHC and five categories in the JACC vs the amount in a day in the CIRCS); modes of outcome (incidence in the JPHC and the CIRCS vs mortality in the JACC); the era of the baseline (the 1990s in the JPHC and the JACC vs the 1980-90s in the CIRCS); follow-up periods; and study populations. Notwithstanding these differences, our study and the two previous studies showed that seaweed intake was inversely associated with the risk of coronary heart disease or stroke.

No intervention trials proved the preventive effect of seaweed on cardiovascular diseases. However, the beneficial impacts of seaweed on blood pressure, lipids, diabetes mellitus, weight reduction, and related factors in humans have been shown in the previous trials[1], which support our and previous observational findings.

As for the bioactive components, alginates and fucoidan (both are polysaccharides), fucosterols (lipids), and fucoxanthin (carotenoids) are contained specifically in seaweed[31]. Alginates, the main polysaccharides of seaweed, contribute to lower

Table 1. Age-adjusted baseline characteristics according to the categories of seaweed intake among 6,169 Japanese men and women aged 40 to 79 years who participated in CIRCS between 1984 and 2000

		Tertiles of seaweed intake, g/day			*P* for overall difference
	None	T1 (0-5.5)	T2 (5.5-15)	T3 (≥ 15)	
Men (*n* = 2,792)					
Number at risk	1,166	514	544	568	
Age at baseline*, years	52.5	51.9	52.9	54.0	< 0.001
Current smoker, %	55.1	52.7	55.6	54.1	0.78
Current drinker, %	73.9	74.7	77.3	73.6	0.42
Body mass index, kg/m^2	23.4	23.5	23.3	23.5	0.52
Systolic blood pressure, mmHg	135	134	134	134	0.38
Diastolic blood pressure, mmHg	83	82	82	83	0.44
Antihypertensive medication use, %	14.4	16.6	16.6	16.1	0.49
Hypertension, %	48.1	46.4	45.1	47.0	0.69
Serum total cholesterol, mg/dL	192	192	193	193	0.85
Casual serum triglycerides, mg/dL	156	160	151	148	0.30
Cholesterol-lowering medication use, %	9.9	12.3	13.3	15.0	0.01
Diabetes mellitus, %	11.3	14.8	13.3	11.7	0.18
Dietary intakes					
Total energy, kcal/day	2,251	2,266	2,278	2,349	0.02
Vegetables, g/day	268	249	254	262	0.12
Fruits, g/day	137	128	118	122	0.15
Seaweed, g/day	0	3	10	35	< 0.001
Fish, g/day	114	111	121	127	0.01
Meat, g/day	57	54	51	51	0.20
Soy, g/day	62	59	67	73	0.01
Total fiber, g/day	14.0	14.3	14.4	15.9	< 0.001
Sodium, g/day	11.3	11.8	11.8	12.9	< 0.001
Women (*n* = 3,377)					
Number at risk	1,312	730	670	665	
Age at baseline*, years	53.4	53.6	54.2	54.4	0.06
Current smoker, %	5.5	3.9	4.2	4.6	0.36
Current drinker, %	10.9	9.8	10.9	10.0	0.85
Body mass index, kg/m^2	23.7	23.6	23.6	23.8	0.50
Systolic blood pressure, mmHg	133	134	134	133	0.31
Diastolic blood pressure, mmHg	80	80	80	80	0.90
Antihypertensive medication use, %	18.8	15.5	18.9	16.0	0.11
Hypertension, %	45.3	40.1	44.7	41.2	0.11
Serum total cholesterol, mg/dL	205	205	207	202	0.13
Casual serum triglycerides, mg/dL	122	126	119	118	0.29
Cholesterol-lowering medication use, %	13.8	10.8	15.4	14.6	0.05
Diabetes mellitus, %	10.6	9.8	11.7	11.8	0.50
Dietary intakes					
Total energy, kcal/day	1,683	1,724	1,693	1,758	0.007
Vegetables, g/day	281	265	270	290	0.008
Fruits, g/day	168	192	173	181	0.02
Seaweed, g/day	0	3	10	34	< 0.001
Fish, g/day	86	89	94	94	0.05
Meat, g/day	41	37	39	41	0.11
Soy, g/day	50	55	63	63	< 0.001
Total fiber, g/day	14.6	15.1	15.5	16.9	< 0.001
Sodium, g/day	9.6	10.0	10.2	11.3	< 0.001

Abbreviations: dL, deciliter; g, gram; kcal, kilocalorie; kg, kilogram; m^2, square meter; mg, milligram; mmHg, millimeter hydrargyrum; *n*, number
*Unadjusted

Table 2. Multivariable adjusted HRs and 95% CIs of ischemic cardiovascular disease (stroke and coronary heart disease) according to the four categories of seaweed intake, CIRCS

		Tertiles of seaweed intake, g/day			
	None	T1 (0-5.5)	T2 (5.5-15)	T3 (≥ 15)	*P* for trend
Men					
Person-years	24,083	10,674	11,359	11,947	
Number at risk	1166	514	544	568	
Total stroke					
Number of cases	98	38	33	36	
Model 1	1.00	0.92 (0.63-1.35)	0.65 (0.44-0.97)	0.62 (0.41-0.92)	0.01
Model 2	1.00	0.93 (0.63-1.36)	0.64 (0.43-0.95)	0.63 (0.42-0.94)	0.01
Intraparenchymal hemorrhage					
Number of cases	21	10	6	8	
Model 1	1.00	1.18 (0.55-2.52)	0.57 (0.23-1.41)	0.71 (0.30-1.66)	0.29
Model 2	1.00	1.10 (0.51-2.36)	0.53 (0.21-1.33)	0.63 (0.26-1.49)	0.19
Subarachnoid hemorrhage					
Number of cases	4	4	1	3	
Model 1	1.00	2.48 (0.61-10.1)	0.56 (0.06-5.03)	1.06 (0.23-4.96)	0.76
Model 2	1.00	3.40 (0.77-15.0)	0.64 (0.07-5.90)	1.32 (0.27-6.44)	0.90
Cerebral infarction					
Number of cases	71	24	26	24	
Model 1	1.00	0.80 (0.50-1.27)	0.70 (0.44-1.11)	0.56 (0.34-0.91)	0.02
Model 2	1.00	0.80 (0.50-1.28)	0.68 (0.43-1.08)	0.59 (0.36-0.97)	0.03
Coronary heart disease					
Number of cases	47	16	22	20	
Model 1	1.00	0.75 (0.42-1.32)	1.03 (0.62-1.71)	1.07 (0.62-1.84)	0.63
Model 2	1.00	0.77 (0.43-1.36)	1.05 (0.63-1.76)	1.10 (0.63-1.92)	0.56
Women					
Person-years	28,173	15,515	13,955	14,542	
Number at risk	1312	730	670	665	
Total strokes					
Number of cases	69	32	29	34	
Model 1	1.00	0.89 (0.58-1.36)	0.85 (0.55-1.31)	0.83 (0.54-1.26)	0.40
Model 2	1.00	0.89 (0.58-1.37)	0.86 (0.55-1.33)	0.85 (0.55-1.31)	0.49
Intraparenchymal hemorrhage					
Number of cases	19	8	5	8	
Model 1	1.00	0.82 (0.36-1.88)	0.54 (0.20-1.45)	0.73 (0.31-1.71)	0.43
Model 2	1.00	0.78 (0.34-1.83)	0.54 (0.20-1.46)	0.65 (0.27-1.55)	0.32
Subarachnoid hemorrhage					
Number of cases	14	7	6	6	
Model 1	1.00	0.91 (0.36-2.26)	0.87 (0.33-2.27)	0.72 (0.27-1.90)	0.50
Model 2	1.00	0.97 (0.39-2.45)	0.93 (0.35-2.46)	0.70 (0.26-1.91)	0.48
Cerebral infarction					
Number of cases	34	17	18	20	
Model 1	1.00	0.99 (0.55-1.79)	1.04 (0.59-1.86)	0.96 (0.54-1.69)	0.90
Model 2	1.00	1.00 (0.55-1.80)	1.02 (0.57-1.83)	1.05 (0.59-1.88)	0.86
Coronary heart disease					
Number of cases	23	10	8	8	
Model 1	1.00	0.81 (0.38-1.71)	0.71 (0.32-1.59)	0.58 (0.26-1.32)	0.20
Model 2	1.00	0.81 (0.38-1.72)	0.70 (0.31-1.57)	0.57 (0.25-1.32)	0.19

Abbreviations: HR, hazard ratio; CIs, confidence intervals
Model 1 was adjusted for age. Model 2 was adjusted for age; body mass index (quartiles); smoking status (never, current, or past smoker); drinking status (never, current, or past drinker); total energy intake; and dietary intakes of vegetables, fruits, fish, meat, soy, and sodium (continuous).

cholesterol levels[32], improved postprandial blood glucose[32], and lower blood pressure[10, 12]. Another polysaccharide, fucoidan, contained only in brown algae (which is the most commonly consumed seaweeds[33])[31], has antioxidant, anticoagulant, antithrombotic, and anti-inflammatory effects[34], as well as cholesterol-lowering[35] and blood pressure-lowering[36] effects. As for an anticoagulant effect, an *in vivo* experiment of Wistar rats demonstrated that the application of fucoidan (ointment containing dry *Fucus* extracts) for 7 days increased the activated partial thromboplastin time (21.3% vs 2.7%, $P<0.05$) and prothrombin time (42.0% vs 6.0%, $P<0.05$) in comparison with the control group (no manipulation). In addition, the prothrombin time after the application of the ointment of dry Fucus extracts was similar to that of heparin application (42.0% vs 41.3%)[37].

The other nutrients, fucosterols, contained as lipids especially in brown and red algae[38], lower blood glucose and blood pressure levels[39]. Fucoxanthin, an algal carotenoid, also has a stronger antioxidant effect than other carotenoids such as α-tocopherol[40]. In addition, although they are not specifically contained in seaweeds, potassium[41] and calcium[42] lower blood pressure levels. Seaweed is also rich in vitamins A, B (including vitamins B_1, B_2, B_6, and B_{12}), C, and E, which have antioxidant effects[43]. The concentration of vitamin C is comparable with that in common vegetables such as tomatoes and lettuce[43, 44]. Taken together, several mechanisms may be involved in the pathophysiology of seaweed–stroke associations. Our observation that the adjustment for mediating factors such as hypertension, dyslipidemia, and diabetes mellitus did not alter the associations suggested that pathways other than blood pressure, cholesterol, and glucose may be relatively essential roles for the prevention of stroke.

The major strengths of our study are its large sample size, prospective design, long follow-up duration, and high follow-up rate. Unlike most Western populations, the Japanese are unique in that they frequently eat seaweeds, which allowed us to examine the association between seaweed intake and the risk of incident ischemic cardiovascular disease. In addition, by adopting the 24 h dietary recall survey, we could estimate the absolute amount of commonly consumed seaweed intake.

Several limitations of our study must be mentioned. First, since we used a single data from the 24 h dietary recall survey to determine the exposure of seaweed intake, we did not take any subsequent dietary changes into account; thus, the participants might have been categorized incorrectly by the single data source for seaweed intake. In the present study, the reproducibility of seaweed intake in the 24 h dietary recall survey was not high (quadratic weighted kappa coefficient=0.24, Spearman's correlation coefficients=0.14) compared with the reproducibility estimated by using repeated food frequency questionnaires in the other study[23] (Spearman's correlation coefficients=0.35). In previous studies, the frequency of seaweed intake was usually one to two times or three to four times a week[22, 23]; therefore, the participants may not necessarily have consumed seaweed the day before the survey. Since such measurement errors would occur randomly across the exposure groups, they likely diluted the association between seaweed intake and risk of cardiovascular disease. Second, we cannot negate the possibility of residual confounding by unmeasured variables such as socioeconomic status. Seaweed intake might reflect healthy dietary patterns[3], but the adjustment for vegetable, fruit, fish, soy, salt, and meat intake did not change the results materially. Finally, no significant results were obtained in women, the reasons for which are unknown to us. The sex difference in the association of seaweed and cardiovascular disease was also found in previous studies[22]. It might be due to the difference in hormones, underlying risk factors of cardiovascular disease (such as smoking and hypertension), and the amount of food intake.

Nevertheless, our findings suggest the usefulness of seaweeds in preventing ischemic cardiovascular disease. Since seaweed can be easily adapted into dietary habits, it could attract worldwide attention as a health food. Although active pathways to metabolic processes of various nutrients in seaweed have been reported, most of them are from animal experiments. In addition, the absorption rates of those nutrients from the digestive tract in humans have not been revealed.

Conclusion

The present study revealed that seaweed intake was inversely associated with the risk of incident total stroke, especially cerebral infarction, among Japanese men.

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No conflicts of interest to declare. The funding agencies for this study made no decisions regarding its study design, data collection, data analysis, manuscript preparation, or decision to publish.

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