Title page

Title: Impact of seaweed intake on health

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19 **Running title:** Seaweed intake and lifestyle-related diseases

Abstract (177 words)

Seaweeds contain minerals, vitamins, soluble dietary fibers, and flavonoids, which are regarded as preventive agents against lifestyle-related diseases. Seaweeds are consumed commonly in East Asian countries including Japan. Thus, intake of seaweeds might contribute to Japanese longevity via prevention of lifestyle-related diseases. Recently, 2 large Japanese cohort studies have reported the association of seaweed intake with reduced risk of cardiovascular diseases. On the other hand, seaweeds also contain iodine and heavy metals such as arsenic species, which are considered to have adverse effects on health. We here reviewed studies of the association between seaweed intake and mortality from or incidence of cancer and cardiovascular diseases, and their risk factors such as blood pressure or serum lipids. We also summarized the adverse effects of iodine and arsenic species in seaweeds. Although seaweeds have not been widely consumed in Western countries, dietary diversification and an increased proportion of immigrants from East Asia may increase seaweed consumption in those countries. Further epidemiological studies including observational and interventional studies are necessary to clarify the effects of seaweeds on disease and health.

INTRODUCTION

Apart from industrial food processing, seaweeds are not widely eaten in Western countries (except for parts of Scotland and Ireland) but are broadly consumed in East Asian countries such as Japan, Korea, and parts of China. Japanese, for example, consumed an average of 10.4 g a day of seaweeds in 2017 [1], which has remained unchanged over the past 10 years [2]. Seaweeds are one of the important ingredients in the Japanese traditional diet. Major species used in food preparation in Japan are brown seaweeds (*Undaria pinnatifida* ["wakame" in Japanese]; *Laminaria* species ["konbu"]; *Hizikia fusiformis* ["hijiki"]), and the laver red and green seaweeds ["nori"]. Nori is often used to make rice balls, and wakame, to make salads and miso soups [3].

Seaweeds contain several nutritional components such as potassium, dietary fiber, carotenoid (fucoxanthin), and protein [4]. The main components of seaweed are soluble fibers such as alginic acid and carrageenan [5]. These nutritional components have beneficial effects on risk factors associated with lifestyle-related diseases including blood pressure, serum lipids, blood glucose, and body weight in animals [6-12] and humans [13-15]. On the other hand, seaweeds contain iodine and heavy metals such as arsenic species, which are considered to have adverse effects on health [16-18].

To shed a spotlight on Japanese food and health, we reviewed epidemiological

54 studies of the effects on health of intake of seaweed, which is one of the unique
55 characteristic Japanese foods. The epidemiological studies of the association of seaweed
56 intake with mortality from or incidence of cancer and cardiovascular diseases are
57 summarized in Table 1, and the epidemiological studies of the association with blood
58 pressure, lipids, diabetes mellitus, weight reduction, and related factors are summarized
59 in Table 2.
60
61 **All-CAUSE MORTALITY**
62 In the preliminary report of the Japan Collaborative Cohort for the Evaluation of Cancer
63 Risk (JACC) study, a nationwide community-based study comprising approximately
64 110,000 men and women aged 40 to 79 years during the baseline period (1988–1990) in
65 Japan [19], they showed that the frequency of seaweed intake was associated with age-
66 and area-adjusted all-cause mortalities: the hazard ratio (HR) (95% confidence interval
67 [CI]) for ≥5 times/week versus <3 times/week of seaweed intake was 0.95 (0.90, 1.00)
68 among men, and 0.89 (0.83, 0.94) among women [19]. In that study, potential confounding
69 variables were not taken into account. No other studies on this issue have been
70 conducted.
71 .

CANCER

Several studies have examined the association between seaweed intake and incidence of or mortality from cancer. The preliminary report from the JACC study did not find any association between frequency of seaweed intake and age- and area-adjusted mortalities from esophageal, liver, urothelial tract, or total cancers for either men or women, nor from uterine cervix or breast cancers for women [19]. However, it showed that seaweed intake was associated with higher mortality from gallbladder cancer in women and with lower mortality from lung, pancreas, and kidney cancers in men [19]. Again, multivariable-adjusted HRs were not shown in that study, and the mechanisms of protection of these cancers were not discussed. A case-control study among men in Shanghai showed that seaweed and kelp intakes were inversely associated with incidence of gallbladder cancer [20]. The Ohsaki Study, a follow-up study of Japanese 32,859 men and women in Northeast Japan, showed no significant association between seaweed intake and incidence of pancreatic cancer in men. (Results on the consumption of seaweeds in women were not analyzed because of poor reliability.) [21]

The Life-Span Study, a follow-up study of atomic bomb survivors in Hiroshima and Nagasaki, found that seaweed consumption was not associated with incidence of breast cancer among 34,759 Japanese women [22]. The JACC study also showed a null

association with mortality for breast cancer [19]. A case-control study involving 362 Korean women who had histologically confirmed breast cancer and their controls reported that intake amount and frequency of gim (a kind of nori) were inversely associated with incidence of breast cancer in premenopausal women [23]. In that study, however, the association was no longer significant after further adjustment for dietary factors. The volume of seaweed intake in Japanese preschool children (aged 3–6 years) was correlated with urinary concentrations of estrone, one of the risk markers of breast cancer. The Spearman correlation coefficient between seaweed intake and estrone levels was -0.144, $p = 0.03$ for boys and -0.147, $p = 0.041$ for girls in that cross-sectional study [24].

In a prospective study of 7,998 men of Japanese ancestry in Hawaii, consumption of seaweeds was associated with an increased incidence of prostate cancer: the crude HR (95% CI) for ≥5 times/week versus ≤1 time/week of seaweed intake was 1.74 (1.05, 2.90) [25]. No associations were reported between frequency of seaweed intake and mortality from prostate cancer in the JACC study [19], nor between frequency of seaweed intake and incidence of prostate cancer in the Life-Span Study [26].

The Japan Public Health Center-Based Prospective (JPHC) study which involved 52,679 women aged 40 to 69 years from 10 communities found that frequency

of seaweed intake at the baseline period (1990–1994) was associated with increased incidence of papillary thyroid carcinoma regardless of menopausal status, and with total thyroid cancer in postmenopausal women in their mean of 14.5-year follow-up: the multivariable-adjusted HR (95% CI) for almost daily versus ≤2 days/week of seaweed intake was 1.86 (1.03, 3.34; *p* for trend = 0.04) for papillary thyroid carcinoma in women and 2.43 (1.18, 4.98; *p* for trend = 0.02) for total thyroid cancer among postmenopausal women [27]. On the other hand, the JACC study showed that seaweed intake was not associated with incidence of thyroid cancer among either premenopausal or postmenopausal women [28]. The authors of the JACC Study stated that a potential reason for the inconsistency between the two studies may be the difference in the incidence rates among the lower seaweed intake category [28].

A cohort study of Japanese-American men showed no significant a positive association between frequency of seaweed intake and incidence of upper aerodigestive tract cancer [29].

As for cancers of the digestive tract, the JACC study reported a positive association between seaweed intake and mortality from colon cancer among men: the HR (95% CI) for ≥5 days/week versus <3 days/week of seaweed intake was 1.46 (1.03, 2.08) [19]. No association was found between frequency of seaweed intake and mortality

126 from rectal or stomach cancers in either men or women [19]. On the other hand, a case-
127 control study in Japan, involving 365 Japanese men and women (mean age, 54.4 years
128 for the cases and 54.6 years for the controls) reported that the frequency of seaweed
129 intake was not associated with the incidence of colon cancer [30].

130 No epidemiological studies have been reported on the association between
131 seaweed intake and either risk of skin or bladder cancer.

132 Most studies on the association between seaweed intake and cancer have been
133 reported from Japan and have shown no evident associations. The evidence on this issue
134 is still limited and future studies are necessary to confirm these findings.

135

136 **CARDIOVASCULAR DISEASE**

137 The mortality rate from ischemic heart disease in Japan has been the lowest in the world
138 [31], which has been considered relevant to Japanese healthy dietary patterns characterized
139 not only by fish, but also by seaweed intake [32, 33]. Recently, 2 large cohort studies
140 reported an association between seaweed intake and cardiovascular diseases in Japan.

141 One is the JACC Study. In 2007, it preliminarily reported an association
142 between seaweed intake and mortality from cardiovascular diseases through the end of
143 2003[19] and recently updated its findings through 2009 [34]. A significantly inverse

association was found between frequency of seaweed intake and mortality from total stroke among women, and non-significantly among men (Figure 1) [34]. No such association was observed for ischemic heart disease.

The other large cohort study, the JPHC study [35], involving 86,113 men and women aged 40 to 69 years, reported that frequency of seaweed intake was inversely associated with incidence of ischemic heart disease, but not with that of stroke or its subtypes, among middle-aged Japanese men and women (Figure 2) [35]. Unlike the JACC study, it found a significantly inverse association of seaweed intake with risk of ischemic heart disease, but not with risk of any stroke subtype. The reasons for this inconsistency warrant discussion. As for stroke, the different results could be due to the different categories of frequency of seaweed intake (4 categories in the JPHC study, 5 categories in the JACC study). The JPHC study did not differentiate the categories of never and <1 day/week in the questionnaire, so it might have missed significant associations. Another possible reason is that unlike the JPHC study, which followed incident strokes, the JACC study followed only stroke deaths, which may be more likely to be severe cases. As for ischemic heart disease, the discrepancy may also be due to the different modes of outcome studied, that is, incidence versus mortality. Validation studies have shown that approximately one-quarter of deaths from ischemic heart

disease as recorded on death certificates were misdiagnosed [36, 37]. Therefore, the association between seaweed intake and mortality from ischemic heart disease in the JACC study could be attenuated. Another possibility, that of differences in the dietary survey methods, study areas, and study periods, should also be noted. Taking the results from the JPHC and the JACC studies together, despite their inconsistency, the possibility remains that seaweed could be beneficial for prevention of both stroke and coronary heart disease, which should be confirmed by future studies.

The possible mechanisms for the protective effect of seaweeds against cardiovascular diseases are a blood pressure-lowering effect as shown in animal studies [6-9] and a serum lipid-controlling effect [10, 11]. In addition, several human studies have shown the impact of seaweed intake on cardiovascular risk factors, as discussed below.

BLOOD PRESSURE, LIPIDS, AND DIABETES MELLITUS

As for the association between seaweed intake and blood pressure levels, a cross-sectional study of Japanese preschool boys and girls reported that the tertiles of seaweed intake calculated from a 3-day dietary record for the lowest tertile (median 0.06 g/day for boys and 0.07 g/day for girls) versus the highest tertile (median 1.11 g/day and 1.30 g/day, respectively) were inversely associated with systolic blood pressure (SBP) among

girls (102.4 versus 96.9 mmHg, p for trend = 0.030) and diastolic blood pressure (DBP) among boys (62.8 versus 59.6 mmHg, p for trend = 0.038) [38]. In a cluster-randomized trial study of Japanese preschool children (39 boys and 42 girls) aged 4 to 5 years, school lunch with 6 sheets of roasted Nori per day for 10 weeks lowered DBP and SBP compared to that without Nori among boys (-6.77 mmHg versus -0.05 mmHg, p = 0.031 for DBP and -8.29 mmHg versus 0.50 mmHg, p = 0.051 for SBP), but not among girls [39]. In a randomized double-blind placebo-control trial, supplementation of 4–6 g/day seaweed capsules lowered SBP more (-10.5 mmHg versus -6.4 mmHg for 2 months) than did 0–4 g/day seaweed capsules among Ecuador participants with at least 1 symptom of metabolic syndrome[40]. Another randomized controlled trial showed that the DBP levels in Japanese hypertensive patients decreased by 8 mmHg after treatment with 5 g wakame powder/day for 8 weeks ($p < 0.05$), whereas the decrease in the nontreated group was not significant [15], and that the difference in the DBP changes after 8 weeks between the 2 groups was significant ($p < 0.05$). Another double-blind crossover trial of 62 untreated mild hypertensive Swedish patients (mean age, 48.2 years) showed a 10.1 mmHg decrease in mean blood pressure levels ($p < 0.01$) among participants given 12 g/day seaweed fiber supplements and a 11.1-mmHg ($p < 0.01$) decrease among those given 24 g/day supplements as compared with the placebo group [41].

As for lipids, a randomized crossover trial reported that Japanese women who were provided a high-fat diet with 4 g dried wakame had a suppressed elevation of serum remnant after 6 hours and of lipoprotein levels after 4 hours as compared with those provided a high-fat diet without 4 g dried wakame, which suggested that wakame intake attenuated the postprandial increase in remnant lipoprotein cholesterol, and chylomicron levels following a fat load [42]. As far as we know, there have been no cross-sectional studies on the association between seaweed intake and serum lipids *per se*. A cross-sectional study in Korea that adjusted for age, family history of type 2 diabetes, smoking status, and physical activity showed a significantly higher odds ratio of prevalent metabolic syndrome with high frequency of seaweed intake [43].

No cohort or case-control studies have been published on the association between seaweed intake and diabetes mellitus. As for trials, 4 intervention studies have examined the association between seaweed intake and risk factors for diabetes mellitus. First, in a randomized controlled trial involving 76 Japanese diabetic patients who were provided algae ("kanten") including 4.5 g dietary fiber and who did exercise for 12 weeks, the patient group had greater reduced body weight, body mass index, and total cholesterol levels, but not HbA1c, fasting plasma glucose, or insulin response, as compared with the control group who did exercise only: -2.8 ± 2.7 kg versus -1.3 ± 2.3

kg (p = 0.008) for body weight; -1.1 ± 1.1 kg/m^2 versus -0.5 ± 0.9 kg/m^2 (p = 0.009) for body mass index; and -0.2 ± 0.7 mg/dL versus 1.0 ± 0.6 mg/dL (p = 0.036) for total cholesterol level [13]. Another randomized controlled trial that studied 20 men and women with diabetes mellitus showed that the intervention group provided a dry seaweed supplement (48 g/day) for 4 weeks had decreased levels (means ± standard deviations) of postprandial blood glucose, triglycerides, and low-density lipoprotein cholesterol as compared with the control group: 254.4 ± 22.8 mg/dL versus 203.1 ± 12.3 mg/dL, p < 0.05 for postprandial blood glucose; 178.3 ± 20.7 mg/dL versus 111.8 ± 17.6 mg/dL, p < 0.05 for triglycerides; and 123.4 ± 13.3 mg/dL versus 95.0 ± 9.0 mg/dL, p < 0.05 for low-density lipoprotein cholesterol [44]. The third randomized controlled trial in Canada, involving 23 participants, showed that a single ingestion of 500 mg brown seaweed extract before the consumption of a carbohydrate-rich meal was associated with a 12.1% reduction in the postprandial insulin response (p = 0.04) and a 7.9% increase in insulin sensitivity (p = 0.05) as compared with the placebo group but did not change the postprandial glucose levels [45]. A recent randomized crossover trial of 26 Japanese participants with untreated type 2 diabetes mellitus reported that the intervention group who consumed 200 g of rice with 4 g of dried wakame had lower blood glucose and insulin levels (means ± standard deviations) at 30 minutes after eating each meal than

234 did the control group who consumed rice only: 142.1 ± 12.7 versus 152.3 ± 16.6 mg/dL,
235 $p < 0.01$ for blood glucose and 25.4 ± 11.7 versus 31.0 ± 18.2, $p < 0.05$ for insulin levels
236 [46].

237 Taken together, these findings indicate that seaweed intake may lower blood
238 pressure and serum lipids such as triglyceride, low-density lipoproteins, and total
239 cholesterol and that seaweed intake may control blood glucose levels, insulin levels, and
240 sensitivity after meals.

241

242 **WEIGHT REDUCTION AND RELATED FACTORS**

243 A double-blind, parallel-intervention study of obese Danish participants (n = 80, aged
244 20–55 years) showed that a 12-week intervention with an energy-restricted diet plus 500
245 mL cold tap water with sodium alginate (15 g fiber) from seaweeds before each of the 3
246 daily main meals decreased body weight more than did the placebo (-6.78 kg versus -
247 5.04 kg, $p = 0.03$) [47]. A single-blind crossover study of 12 overweight and obese men
248 (mean age, 40.1 years) in the United Kingdom showed that addition of 4% of seaweed
249 (*Ascophyllum nodosum*) to breakfast bread lowered their energy intake by 16.4% as
250 compared with control bread [48].

251 In a randomized double-blind placebo-control trial conducted in Japan, the

intervention with 4–6 g/day powdered seaweed (wakame) capsules, compared with that with 0–4 g/day powdered seaweed capsules, reduced waist circumference more (5.5 cm versus 3.1 cm for 2 months) among women, but no changes were observed for body weight, inflammation biomarkers, or lipids [40].

A clinical trial of healthy Japanese women suffering from low defecation frequency (3–5 times/week) (n = 22, aged 40 ± 6.8 years) showed that a 2-week intervention with 4 g of dried wakame per day increased the fraction of bifidobacteria as a percentage of all fecal bacteria, indicating that it may have prebiotic properties [49].

Collectively, the results of these intervention studies show that seaweed intake may reduce body weight and waist circumference.

POTENTIAL ADVERSE EFFECTS OF SEAWEED INTAKE

ARSENIC

A major health concern related to seaweeds is that they contain arsenic. Arsenic species could be categorized into toxic (inorganic arsenic, which is a class I carcinogen), nontoxic (arsenobetaine), or potentially toxic (fat-soluble arsenic, arsenosugars, and other organoarsenicals) [50]. The adverse effects of inorganic arsenics on health include deoxyribonucleic acid damage, which predisposes a cell to carcinogenesis [16]. Exposure

to inorganic arsenic causes bladder, skin, and lung cancers and has been classified as carcinogenic to humans by the International Agency for Research against Cancer [16]. Consumption of arsenic has been reported to have an adverse impact on risk of cardiovascular disease and diabetes [17, 18]. Seaweeds, particularly hijiki, naturally accumulate arsenic [51]. One portion (20 g) of wet hijiki contains 0.22 mg of inorganic arsenic, which exceeds the tolerable intake level per day defined by the World Health Organization [52]. However, no evidence has been shown of effects on health of arsenic poisoning derived from the inorganic arsenic contained in hijiki [53], and it has been suggested that harmful effects on individuals' health would be unlikely unless the individuals consume extremely high amounts of hijiki [53].

IODINE

Seaweeds, especially konbu [54], are rich in iodine and are the major source of iodine intake in Japanese [55, 56]. In a double-blind randomized crossover study involving 25 healthy postmenopausal women (mean age, 58 years), supplementation of seaweed (*Alaria esculenta*) capsules (5 g/day) containing 475 μg of iodine versus placebo (maltodextrin) for 7 weeks increased serum thyroid-stimulating hormone (1.69 versus 2.19 μU/mL, $p < 0.0001$) [57]. A case-control study [58] and a case report [59] indicated that

288 excess intake of iodine mainly from seaweeds by mothers during pregnancy or breast-
289 feeding led to their infants having hyperthyrotropinemia or hypothyroidism. Konbu
290 iodine-induced hypothyroidism was reported 6 times more frequently in coastal areas of
291 Japan in which konbu was produced [60]. However, nutrients contained in seaweeds are
292 basically calculated from the raw weight before cooking and processing, and most of the
293 konbu was consumed as soup stock, not directly in its raw form. The net iodine intake in
294 Japanese was estimated to be approximately 50% of the usual iodine intake [61]. An
295 ecological study showed that iodine deficiency was associated with mortality from
296 breast cancer [62]. However, as mentioned above, prospective studies showed no
297 association between seaweed intake and risk of breast cancer [19, 22].
298
299 **CONCLUSIONS**
300 Among middle-aged Japanese men and women, studies showed that seaweed intake was
301 inversely associated with incidence of ischemic heart disease and mortality from stroke
302 probably via blood-pressure and lipid-lowering effects. The evidence for the effect of
303 seaweeds on cancer is limited and inconsistent. Although seaweeds have not been
304 widely consumed in Western countries, dietary diversification and an increased
305 proportion of immigrants from East Asia may lead to an increase in its consumption in

306 those countries. Further studies including observational and interventional studies are
307 required to elucidate the effects of seaweeds on diseases and health.
308
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312 **Conflict of Interest**
313 The authors have no conflict of interest to declare.

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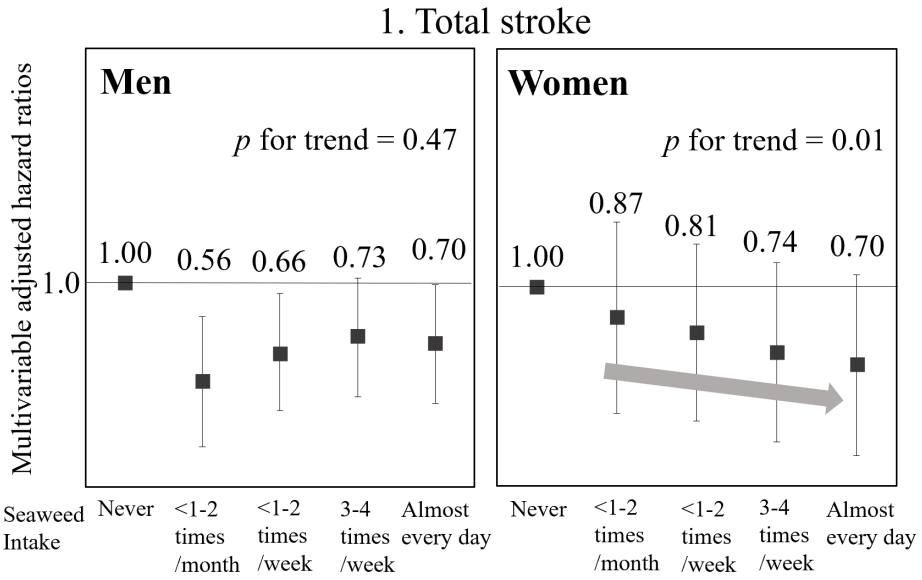
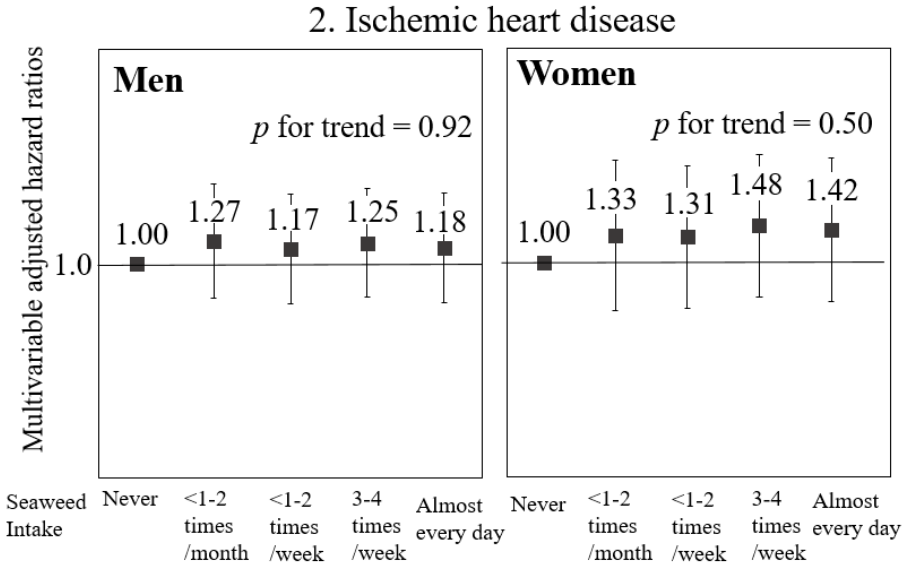
Figure 1. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality from total stroke and ischemic heart disease according to the frequency of seaweed intake among men and women in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk study

Figure 2. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incidence of total stroke and ischemic heart disease according to frequency of seaweed intake among men and women in the Japan Public Health Center-Based Prospective study

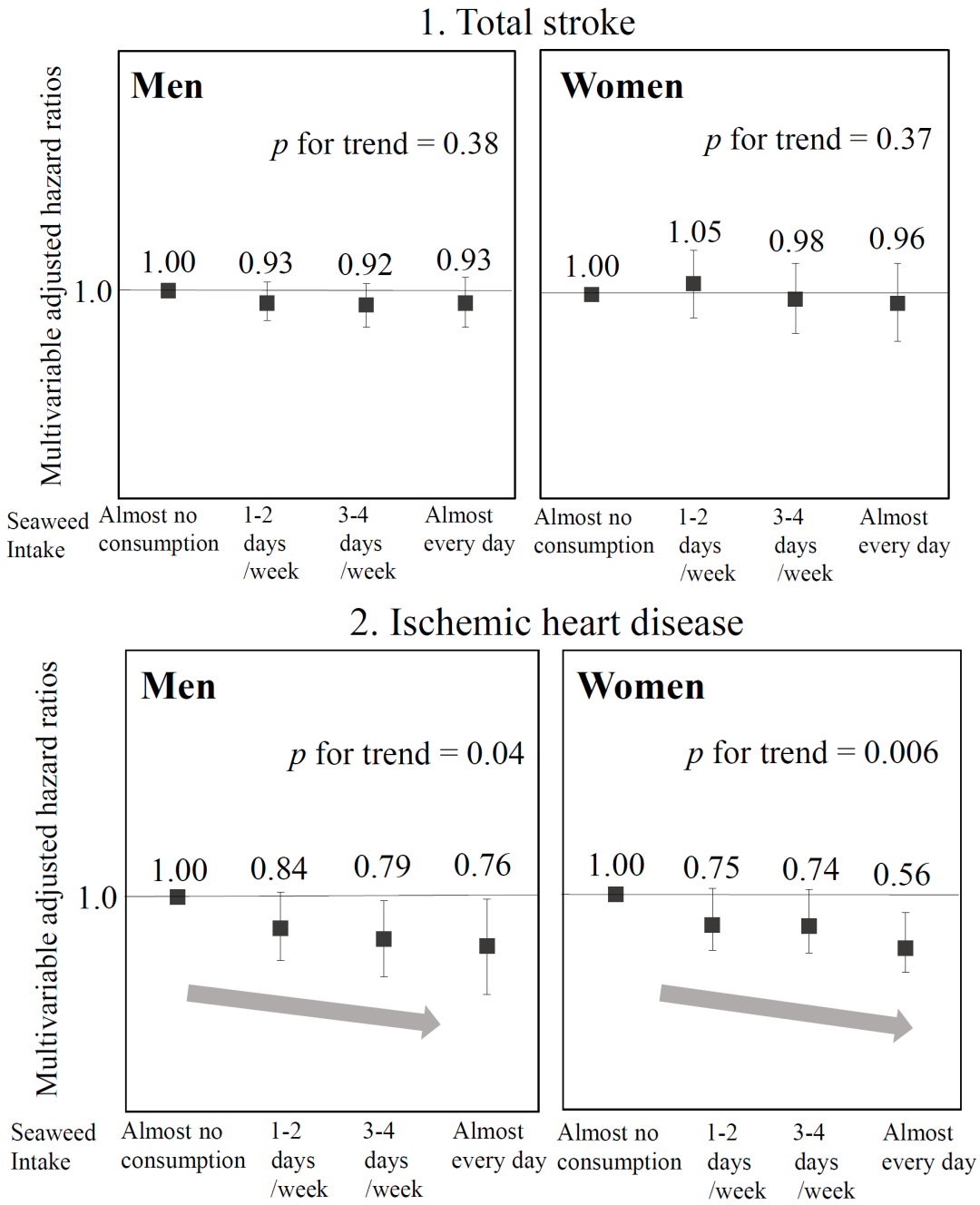
Figure 1. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality from total stroke and ischemic heart disease according to the frequency of seaweed intake among men and women in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk study





HRs (95% CIs) were derived from Cox proportional hazards regression models. All the models were stratified by area and adjusted for age, mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, perceived mental stress, walking time, sport participation, education levels, total energy intake, and dietary intakes of vegetables, fruits, meat, fish, and salt.

Figure 2. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incidence of total stroke and ischemic heart disease according to frequency of seaweed intake among men and women in the Japan Public Health Center-Based Prospective study



HRs (95% CIs) were derived from Cox proportional hazards regression models. All the models were stratified by area and adjusted for age, body mass index, leisure-time physical activity, smoking status, alcohol intake, history of hypertension or diabetes mellitus, treatment for hypercholesterolemia, total energy intake, and dietary intakes of vegetables, fruits, red meat, processed meat, fish, soy, green tea, and salt.

Table 1. Summary of studies investigating the associations between seaweed intake and all-cause mortality, cancer and cardiovascular diseases in human

Authors	Published	Country	Study types	Participants	Exposure	Frequency or quantiy	Outcome		Results [hazard ratio (95%CI) or odds ratio (95%CI)]		Reference
									Men	Women	
Iso and Kubota	2007	Japan	Prospective study	46,395 men and 64,190 women	Seaweed intake	<3 times/week versus ≥5 times/week	Mortality	All cause mortalities	0.95 (0.90, 1.00)	0.89 (0.83, 0.94)	19
								All cancers	0.93 (0.86, 1.01)	1.01 (0.91, 1.12)	
								Esophageal cancer	1.20 (0.81, 1.80)	0.94 (0.36, 2.50)	
								Stomach cancer	1.04 (0.87, 1.25)	1.16 (0.89, 1.50)	
								Colon cancer	1.46 (1.03, 2.08)	1.00 (0.71, 1.41)	
								Rectal cancer	1.14 (0.77, 1.70)	1.48 (0.85, 2.58)	
								Livercancer	0.92 (0.73, 1.17)	0.96 (0.69, 1.36)	
								Gall bladder cancer	0.93 (0.51, 1.71)	1.91 (1.08, 3.37)	
								Pancreas cancer	0.62 (0.43, 0.89)	1.02 (0.73, 1.42)	
								Lung cancer	0.77 (0.65, 0.92)	0.76 (0.56, 1.03)	
								Breast cancer	-	0.86 (0.53, 1.40)	
								Uterine cervix cancer	-	1.16 (0.50, 2.69)	
								Prostate cancer	0.91 (0.61, 1.35)	-	
								Kidney cancer	0.40 (0.17, 0.94)	0.80 (0.25, 2.53)	
								Urothelial cancer	1.08 (0.64, 1.83)	0.65 (0.28, 1.55)	
Nelson et al.	2017	China	Case-controll study	422 men and 687 women	Seaweed and kelp	Contenuous	Incidence	Gall bladder cancer	0.65 (0.47, 0.91)	0.88 (0.70, 1.09)	20
Shigihara et al.	2014	Japan	Prospective study	16,065 men and 16,794 women	Seaweed intake	Lowest tertiles versus highest tertiles	Incidence	Pancreas cancer	0.92 (0.46, 1.84)	-	21
Key et al.	1999	Japan	Prospective study	34,759 women	Seaweed intake	≤1 time/week versus ≥5 times/week	Incidence	Breast cancer	-	0.89 (0.69, 1.16)	22
Yang et al.	2010	Korea	Case-controll study	724 women	Gim intake	Lowest quintiles versus highest quintiles (continuous)	Incidence	Breast cancer	-	0.43 (0.26, 0.70)	23
					Gim frequency	Lowest quintiles versus highest quintiles (frequency)				0.51 (0.30, 0.84)	
					Miyeok intake	Lowest quintiles versus highest quintiles (continuous)				0.89 (0.55, 1.44)	
					Miyeok frequency	≤1 time/month versus ≥2–4 times/week				0.85 (0.53, 1.35)	
Severson et al.	1989	US, Hawaii	Prospective study	7,999 Japanese ancestry men	Seaweed intake (Nori, konbu, other seaweeds)	≤1 time/week versus ≥5 times/week	Incidence	Prostate cancer	1.74 (1.05–2.90)	-	25
Allen et al.	2004	Japan	Prospective study	18,115 men	Seaweed intake	<2 times/week versus almost daily	Incidence	Prostate cancer	0.86 (0.60–1.24)	-	26
Michikawa et al.	2012	Japan	Prospective study	52,679 women	Seaweed intake	2 days/week or less versus almost daily	Incidence	Papillary thyroid cancer	-	1.86 (1.03, 3.34)	27
Wang et al.	2016	Japan	Prospective study	35,687 women	Seaweed intake	≤1-2 times/week versus daily or almost daily	Incidence	Thyroid cancer	-	1.15 (0.69, 1.89)	28
Chyou et al.	1995	US, Hawaii	Prospective study	7,995 Japanese-American men	Seaweed intake (Noru, konbu other seaweeds)	≤1 time/week versus ≥5 times/week	Incidence	Upper aerodigestive tract cancer	2.01 (1.04, 3.91)	-	29
Ping et al.	1998	Japan	Case-control study	365 among men and women	Seaweed intake	Moderate or a little versus frequent	Incidence	Colon cancer	0.80 (0.50, 1.27)		30
Iso and Kubota	2007	Japan	Prospective study	46,395 men and 64,190 women	Seaweed intake	<3 times/week versus ≥5 times/week	Morttality	Ischemic heart disease	0.93 (0.76, 1.14)	0.90 (0.70, 1.14)	19
								Total stroke	1.03 (0.90, 1.18)	0.78 (0.67, 0.90)	
Kishida et al.	2020	Japan	Prospective study	40,234 men and 55,981 women	Seaweed intake	Never versus almost every day	Morttality	Ischemic heart disease	1.18 (0.66, 2.14)	1.42 (0.66, 3.05)	34
								Total stroke	0.70 (0.49, 0.99)	0.70 (0.46, 1.06)	
Murai et al.	2019	Japan	Prospective study	40,707 men and 45,406 women	Seaweed intake	Almost no versus almost daily consumption	Incidence	Ischemic heart disease	0.76 (0.58, 0.99)	0.56 (0.36, 0.85)	35
								Total stroke	0.93 (0.81, 1.08)	0.96 (0.81, 1.15)	

Table 2. Summary of studies investigating the associations between seaweed intake and blood pressure, lipids, diabetes mellitus, weight reduction and related factors in human

Authors	Published	Country	Study types	Participants	Exposure	Frequency or quantiy	Outcome	Results		Reference
								Men	Women	
Wada et al.	2011	Japan	Cross-sectional study	223 boys and 194 girls of preschool children	Seaweed	The lowest tertile (median 0.06 g/day for boys and 0.07 g/day for girls) versus the highest tertile (median 1.11 g/day and 1.30 g/day, respectively)	Systolic blood pressure	100.0 mmHg versus 98.1 mmHg (p for trend = 0.31)	102.4 mmHg versus 96.9 mmHg (p for trend = 0.030)	38
							Diastolic blood pressure	62.8 mmHg versus 59.6 mmHg (p for trend = 0.038)	65.1 mmHg versus 61.2 mmHg (p for trend = 0.25)	
Wada et al.	2020	Japan	Cluster-randomized trial study	39 boys amd 42 girls of preschool children	Nori	Standard meals at school lunch with or without 1.76 g (6 sheets)/ day of roasted nori for 10 weeks	Systolic blood pressure	−8.29 mmHg versus 0.50 mmHg (p = 0.051)	-2.60 mmHg versus -3.07 mmHg (p = 0.90)	39
							Diastolic blood pressure	-6.77 mmHg versus -0.05 mmHg (p = 0.031)	-1.16 mmHg versus -4.29 mmHg (p = 0.35)	
Teas et al.	2009	Ecuador	Double-blinded placebo-controlled trial study	13 men and 14 women at least one symptom of the metabolic syndrome	Wakame	Supplementation of 4 and 6 g/day seaweed capsules versus supplementation of 0 and 4 g/day seaweed capsules (control) for each 4week	Systolic blood pressure	-10.5 versus -6.4 mmHg		40
Hata et al.	2001	Japan	Randomized controlled trial study	12 men and 24 women with hypertension	Wakame	5 g/day wakame powder versus control for 8 weeks	Systolic blood pressure	The difference in systolic blood pressure changes among intervention group versus control after 4 weeks ($p < 0.05$) .		15
							Diastolic blood pressure	The difference in diastolic blood pressure changes among intervention group versus control after 4 weeks ($p < 0.01$) and 8weeks ($p < 0.05$)		
Krotkiewski et al.	1991	Sweden	Double-blind crossover trial study	62 men and women with untreated mild hypertension	Seaweed fiber supplements	12 g/day versus placebo for 4 weeks	Mean blood pressure	-10.1mmHg versus placebo ($p < 0.01$)		41
						24 g/day versus placebo for 4 weeks	Mean blood pressure	-11.1 mmHg versus placebo ($p < 0.01$)		
Yoshinaga et al.	2019	Japan	Randomized crossover trial study	10 women with normolipidemia or mild hypertriglyceridemia	Wakame	A high-fat diet with or without 4 g dried wakame	Serum remnant like particle-cholesterol (RemL-C)	-	Intervention group versus placebo after 6 hours ($p < 0.05$)	42
							Serum lipoprotein levels	-	Intervention group versus placebo after 4 hours ($p < 0.05$)	
							Triglyceride levels	-	Not significant	
Shin et al.	2009	Korea	Cross-sectional study	7,081 men	Seaweed intake	Less than 1 time/week versus more than 4-6 times/week	Metabolic syndrome was defined as having three or more of the following conditions: obesity, high blood pressure, low high-density lipoprotein cholesterol level, high triglyceride level, waist circumference and high fasting blood glucose level	Odds ratio (95% confidence interval): 1.25 (1.05, 1.50)	-	43
Maeda et al.	2005	Japan	Randomized controlled trial study	28 men and 48 women with diabetes mellitus	Kanten	Conventional diet with or without provided algae ("kanten") including 4.5 g dietary fiber for 12 weeks	Body weight	-2.8 ± 2.7 kg versus -1.3 ± 2.3 kg ($p = 0.008$)		13
							Body mass index	-1.1 ± 1.1 kg/m^2 versus -0.5 ± 0.9 kg/m^2 ($p = 0.009$)		
							Total cholesterol levels	-0.2 ± 0.7 mmol/dL versus 1.0 ± 0.6 mmol/dL ($p = 0.036$)		
							HbA1c	-0.4 ± 0.9% versus 0.2 ± 0.6 % ($p = 0.192$)		
							Fasting plasma glucose	-0.4 ± 1.3 mmol/L versus 0.5 ± 1.3 mmol/L ($p = 0.783$)		
							Homeostasis model assessment-insulin resistance	-0.765 ± 1.599 versus 0.732 ± 1.39 ($p = 0.924$)		
Kim et al.	2008	Korea	Randomized controlled trial study	9 men and 11 women with diabetes mellitus	Dry powdered sea tangle and sea mustard	48 g/day dry seaweed supplement versus placebo for 4 weeks	Postprandial blood glucose levels	203.1 ± 12.3 mg/dL versus 254.4 ± 22.8 mg/dL ($p < 0.05$)		44
							Triglyceride levels	111.8 ± 17.6 mg/dL versus 178.3 ± 20.7 mg/dL ($p < 0.05$)		
							Low density lipoprotein-cholesterol levels	95.0 ± 9.0 mg/dL versus123.4 ± 13.3 mg/dL ($p < 0.05$)		
Paradis et al.	2011	Canada	Double-blind, randomized, placebo-controlled crossover study	11 men and 12 women	Brown seaweed (Ascophyllum nodosum and Fucus vesiculosus)	500 mg brown seaweed extract versus placebo before the consumption of a carbohydrate-rich meal	Postprandial insulin response	12.1% reduction versus placebo ($p = 0.04$)		45
							Insulin sensitivity	7.9% increase versus placebo ($p = 0.05$)		
							Glucose response	Not significant		
Yoshinaga et al.	2019	Japan	Randomized crossover trial study	15 men and 11 women with untreated type 2 diabetes mellitus	Dried wakame	200 g of rice with or without 4 g of dried wakame	Blood glucose levels	142.1 ± 12.7 mg/dL versus 152.3 ± 16.6 mg/dL after 30 minutes ($p < 0.01$)		46
							Insulin levels	25.4 ± 11.7 μU/mL versus 31.0 ± 18.2 μU/mL after 30 minutes ($p < 0.05$)		
Teas et al.	2009	Ecuador	Double-blinded placebo-controlled trial study	13 men and 14 women at least one symptom of the metabolic syndrome	Wakame	Supplementation of 4 and 6 g/day seaweed capsules versus supplementation of 0 and 4 g/day seaweed capsules (control) for each 4week	Waist circumference	-2.2 cm versus -2.3 cm	-5.5 cm versus -3.1 cm	40
Georg Jensen et al.	2012	Denmark	Double-blind, parallel-intervention study	26 men and 54 women with obesity	Sodium alginate from seaweed	An energy-restricted diet plus 500 mL cold tap water with or without sodium alginate (15 g fiber) from seaweeds before each of the 3 daily main meals for 12 weeks	Body weight	-6.78 ± 3.67 kg versus -5.04 ± 3.40 kg ($p = 0.03$)		47
Hall et al.	2012	United Kingdom	Single-blind crossover study	12 overweight or obese men	Seaweed (Ascophyllum nodosum)	Bread with or without 4 % of seaweed (Ascophyllum nodosum) at breakfast	Eenergy intake	-16.4 % versus control after 4 hours meals ($p=0.006$)	-	48
Yoshinaga et al.	2018	Japan	Clinical trial study	22 healthy women suffering from low defecation frequency	Dried wakame	4 g/day of dried wakame for 2 weeks	Defecation days	-	5.55 ± 1.41 times/week versus 4.55 ± 0.88 times/week ($p = 0.004$)	49
							Stool volumea	-	4.98 ± 1.08 times/week versus 3.98 ± 0.49 times/week ($p = 0.001$)	
							Defecation frequency	-	12.7 ± 8.3 pieces/week versus 9.03 ± 5.02 pieces/week ($p = 0.004$)	
							Bifidobacterium of fecal microbiota	-	34.73 % versus 25.84 % ($p < 0.05$)	