



Seaweed intake and risk of cardiovascular disease: the Japan Public Health Center based Prospective (JPHC) Study

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Title: Seaweed intake and risk of cardiovascular disease: the Japan Public Health Center-based Prospective (JPHC) Study

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Short running head: Seaweed intake and incident cardiovascular disease

Abbreviations used: PHC = public health center, FFQ = food frequency questionnaire, HR = hazard ratio, CI = confidence interval

1 ABSTRACT

2 **Background:** The minerals, vitamins, soluble dietary fibers, and flavonoids of seaweed are
3 protective for prevent cardiovascular diseases. However, the association between seaweed
4 intake and risk of cardiovascular disease has not been established.

5 **Objectives:** We examined the dietary intake of seaweed and its impact upon stroke and
6 ischemic heart disease risk among a Japanese study population.

7 **Design:** We surveyed 40,707 men and 45,406 women from 2 large cohorts (age range: 40–69
8 years). Seaweed intake was determined by food frequency questionnaire at baseline (1990–
9 1994). Incidences of stroke and ischemic heart disease were ascertained until the end of 2009
10 (Cohort I) or 2012 (Cohort II). Sex-specific cardiovascular disease hazard ratios (95%
11 confidence intervals) were estimated using Cox proportional hazard models after
12 stratification by area and adjustment for cardiovascular risk and dietary factors.

13 **Results:** During 1,493,232 person-years of follow-up, 4,777 strokes (2,863 ischemic stroke,
14 1361 intraparenchymal hemorrhages and 531 subarachnoid hemorrhages) and 1,204 ischemic
15 heart disease cases were identified. Among men, the multivariable hazard ratios for almost
16 daily consumption versus almost no consumption of seaweed were only seen in ischemic
17 heart disease: 0.76 (0.58, 0.99; *P* for trend = 0.04) and total cardiovascular diseases: 0.88
18 (0.78, 1.00; *P* for trend = 0.08). Among women, such inverse associations were 0.56 (0.36,
19 0.85; *P* for trend = 0.01) for ischemic heart disease, and 0.89 (0.76, 1.05; *P* for trend = 0.10)
20 for total cardiovascular diseases. No significant associations were observed between seaweed
21 intake and risk of total stroke or stroke types among either men or women.

22 **Conclusions:** Seaweed intake was inversely associated with risk of ischemic heart disease.

23 **Keywords:** epidemiology, follow-up study, ischemic heart disease, risk factor, diet

24 INTRODUCTION

25 Seaweed, outside of industrial food processing, is not widely eaten in the West but is broadly
26 consumed in East Asian countries. It contains healthy components such as high levels of
27 potassium, carotenoid, and dietary fiber (1, 2), and the most commonly used seaweeds in
28 food preparation include the following species: brown seaweeds (*Undaria pinnatifida*
29 [*Wakame* in Japanese], kelp (*Laminaria* [*Konbu*], *Hizikia fusiformis* [*Hijiki*]), red seaweeds
30 and green seaweeds (*Laver* [*Nori*]). Although seaweed consumption is not a traditional part of
31 the Western diet, the globalization of cuisine and an increased proportion of Asian
32 immigrants may work to increase future consumption in Western countries.

33 Previous studies showed that seaweed components, such as carotenoids, peptides, and
34 fiber were related to lower levels of serum total cholesterol, blood pressure, body weight and
35 blood glucose in both animals (3–8) and humans (9–14). As the Japan Public Health Center-
36 based Prospective (JPHC) Study showed that dietary fiber was associated inversely with risk
37 of cardiovascular disease (15), seaweed intake may be prophylactic in this regard.

38 However, an association between seaweed intake and the incidence of cardiovascular
39 disease has not been established. The aim of the present study was therefore to determine any
40 associations between dietary intake of seaweed and risks of total stroke, stroke types
41 (ischemic stroke, intraparenchymal hemorrhage and subarachnoid hemorrhage), ischemic
42 heart disease (myocardial infarction and sudden cardiac death) and total cardiovascular
43 diseases among Japanese men and women. As the Japanese are a unique population which
44 consumes extremely high amounts of seaweeds compared to the rest of the world (2), any
45 beneficial impact of seaweed may be more easily detected.

46 **SUBJECTS AND METHODS**

47 **Study population**

48 The JPHC study consists of two subcohorts based on public health center (PHC) areas;
49 Cohort I (started in 1990, five PHC areas, participants aged 40–59 years) and Cohort II
50 (started in 1993, six PHC areas, participants aged 40–69 years). The study design has been
51 described in detail previously (16). The JPHC study was approved by the institutional review
52 boards of the National Cancer Center, Osaka University and the University of Tsukuba.

53 The JPHC Study is an ongoing cohort study comprising a community-based sample of
54 140,420 Japanese participants (68,722 men and 71,698 women) that follows up on incidences
55 of cancer and cardiovascular diseases. However, participants in two PHC areas (Tokyo and
56 Osaka) were excluded from the present study because the incidence of cardiovascular disease
57 was unable to be followed up in these two communities, leaving 116,896 remaining
58 participants as eligible for the follow-up study. Participants were asked to complete self-
59 administered questionnaires about their lifestyles and medical histories. Informed consent
60 was obtained before questionnaire completion or was sometimes obtained from community
61 leaders instead of individuals as this was common practice for informed consent in Japan at
62 that time.

63 **Baseline questionnaire**

64 A self-administered questionnaire included demographic characteristics, medical history,
65 physical activity level, smoking, drinking, and dietary habits. This questionnaire, including a
66 food frequency questionnaire (FFQ), was distributed to all eligible study participants in 1990
67 for Cohort I and in 1993–94 for Cohort II. The FFQ included 44 food items for Cohort I and
68 52 food items for Cohort II. Both cohort FFQs included an item about typical seaweed intake
69 and contained four or five frequency categories for seaweeds (*Wakame*, *Konbu*, *Nori* and
70 more), ranging from “almost never,” “1–2 days/week,” “3–4 days/week” to “almost daily,” in

71 Cohort I and from “rarely,” “occasionally,” “1–2 days/week,” “3–4 days/week” to “almost
72 daily,” in Cohort II. For analysis, we combined the data from both cohorts, classifying the
73 participants into four groups according to their frequencies of seaweed intake: “almost no
74 consumption (almost never, rarely or occasionally)”, “1–2 days/week”, “3–4 days /week”,
75 and “almost daily consumption.” Validation of the FFQ was done by comparing the
76 frequency of seaweed intake from FFQ to that from dietary records over seven consecutive
77 days in each of four seasons (Spring, Summer, Fall and Winter). The Spearman’s correlation
78 coefficients between the frequency of seaweed intake based on the FFQ and dietary records
79 among subsamples of 122 men and 125 women in Cohort I and 176 men and 178 women in
80 Cohort II were moderate: 0.37 and 0.33, respectively, in Cohort I (17) and 0.27 and 0.40,
81 respectively, in Cohort II (unpublished data).

82 **Stroke and ischemic heart disease registry**

83 The nine PHC areas were comprised of 78 total hospitals, which were core hospitals capable
84 of treating cardiovascular disease events. Physicians in the hospitals, PHCs, or research
85 physician-epidemiologists (all blinded to patient lifestyle data) reviewed the medical records
86 of cohort participants at each hospital and extracted clinical information, including brain
87 images, electrocardiographs, and enzyme test results, onto cohort-specific registration forms.
88 To confirm the fatal cardiovascular disease events, we used the information on death
89 certificates. All death certificates were forwarded to the PHC in the area of residency, and the
90 mortality data was sent to the Ministry of Health, Welfare and Labor to be coded for national
91 vital statistics. As registration of deaths is required by the Family Registration Law in Japan,
92 we were assured that all relevant causes of deaths were recorded.

93 Stroke was confirmed according to the criteria of the National Survey of Stroke (18),
94 which requires the presence of focal neurological deficits of sudden or rapid onset lasting at
95 least 24 hours or until death. Stroke was classified into ischemic strokes, intraparenchymal

96 hemorrhages, and subarachnoid hemorrhages. As participating hospitals were equipped with
97 computed tomography and/or magnetic resonance imaging scans, imaging was available for
98 97% of registered stroke events.

99 Ischemic heart disease was defined as myocardial infarction and sudden cardiac death.
100 Myocardial infarction was confirmed in the medical records according to the criteria of the
101 Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) project (19),
102 which requires typical chest pain and evidence from electrocardiography and/or cardiac
103 enzyme levels. For those cases with typical prolonged chest pain (≥ 20 min) but not confirmed
104 by electrocardiography or cardiac enzyme tests, a tentative myocardial infarction diagnosis
105 was made and these were included in myocardial infarction cases. Deaths within 28 days of
106 the onset of myocardial infarction and sudden cardiac deaths were regarded as fatal coronary
107 events while sudden cardiac death was defined as a death of unknown origin that occurred
108 within 1 hour of the event onset. The primary outcome of this study is incident cardiovascular
109 diseases (total stroke, stroke types and ischemic heart disease) and both fatal and nonfatal
110 cases were included.

111 Total cardiovascular disease was defined as total stroke, stroke types and ischemic heart
112 disease, whichever occurred first, during the follow-up.

113 **Statistical analysis**

114 Follow-ups were started from the completion of the questionnaire and ended on the dates of
115 death, emigration, incident stroke/ischemic heart disease events, or the end of either 2009 (for
116 Cohort I) or 2012 (for Cohort II), whichever came first.

117 Within the pool of 116,896 participants, we excluded those who were lost to, or refused
118 follow-up (n=240), leaving a total of 116,656 people from the two cohorts (Cohorts I and II)
119 who were eligible for participation in the present study. Of these, 94,275 participants (81%)
120 completed the baseline questionnaires, including information on seaweed intake. In addition,

121 we excluded persons who had histories of stroke, angina pectoris, myocardial infarction or
122 cancer at the time of the baseline questionnaires (n=3,630). We further excluded persons with
123 a total energy intake of less than 2.5 or more than the 97.5 percentile (n=4,532). Ultimately,
124 86,113 people (40,707 men and 45,406 women) were included in the present study.

125 Sex-specific, age-adjusted mean values and prevalence of selected factors were
126 calculated and compared among the frequencies of seaweed intake using linear or logistic
127 regression analyses. The person-years of follow-up for each participant were calculated from
128 the baseline to the first endpoint which was defined as a cardiovascular event, a death, a
129 move from the community, or the end of the follow-up period (2009 for Cohort I and 2012
130 for Cohort II).

131 Sex-specific, area (nine PHCs) -stratified and age (continuous) -adjusted hazard ratios
132 (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard
133 models. We confirmed the proportional hazards assumption according to the frequency of
134 seaweed intake by time interactions, and found that the assumption was not violated. For
135 seaweed intake categories, dummy variables were created, and the almost no consumption
136 group was regarded as the reference. We further adjusted for body mass index (quintile),
137 histories of hypertension and diabetes mellitus, including treatment (yes or no), treatment for
138 hypercholesterolemia (yes or no), leisure-time physical activity (no, 1–3 days/month, 1–2
139 days/week, 3–4 days/week and almost every day), smoking status (never, ex-smoker and
140 current smoker), alcohol intake (0, 1–149, 150–299, 300–449 and 450 g/week or more),
141 quartiles of total energy intake, dietary intakes of vegetables, fruits, red meat, processed meat,
142 fish, soy, green tea and sodium. The food intakes were estimated by the Japan Food Table, 5th
143 version. Trend tests were performed by allocating scores of 0, 1.5, 3.5 and 6 for each seaweed
144 intake groups.

145 The socio-economic status may be an important confounding factor, but we did not have

146 information except for education levels in subcohort (Cohort I). Therefore, we additionally
147 performed subgroup analyses in Cohort I adjusting for education levels (junior high school or
148 less, high school, and university or higher education).

149 We used SAS version 9.4 software (SAS Institute Inc, Cary, NC) for the analyses. All
150 probability values for statistical tests were two-tailed, and values where $p < 0.05$ were regarded
151 as statistically significant.

152

153

154 RESULTS

155 The baseline survey revealed that those respondents who consumed seaweeds frequently
156 tended to consume more energy-adjusted dietary intakes of vegetables, fruits, red and
157 processed meat, fish, soy and sodium, and as well as have lower proportions of current
158 smokers among both men and women.

159 During 1,493,232 person-years of follow-up in 86,113 men and women, 5,873 (3,611 in
160 men and 2,262 in women) incident cases of total cardiovascular disease, including 2,863
161 (1,805 in men and 1,058 in women) ischemic strokes, 1,361 (805 in men and 556 in women)
162 intraparenchymal hemorrhages, 531 (180 in men and 351 in women) subarachnoid
163 hemorrhages, 1,204 (884 in men and 320 in women) ischemic heart disease events were
164 identified. Total seaweed intake by the participants ranged from a mean value of 0.3 g/day in
165 the almost no consumption to 4.7 g/day in the almost daily consumption groups among men
166 and 0.2 g/day to 3.9 g/day, respectively, among women (**Table 1**).

167 Seaweed intake was inversely associated with risk of ischemic heart disease among men
168 and women. The multivariable HRs (95% CIs) for the almost daily consumption versus the
169 almost no consumption groups were 0.76 (0.58, 0.99; *P* for trend=0.04) for ischemic heart
170 disease and 0.88 (0.78, 1.00; *P* for trend=0.08) for total cardiovascular disease among men
171 (**Table 2**). The multivariable HRs (95% CIs) among women were 0.56 (0.36, 0.85; *P* for
172 trend=0.01) for ischemic heart disease and 0.89 (0.76, 1.05; *P* for trend=0.10) for total
173 cardiovascular diseases (**Table 3**).

174 To examine any potential reverse causation for the frequency of seaweed intake and risk
175 of cardiovascular disease, we performed the same analyses but excluded early events (≤ 5 years
176 from the baseline). These associations did not materially alter any outcomes among either men
177 or women (data not shown). When we further adjusted for education levels in this subgroup
178 (Cohort I, $n=39,176$), these associations were not materially altered for any outcomes among

179 either men or women (data not shown).

180

181 **DISCUSSION**

182 In this large, prospective study of middle-aged Japanese men and women, we found an
183 inverse association between seaweed intake and risk of ischemic heart disease that was more
184 pronounced among women. To our knowledge, this is the first study to show an association
185 between seaweed intake and risk of incident cardiovascular disease. Another previous
186 Japanese cohort study showed a significant inverse association between the frequency of
187 seaweed intake and age-adjusted mortality from stroke (not ischemic heart disease) among
188 women, but not among men (20). In that study, however, the adjustment for potential
189 confounding factors was not conducted and the risk of cardiovascular disease mortality,
190 instead of incidence, was examined.

191 One possible mechanism for the protective effect of seaweed against the risk of ischemic
192 cardiovascular disease is a lipid-lowering effect as shown in a previous study of
193 apolipoprotein E-deficient mice where fucoidan contained in seaweed regulated the
194 metabolism of serum lipids by increasing lipoprotein lipase activity (21), reducing blood
195 levels of triglycerides and low-density lipoprotein cholesterol. Furthermore, the
196 supplementation of a high-fat diet with 5% fucoidan for 12 weeks attenuated the development
197 of atherosclerosis and plaque formation compared to a high-fat diet alone (21). Another
198 possible mechanism is a blood pressure lowering effect. Peptides isolated from *wakame* have
199 inhibitory activity for the angiotensin-1-converting enzyme, leading to decreases in blood
200 pressure in spontaneously hypertensive rats (6). In humans, a randomized controlled trial
201 showed that diastolic blood pressure levels in hypertensive patients decreased by 8 mmHg
202 after treatment with 5 g/day *wakame* powder for 8 weeks, whereas the decrease in the non-
203 treated group was not significant (9). In addition, a double-blinded crossover trial using a 4-
204 week supplement of 12 or 24g/day, but not 6g/day seaweed fiber showed that untreated mild
205 hypertensive patients saw a significant decrease in mean blood pressure compared with the

206 placebo group (11). Accordingly, another study in a spontaneously hypertensive rat model
207 using 1% NaCl supplementation in drinking water showed a 4-fold increase in fecal sodium
208 excretion in the intervention group fed on 10% alginic acid (the main soluble fiber of
209 seaweed) compared with a control group fed on 10% kaolin (22). Ikeda et al. (4) reported that
210 blood pressure levels in stroke-prone spontaneously hypertensive rats given 0.5% NaCl-
211 supplemented drinking water and *wakame* powder did not differ with groups given cellulose
212 or kaolin control supplements. However, the mean life-span of the *wakame* powder group
213 was significantly extended compared to controls (77 days for *wakame* group vs. 62 days for
214 the control group). In that study, neuronal cell injury after 4-day hypoxic insult was
215 attenuated in a dose-dependent fashion by the addition of 152 or 1520 nmol/L fucoxanthin
216 isolated from seaweeds, suggesting that *wakame* may have a beneficial effect on stroke
217 independent of blood pressure-lowering effect (4). In the present study, the adjustment for
218 history of hypertension and treatment of hypercholesterolemia did not alter the results. These
219 variables, however, were not minute so that the residual confounding may remain.

220 Seaweed intake may be a marker of healthy dietary patterns. A previous principal
221 component analysis run in the JPHC Study identified that seaweed intake consisted of a
222 ‘prudent’ (healthy) dietary pattern that involved vegetables, fruit, potatoes, soy products,
223 mushrooms, seaweed, fish, and green tea (23). Among these foods, potatoes and mushrooms
224 were not adjusted in our analysis, because these intakes were not confounded for the
225 association with the risk of ischemic heart disease in our cohort (data not shown).
226 Furthermore, when we adjusted for modified DASH dietary score (including vegetables,
227 fruits, red and processed meat intake, dairy instead of low-fat dairy, soy instead of nuts and
228 legumes, sodium, and sweetened beverages), the results did not change materially (data not
229 shown). Therefore, these results support that seaweed may lower the risk of cardiovascular
230 disease independent of healthy dietary pattern.

231 Some kinds of seaweed, particularly *Hizikia fusiformis* (*Hijiki*), are rich in inorganic
232 arsenic, which has been suggested to be associated with increased risk of cardiovascular
233 disease (24). Potential mechanisms for arsenic-related atherosclerosis include endothelial
234 dysfunction, smooth-muscle proliferation, and enhanced platelet aggregation (25). However,
235 we did not find any adverse effect of seaweed on cardiovascular diseases suggesting that
236 adverse impact of arsenic, if any, may be overwhelmed by the beneficial effect of seaweed as
237 discussed above. Furthermore, inorganic arsenic in *Hijiki* could be removed by soaking in
238 water and boiling when cooking (26, 27).

239 The strengths of the present study included its large sample size, a population-based
240 prospective design, a high follow-up rate, the use of validated FFQ and cardiovascular
241 incident data, and the extensive adjustment for potentially important confounding factors,
242 including physical activity level, smoking status, alcohol intake, and other food items.
243 Japanese are a unique population who consume an extremely high amount of seaweeds,
244 which allowed us to perform associative studies of a large distribution of seaweed intake with
245 incident cardiovascular disease. As seaweed in non-Asian countries is mostly used in
246 industrial food processing, this type of study could not be performed in Western populations.

247 Several limitations in the present study warrant discussion. First, although validated by
248 dietary records, the use of an FFQ inevitably leads to seaweed intake misclassification. The
249 low correlation coefficients between the frequency of seaweed intake (based on FFQ) and
250 dietary records suggest that the self-reported intake is subject to measurement errors.
251 However, as any misclassification was likely to be random concerning the outcome, this was
252 not thought to impact the results greatly. Second, we could not negate the possibility of
253 residual confounding by unmeasured variables such as socio-economic status. When we
254 further adjusted for education levels (junior high school or less, high school, and university or
255 higher education) in the subgroup, there were no substantial changes in the results for either

256 men or women (not shown in Table).

257 In conclusion, seaweed intake was significantly and inversely associated with risk of
258 ischemic heart disease. Our results suggest that a high seaweed intake may have a beneficial
259 effect on cardiovascular disease among middle-aged men and women.

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265

266 **Conflict of Interest:** none declared.

267

268 **The author's responsibilities were as follows:** UM: designed the analysis plan; UM, KY
269 and HI: wrote the manuscript and had primary responsibility for the final content; UM:
270 performed statistical analysis; MI, NS and ST: contributed to the acquisition of data; and all
271 authors: contributed to the interpretation of data, contributed to revising the manuscript
272 critically of the manuscript. None of the authors reported a conflict of interest related to the
273 study.

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Table 1. Baseline cardiovascular risk factors and selected dietary variables among 40,707 men and 45,406 women according to the frequency of seaweed intake¹

	Men					Women				
	Frequency of seaweed intake									
	Almost no consumption	1-2 days/week	3-4 days/week	Almost daily consumption	<i>P</i> for difference	Almost no consumption	1-2 days/week	3-4 days/week	Almost daily consumption	<i>P</i> for difference
Number at risk	9,033	14,067	11,826	5,781		6,537	13,351	16,197	9,321	
Age at baseline, mean	52.7±8.7	51.0±7.7	51.7±7.7	52.6±7.6	0.07	54.2±8.9	51.3±7.9	51.9±7.6	52.4±7.5	<0.001
Body mass index, kg/m ²	23.5±3.0	23.5±2.9	23.5±2.8	23.4±2.9	0.002	23.6±3.4	23.5±3.1	23.5±3.2	23.5±3.1	0.009
Treatment for hypertension, %	18.1±39.2	18.3±38.0	18.5±38.8	19.2±40.0	0.02	17.8±40.2	17.6±37.2	17.4±37.6	17.8±38.6	0.24
Treatment for hypercholesterolemia, %	1.0±10.3	1.1±10.3	1.6±12.4	1.6±12.6	<0.001	1.1±12.0	2.0±13.4	2.2±14.7	2.3±15.3	<0.001
Treatment for diabetes mellitus, %	6.4±24.8	5.9±23.1	6.4±24.5	6.9±25.8	0.05	3.3±18.8	3.0±16.6	2.9±16.7	2.8±16.7	0.29
Current smokers, %	56.7±49.6	52.0±50.0	51.1±50.0	48.9±50.0	<0.001	8.0±26.6	6.0±30.3	4.8±21.6	4.1±19.8	<0.001
Alcohol intake ≥450 ml/week, %	24.8±43.1	21.6±41.1	22.2±41.6	22.0±41.7	0.002	4.8±21.5	3.5±18.4	2.7±16.1	3.3±17.7	0.04

Leisure-time physical activity \geq 3 times/week, %	8.2 \pm 27.9	9.1 \pm 28.4	10.1 \pm 30.1	11.6 \pm 32.4	<0.001	7.8 \pm 27.9	7.0 \pm 24.9	8.8 \pm 28.2	11.2 \pm 31.7	<0.001
Dietary intake ²										
Total energy intake, kcal/day	1,662 \pm 479	1,852 \pm 499	1,992 \pm 500	2,080 \pm 502	<0.001	1,072 \pm 250	1,213 \pm 306	1,326 \pm 328	1,425 \pm 359	<0.001
Vegetable intake, g/day	58 \pm 41	100 \pm 47	128 \pm 48	158 \pm 60	<0.001	73 \pm 52	102 \pm 60	126 \pm 63	154 \pm 76	<0.001
Fruit intake, g/day	51 \pm 64	68 \pm 72	81 \pm 82	94 \pm 103	<0.001	84 \pm 67	97 \pm 80	109 \pm 85	122 \pm 104	<0.001
Red meat intake, g/day	16.5 \pm 11.7	21.1 \pm 13.8	24.4 \pm 16.2	25.2 \pm 18.7	<0.001	14.9 \pm 9.4	17.0 \pm 11.5	18.5 \pm 13.2	19.2 \pm 16.0	<0.001
Processed meat intake, g/day	2.6 \pm 3.1	3.5 \pm 3.7	4.1 \pm 4.2	4.3 \pm 5.0	<0.001	2.9 \pm 3.0	3.3 \pm 3.5	3.6 \pm 3.9	3.8 \pm 4.7	<0.001
Fish intake, g/day	50 \pm 36	51 \pm 33	59 \pm 35	67 \pm 41	<0.001	39 \pm 27	42 \pm 26	48 \pm 28	54 \pm 32	<0.001
Soy intake, g/day	42 \pm 26	48 \pm 25	58 \pm 25	68 \pm 25	<0.001	42 \pm 25	47 \pm 23	54 \pm 23	62 \pm 23	<0.001
Green tea intake, ml/day	446 \pm 360	406 \pm 334	411 \pm 331	419 \pm 332	<0.001	431 \pm 328	398 \pm 312	409 \pm 310	403 \pm 306	0.07
Seaweed intake, g/day	0.3 \pm 0.1	1.1 \pm 0.2	2.4 \pm 0.5	4.7 \pm 1.1	<0.001	0.2 \pm 0.1	0.9 \pm 0.2	2.0 \pm 0.5	3.9 \pm 0.9	<0.001
Sodium intake, g/day	4.1 \pm 1.7	4.8 \pm 2.0	5.3 \pm 2.1	5.7 \pm 2.2	<0.001	3.8 \pm 1.4	4.2 \pm 1.8	4.5 \pm 1.9	4.7 \pm 2.0	<0.001

¹Sex-specific, age-adjusted mean (unadjusted standard deviations), or age-adjusted percentages were calculated according to the frequency of seaweed intake using linear or logistic regression analysis.

²Energy-adjusted values except for total energy intake.

*P-values for the overall difference using analysis of covariance.

Table 2. Multivariable-adjusted HRs and 95% confidence intervals for risk of incident total cardiovascular diseases, total stroke, stroke types and ischemic heart disease according to the frequency of seaweed intake among 40,707 men¹

	Frequency of seaweed intake				<i>P</i> for trend
	Almost no consumption	1-2 days/week	3-4 days/week	Almost daily consumption	
Number of men at risk	9,033	14,067	11,826	5,781	
Person years	144,764	237,476	199,746	96,497	
Total stroke, n	646	916	813	429	
Model 1	1.00	0.87 (0.78, 0.97)	0.85 (0.76, 0.95)	0.88 (0.77, 0.998)	0.08
Model 2	1.00	0.93 (0.83, 1.04)	0.91 (0.81, 1.03)	0.93 (0.80, 1.07)	0.35
Ischemic stroke, n	434	571	526	274	
Model 1	1.00	0.83 (0.73, 0.95)	0.83 (0.73, 0.96)	0.84 (0.71, 0.98)	0.08
Model 2	1.00	0.89 (0.77, 1.02)	0.91 (0.78, 1.05)	0.91 (0.76, 1.09)	0.53
Intraparenchymal hemorrhage, n	173	274	238	120	
Model 1	1.00	0.95 (0.78, 1.17)	0.93 (0.75, 1.15)	0.94 (0.73, 1.20)	0.59
Model 2	1.00	1.03 (0.83, 1.27)	0.98 (0.78, 1.24)	0.94 (0.71, 1.24)	0.52
Subarachnoid hemorrhage, n	37	65	44	34	
Model 1	1.00	0.89 (0.58, 1.39)	0.66 (0.41, 1.08)	1.04 (0.62, 1.75)	0.90
Model 2	1.00	0.94 (0.59, 1.50)	0.67 (0.40, 1.14)	1.01 (0.56, 1.79)	0.80

Ischemic heart disease, n	220	303	246	115	
Model 1	1.00	0.83 (0.69, 0.997)	0.77 (0.63, 0.94)	0.72 (0.57, 0.91)	0.007
Model 2	1.00	0.87 (0.70, 1.03)	0.79 (0.64, 0.98)	0.76 (0.58, 0.99)	0.04
Total cardiovascular diseases, n	846	1192	1038	535	
Model 1	1.00	0.86 (0.78, 0.95)	0.83 (0.76, 0.92)	0.84 (0.75, 0.95)	0.006
Model 2	1.00	0.91 (0.82, 1.00)	0.88 (0.79, 0.98)	0.88 (0.78, 1.00)	0.08

¹HRs (95% CIs) were derived from Cox proportional hazards regression models. Model 1 was stratified by area and adjusted for age.

Model 2 was adjusted further for body mass index, leisure-time physical activity, smoking status, alcohol intake, histories of hypertension or diabetes mellitus, treatment for hypercholesterolemia, total energy intake, dietary intakes of vegetables, fruits, red meat, processed meat, fish, soy, green tea and salt.

Table 3. Multivariable-adjusted HRs and 95% confidence intervals for risk of incident total cardiovascular diseases, total stroke, stroke types and ischemic heart disease according to the frequency of seaweed intake among 45,406 women¹

	Frequency of seaweed intake				<i>P</i> for trend
	Almost no consumption	1-2 days/week	3-4 days/week	Almost daily consumption	
Number of women at risk	6,537	13,351	16,197	9,321	
Person years	113,514	239,797	292,681	168,757	
Total stroke, n	309	567	680	417	
Model 1	1.00	0.96 (0.83, 1.11)	0.88 (0.76, 1.01)	0.88 (0.75, 1.03)	0.05
Model 2	1.00	1.05 (0.90, 1.22)	0.98 (0.84, 1.15)	0.96 (0.81, 1.15)	0.36
Ischemic stroke, n	186	314	348	210	
Model 1	1.00	0.96 (0.79, 1.15)	0.80 (0.66, 0.97)	0.78 (0.63, 0.97)	0.004
Model 2	1.00	1.05 (0.86, 1.28)	0.93 (0.76, 1.15)	0.90 (0.71, 1.14)	0.16
Intraparenchymal hemorrhage, n	73	150	207	126	
Model 1	1.00	1.06 (0.79, 1.42)	1.14 (0.85, 1.51)	1.14 (0.84, 1.55)	0.35
Model 2	1.00	1.16 (0.86, 1.57)	1.29 (0.95, 1.75)	1.25 (0.89, 1.76)	0.23
Subarachnoid hemorrhage, n	48	102	124	77	

Model 1	1.00	0.91 (0.63, 1.30)	0.83 (0.58, 1.18)	0.84 (0.57, 1.24)	0.37
Model 2	1.00	0.94 (0.64, 1.37)	0.81 (0.55, 1.20)	0.78 (0.51, 1.20)	0.18
Ischemic heart disease, n	74	89	109	48	
Model 1	1.00	0.72 (0.53, 0.996)	0.71 (0.52, 0.97)	0.52 (0.36, 0.77)	0.002
Model 2	1.00	0.75 (0.54, 1.05)	0.74 (0.52, 1.04)	0.56 (0.36, 0.85)	0.01
Total cardiovascular diseases, n	376	647	779	460	
Model 1	1.00	0.92 (0.81, 1.05)	0.85 (0.74, 0.97)	0.82 (0.71, 0.95)	0.004
Model 2	1.00	0.99 (0.86, 1.14)	0.94 (0.82, 1.09)	0.89 (0.76, 1.05)	0.10

¹HRs (95% CIs) were derived from Cox proportional hazards regression models. Model 1 was stratified by area and adjusted for age.

Model 2 was adjusted further for body mass index, leisure-time physical activity, smoking status, alcohol intake, histories of hypertension or diabetes mellitus, treatment for hypercholesterolemia, total energy intake, dietary intakes of vegetables, fruits, red meat, processed meat, fish, soy, green tea and salt.