Intake of fish and long-chain n-3 polyunsaturated fatty acids and risk of diseases in a Japanese population: a narrative review

Running title: Fish/n-3 fatty acids and risk of diseases in Japanese

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Abstract

Since the 1970s, the potential benefit of fish intake in terms of noncommunicable diseases has been one of the most important themes in disease prevention. Epidemiological studies have revealed the extent to which fish consumption affects the incidence of and mortality from diseases. Meta-analyses summarized the effect of fish and long-chain n-3 polyunsaturated fatty acid intake on noncommunicable diseases, especially cardiovascular diseases in Western countries. However, few reviews have spotlighted the effect of fish intake in East-Asian countries that have high population levels of fish intake such as Japan. We narratively reviewed the epidemiological studies concerned with the associations of fish and long-chain n-3 polyunsaturated fatty acid intake with risk of noncommunicable diseases, mainly of cardiovascular disease, among Japanese, whose fish intake has been twice or more than that of most Westerners. Overall, fish or LC n-3 PUFA intake may be beneficial for prevention of noncommunicable diseases, especially coronary heart disease and heart failure in Japanese as well as in Westerners. However, the beneficial effects of their intakes seemed to be nonlinear and varied according to disease severity and culture. Studies on other noncommunicable disease were also narratively reviewed.

Introduction

Since 1978, when Dyerberg and colleagues hypothesized that eicosapentaenoic acid (EPA) was preventive against thrombosis and atherosclerosis, the beneficial effects of fish and/or long-chain n-3 (ω-3) polyunsaturated fatty acid (LC n-3 PUFA) intakes on health has been one of the major research and public health interests (1). Many epidemiological studies conducted since the 1980s revealed the beneficial effect of fish intake on risk of coronary heart disease (CHD) (2, 3). The Seven Countries Study showed an ecological finding that the CHD mortalities of the areas studied (Northern Europe, Southern Europe Inland, Southern Europe Mediterranean, United States, Serbia, and Japan) varied even in the same serum total cholesterol strata: the Southern Europe Mediterranean area and Japan showed a lower mortality from CHD than those of the other countries (4). Later, the Mediterranean and Japanese diets came to be regarded as good for CHD prevention. Fish intake is a common feature of both diets. Fish contains a variety of nutrients, such as LC n-3 PUFA, protein, taurine, vitamin B, vitamin D, magnesium, and zinc. Of these, LC n-3 PUFA, which is rich in fish oil, plays an important role in disease prevention. LC n-3 PUFA improves cell membrane fluidity as well as anti-inflammatory, antithrombotic, and antiarrhythmic effects and increased high-density lipoprotein (HDL) cholesterol and lowered triglycerides (5-11). As these beneficial effects of fish intake became apparent, epidemiological studies expanded the

scope of investigation to examine the association for cardiovascular risk factors, cerebrovascular disease, cancer, and all-cause death. There may be a threshold effect between fish or LC n-3 PUFA intake and risk of various diseases (12). However, the association between high fish and/or LC n-3 PUFA intake and risk of diseases has been inconsistent, partly because the distribution of fish and LC n-3 PUFA intakes differ across populations (ie, Western vs East-Asian populations). There are some European countries where people consume fish to the same extent as Japanese, such as Iceland, Norway, Spain, and Portugal. According to national nutritional surveys, average fish intake among middle-aged men was 92 to 108 g/day in Japan in 2002, 74 g/day in Korea in 2007, 62 g/day in Iceland in 2002, and 7 g/day in the United States in the period from1994 to 1996 and in 1998 (13). Recently, however, fish consumption in Japanese adult men has been decreasing: according to a 2018 national nutritional survey, it was 77 g/day (14).

In this narrative review based on a search of PubMed and an authors' database, we present the evidence related to associations between fish and/or LC n-3 PUFA intakes and cardiovascular diseases (coronary heart disease, stroke, cardiovascular disease, aortic disease, and atherosclerosis) (Table 1), all-cause death, and other diseases (cancer, dementia and cognitive dysfunction, autoimmune disease, and other diseases and

symptoms) (Table 2) in Japanese people.

Dietary fish and long-chain n-3 polyunsaturated fatty acids intakes and their biomarkers among Japanese

The methods of preparing and eating fish in Japan are different from those in Western countries. Japanese usually eat fish with the addition of salty flavoring, such as fresh fish (eg, sashimi, or raw fish) with soy sauce, baked fish with salt, and/or boiled fish with soy sauce or miso, whilst Americans traditionally eat fish with the addition of oily flavoring, such as sautéed or fried fish with lard. The proportion of serum LC n-3 PUFA in men was high in Japanese living in Japan, followed by Japanese Americans and Americans living in the United States in 1987 and 2002-2006 (15, 16). Likewise, compared with Icelanders and US white men, Japanese men consumed larger amounts of fish and had higher levels of serum LC n-3 PUFA (13).

A. Coronary heart disease (CHD)

For Westerners, the association between fish and/or LC n-3 PUFA intake and risk of CHD has been investigated in several prospective studies. For example, a study of American middle-aged men showed that men with daily fish intake of 35 g/day or more had a lower risk of death from CHD and myocardial infarction (MI) (3). Another study of American older men and women showed that participants with tuna/other fish intake

of 2 or more times a week had a lower risk of ischemic heart disease death, and participants with tuna/other fish intake of 3 times or more a week had a lower risk of arrhythmic ischemic heart disease death than did participants who consumed fish less than once a month (17). A recent meta-analysis showed an inverse association between dietary fish intake and risk of CHD on the basis of 22 prospective studies, including a Japanese study (18). In that meta-analysis, the risk of CHD was decreased by approximately 15% with increased intake of fish of up to 250 g/day. A science advisory from the American Heart Association stated that the benefit of seafood meal intake was evident for persons whose basic seafood intake was low (19). The Cochrane Database of Systematic Reviews for n-3 PUFA was recently updated and showed that increasing LC n-3 PUFA intake was slightly associated with reduced risk of incidence of and mortality from CHD (20).

On the other hand, in some European countries with a high level of fish intake such as Spain and Iceland, an association between fish intake or LC n-3 PUFA and risk of CHD was not observed (21, 22). A prospective study of 41,091 Spanish men and women whose mean fish, EPA, and docosahexaenoic acid (DHA) intake were 63 g/day, 0.2 g/day, and 0.4 g/day, respectively, showed no association between EPA and DHA intake and risk of CHD (21). The prevalence association study of 2966 Icelandic older

75 women, in which 89% of them consumed 2 or more portions of fish a week in midlife,
76 did not find any associations between fish intake in adolescence or midlife and
77 prevalent CHD (22) but did find an association between fish-liver oil and prevalent
78 CHD.

79 Several Japanese prospective studies showed that fish or LC n-3 PUFA intake was
80 associated with lowered risk of incident CHD and MI but not with mortality from them
81 (23-28), whilst a nested case-control study from the Japan Public Health Center-Based
82 Prospective (JPHC) study showed that plasma LC n-3 PUFA of total fatty acids was
83 inversely associated with risk of fatal coronary events and sudden cardiac death, but not
84 with total CHD (29). Another study, the Circulatory Risk in Communities Study
85 (CIRCS), showed no association between risk of CHD and serum EPA,
86 docosapentaenoic acid (DPA), or DHA levels (30). As for preserved fish products, the
87 JPHC study showed an inverse association between dried and salted fish intake and risk
88 of MI (31).

89 As described, the results of studies of Japanese, as well as those of some
90 European countries, related to high fish intake, showed a generally weaker effect of fish
91 and LC n-3 PUFA intake on coronary heart disease, especially for mortality. The
92 difference in the results between Japanese and most Westerners should be based on their

different distributions of fish intake. For example, the median amount of fish intake in the lowest and highest quintiles were 23 g/day and 180 g/day in the JPHC Study (24), whereas the respective amounts in a US study were 0 g/day and 35 g/day (3).

A pooled analysis of 19 studies of 16 countries, comprising 13 Western countries and 3 countries (Israel, Costa Rica, and Singapore), showed inverse associations between biomarkers of DHA and DPA (but not EPA) and risk of fatal CHD, but no associations were found for nonfatal MI (32). Another meta-analysis on circulating LC n-3 PUFA showed that EPA and DHA levels were inversely associated with risk of coronary fatal events including fatal or nonfatal MI, CHD, coronary insufficiency, coronary death, angina, angiographic coronary stenosis, and sudden cardiac death (33). In Japan, two nested-case control studies were performed. The JPHC study found an inverse association between plasma LC n-3 PUFA (EPA + DPA + DHA) and risk of fatal coronary events, but not of incident CHD (29). In that study, EPA was inversely associated with risk of fatal CHD, and DHA was inversely associated with risk of fatal CHD and sudden cardiac death; DPA was not associated with risk of CHD (29). On the other hand, the CIRCS did not find such associations of serum EPA, DPA, and DHA with risk of CHD (30).

An antiarrhythmic effect, which is a major factor contributing to the prevention

111 of death from CHD, has been regarded to appear with small amounts of fish and LC n-3
112 PUFA intake, whilst triglyceride-lowering and antithrombotic effects appear with larger
113 amounts (12). This was in line with the finding of the Nurses' Health Study showing
114 that fish intake was inversely associated with the risk of fatal CHD, but not with the risk
115 of nonfatal MI (34). However, randomized control trials showed that small amounts of
116 LC n-3 PUFA supplementation, about 1000 mg/day, did not lower the risk of ventricular
117 arrhythmia or death from arrhythmia (35, 36), and a large amount of supplementation of
118 about 3600 mg/day lowered the risk of ventricular tachyarrhythmia (37). The
119 antiarrhythmic effect obtained from a small amount of LC n-3 PUFA supplementation is
120 still controversial; however, these trials could not examine the effect of a long-term
121 small amount of LC n-3 PUFA. In any case, the difference in the results of these
122 Western and Japanese studies could be explained by the fact that most Japanese
123 consume fish at levels that are higher than the levels providing an antiarrhythmic effect.
124 The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a randomized
125 clinical trial of 18,645 Japanese men and women with a total cholesterol of 252 mg/dL
126 or greater and with statin medication, demonstrated that EPA supplementation, at 1800
127 mg/day, significantly lowered the risk of major coronary events, namely, sudden cardiac
128 death, fatal and nonfatal MI, and other nonfatal events including unstable angina

129 pectoris, angioplasty, stenting, and coronary artery bypass grafting (38). For CHD, EPA
130 supplementation 19% lowered the risk of nonfatal coronary events (including unstable
131 angina), but not of coronary death or fatal/nonfatal MI (38). The JELIS is an important
132 study because it showed the effect of EPA supplementation on risk of coronary events in
133 patients receiving statin medication. However, the JELIS had some limitations. Its open
134 interventional design might have led to bias from physician-initiated endpoints, such as
135 unstable angina and coronary revascularization. After the JELIS, the Reduction of
136 Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) of 8179
137 men and women was conducted. The study participants were aged 45 years or older
138 with established cardiovascular disease (CVD) or aged 50 years or older with diabetes
139 mellitus and at least one additional cardiovascular risk factor. At entry screening, they
140 were receiving statin therapy, had a fasting triglyceride level of 135-499 mg/dL, and a
141 low-density lipoprotein cholesterol level of 41 to 100 mg/dL. After a median 4.9-year
142 follow-up, they showed reduced risk of coronary events with 4000 mg/day EPA
143 supplementation (39). The REDUCE-IT adopted a double-blind design and showed the
144 effect of EPA supplementation on hard endpoints, namely, cardiovascular death,
145 nonfatal MI, and nonfatal stroke. These results showed the beneficial impact of EPA
146 supplementation on prevention of coronary events among high-risk patients receiving

147 statin medication.

148

149 **B. Heart failure**

150 An inverse association between fish intake and risk of heart failure was first reported in
151 the Cardiovascular Health Study (40). In Japan, the Japan Collaborative Cohort Study
152 for Evaluation of Cancer Risk (JACC) study showed a significant inverse association
153 between fish or LC n-3 PUFA intake and mortality from heart failure (23).

154 A meta-analysis conducted by Djoussé et al concluded that dietary intake of both
155 fish (5 studies) and LC n-3 PUFA (6 studies) intakes was inversely associated with risk
156 of heart failure, and in a dose-response manner (41). A more recent meta-analysis of 8
157 Western studies also showed an inverse association between fish intake and risk of heart
158 failure (18).

159 According to these results, fish and LC n-3 PUFA intake are beneficial for
160 prevention of heart failure. Plausible mechanisms for lowering mortality from heart
161 failure may be similar to those for CHD. In addition, LC n-3 PUFA may improve
162 cardiac structure, function, and hemodynamics (42).

163

164 **C. Stroke**

In Japan, five prospective cohort studies and a nested case-control study examined the association between fish or LC n-3 PUFA intake and the incidence of or mortality from stroke (23, 26, 28, 43-45). A prospective study based on six prefecture cohorts showed an inverse association between fish intake and mortality from total stroke and cerebral hemorrhage, but not mortality from cerebral embolism or thrombosis (44). Another prospective study, the Life Span Study, showed a significant inverse association between fish product intake and mortality from total stroke and intracerebral hemorrhage, but not mortality from cerebral infarction (43). Other prospective studies showed no significant association between fish or LC n-3 PUFA intake and incidence of or mortality from stroke (23, 26, 28). A nested case-control study showed no association between serum proportions of n-3 polyunsaturated fatty acids and risk of stroke (45).

A prospective study of Spanish men and women who took fish intake frequently showed no association between lean fish, fatty fish, and total fish consumption and risk of stroke (46).

A recent meta-analysis of 12 studies from Europe and 8 studies from United States showed an inverse association between fish intake and risk of stroke among participants whose fish intake range was 0 to 130 g/day (18). Whether a further risk reduction would be observed with higher fish intakes among Western populations remains uncertain. The

183 Cochrane review showed no association between LC n-3 PUFA supplementation and
184 risk of stroke (20).

185 Interventional studies also examined the effect of EPA supplementation on risk of
186 stroke. The JELIS did not show a significant association between them (38), whilst the
187 REDUCE-IT showed a significantly lower risk of fatal and nonfatal stroke among
188 participants with EPA supplementation (39).

189 Taken together, the findings on the association for risk of stroke were inconsistent
190 and the impact of fish intake on risk of stroke was probably weaker than that on risks of
191 CHD and heart failure.

192

193 **D. Cardiovascular disease (CVD)**

194 Three prospective cohort studies examined the association between fish or LC n-3
195 PUFA intake and CVD mortality in Japanese (23, 28, 47). Two of those studies showed
196 an inverse association between fish or LC n-3 PUFA intake and mortality from CVD
197 (23, 28). The other study showed a marginally inverse association between fish oil (LC
198 n-3 PUFA) intake and mortality from CVD in women, but not in men (47). A
199 prospective study showed an inverse association between dried and salted fish intake
200 and risk of CVD (31).

A recent meta-analysis of 8 studies including 2 Japanese studies indicated that fish intake was inversely associated with risk of CVD mortality in Asians, but not in Westerners (48). In Asians, fish intake up to 60 g a day was linearly associated with reduced risk of CVD mortality, and the association became flat after 60 g a day. In Westerners, risk of CVD mortality was rapidly decreased with up to 20 g a day of fish intake, and the association became null after 20 g a day. The Cochrane Review reported that LC n-3 PUFA supplementation was inversely associated with mortality from CVD, but not with risk of CVD (20).

The differential effect of high fish intake between Asians and Westerners may be due to the difference in the ways of eating and preparing fish. As stated in the section of dietary intake of fish and LC n-3 PUFA in Japan, Westerners usually eat sautéed fish and fish fried with lard. Therefore, a large amount of fish intake can lead to excessive fat intake in Westerners. In fact, a study of African Americans showed that excessive fried fish intake was positively associated with risk of CVD (49), and a study of Americans showed that frequent intake of fried fish was positively associated with risk of heart failure (40).

E. Aortic disease (aortic dissection and aneurysm)

219 Recently, a pooled analysis of 8 cohort studies of Japanese community inhabitants,
220 comprising 366,048 men and women, was conducted to examine the association
221 between fish intake and mortality from aortic disease, namely, aortic dissection and
222 aneurysm (50). That study showed that participants who seldom took fish showed 1.93
223 times (95% CI: 1.13–3.31) higher mortality from total aortic disease, as compared with
224 participants who took fish 1 to 2 times a week.
225
226 **F. Atherosclerosis**
227 An ecological study of Japanese showed that the inhabitants of a fishing village showed
228 lower indices of hypertensive cardiovascular remodeling, such as left ventricular mass
229 index and intima-media thickness of the common carotid and internal carotid arteries, as
230 compared with the inhabitants of a farming village (51). Another ecological study of
231 Japanese also reported a difference in atherosclerosis between fishing and farming
232 villages, finding that both the male and the female inhabitants of the fishing village had
233 thinner intima-media thickness and a lower number of plaques in the common carotid
234 artery (52). Cross-sectional studies of Japanese showed that fish intake was not
235 correlated with carotid atherosclerosis (53, 54), whilst LC n-3 PUFA intake was
236 inversely correlated with carotid atherosclerosis estimated by ultrasonography (54, 55).

237 Serum DHA, but not EPA and total marine n-3 fatty acids, was inversely correlated with
238 coronary artery calcification measured by computed tomography (56). The proportion
239 of marine derived n-3 fatty acids of serum fatty acids was inversely correlated with
240 intima-media thickness in the common carotid artery (16).

241 The number of epidemiological studies carried out in Westerners is limited, and
242 the results were inconsistent (57, 58). A cross-sectional study of Italians showed that
243 high habitual fish consumption was inversely correlated with prevalence of carotid
244 atherosclerosis estimated by ultrasonography (57), whilst a prospective cohort study of
245 Norwegians showed no significant association between them (58). An international
246 cross-sectional study showed an almost two-fold higher level of serum marine-derived
247 n-3 PUFA in Japanese than in white and Japanese Americans and that the intima-media
248 thickness of the common carotid artery was the thinnest in Japanese (16).

249 Although the evidence was limited, fish and LC n-3 PUFA intake could be
250 beneficial for the prevention of atherosclerosis. Potential mechanisms for the beneficial
251 effect of fish on the attenuation of atherosclerosis include not only the reduction of
252 platelet aggregability, the inhibition of inflammation and endothelial dysfunction, and
253 the lowering of blood pressures and triglycerides by LC n-3 PUFA, but also the other
254 nutrients from fish such as vitamin D, potassium and other PUFAs (5-11, 48). Some or

255 all of these mechanisms could be applied for CHD, stroke, heart failure, aortic disease,
256 and chronic inflammatory diseases.
257
258 **G. All-cause death**
259 Findings related to the association between fish or LC n-3 PUFA intake and risk of all-
260 cause death among Japanese have been inconsistent. A prospective cohort study of
261 Japanese living in Takayama showed that fish oil (LC n-3 PUFA) intake was inversely
262 associated with risk of all-cause death in women, but not in men (47). The JACC Study
263 showed a marginally inverse association between fish intake and risk of all-cause death
264 (23). Another cohort study showed that serum DHA levels and the EPA/arachidonic acid
265 ratio were inversely associated with risk of all-cause death (59).
266 A recent meta-analysis of 6 Western studies and 3 Asian studies, including the two
267 Japanese studies described above, indicated that fish intake was inversely associated
268 with risk of all-cause death and that this association was evident in Asians, but not in
269 Westerners (48). For Westerners, it showed a U-shape association (48). Such a
270 difference might be due to different ways of food preparation and eating (48). On the
271 other hand, the Cochrane Review found no association between LC n-3 PUFA
272 supplementation and risk of all-cause death (20).

H. Cancer

The Takayama Study showed no association between fish oil (LC n-3 PUFA) intake and all-cancer mortality (47). The JPHC study showed a positive association between dried and salted fish intake and risk of total cancer (31). A prospective study and 2 case-control studies of Japanese examined the association between fish or LC n-3 PUFA intake and risk of breast cancer (60-62). A prospective study and one of the case-control studies showed no significant association between them (60, 61), whilst another case-control study found that among postmenopausal women, the group with the highest amount of cooked/raw fish intake (5+ times/week) had a 25% lower risk of breast cancer, as compared with the group with the lowest intake (1–3 times/month or less) (62). As for pancreatic cancer, the JPHC study showed an inverse association between marine n-3 PUFA and DHA intakes and risk of pancreatic cancer (63). A case-control study of Japanese men showed a marginally inverse association between fish intake and risk of prostate cancer (64). The Ohsaki prospective cohort study showed that fish intake was marginally and inversely associated with risk of prostate cancer among men aged 70 years or older, but not among men aged 40 to 69 years (65). As for risk of gastric cancer, the JPHC study based on cohort I showed a positive association with

291 preserved salted fish intake (66). The JPHC study based on cohorts I and II also showed
292 a positive association between dried and salted fish intake and risk of gastric and
293 colorectal cancer (31). As for hepatocellular carcinoma, the JPHC study showed an
294 inverse association between the consumption of n-3 PUFA-rich fish, EPA, DPA, and
295 DHA and risk of hepatocellular carcinoma (67). As for uterus adenocarcinoma risk, a
296 case-control study of Japanese women showed an inverse association between fish
297 intake and the risk (68). As for malignant lymphoma, a case-control study of Japanese
298 men and women showed that women who consumed 3 to 4 dishes or more of fish a
299 week had 33% lower odds of malignant lymphoma than did those who consumed fish
300 occasionally or less, but such an association was not observed among men (69).
301 On the basis of these findings, evidence-based cancer prevention
302 recommendations for Japanese were developed in 2018 (70), but recommendations on
303 fish intake for cancer prevention were not made owing to the limited evidence.
304 Worldwide, a meta-analysis of 10 studies showed no significant association
305 between fish intake and risk of total cancer mortality (71). Another meta-analysis
306 showed an inverse association between fish intake and risk of gastrointestinal and liver
307 cancers (72, 73).
308 Taken together, fish intake in general might be beneficial for cancer prevention.

309 Although its mechanisms are not understood, some potential mechanisms were
310 revealed, such as the effect of inhibition of growth signal transduction and induction of
311 cancer cell apoptosis by LC n-3 PUFA (74, 75). However, preserved salted fish intake
312 may raise the risk of gastric cancer probably owing to high sodium concentrations and
313 nitrate, a carcinogenic agent.
314
315 **I. Dementia and cognitive dysfunction**
316 The Ohsaki cohort 2006 study of Japanese showed that fish intake was inversely
317 associated with risk of disabling dementia (76). On the other hand, a nested-case control
318 study of Japanese under the CIRCS found no association of serum EPA and DHA levels
319 with risk of disabling dementia but did find an association with alpha-linolenic acid
320 levels (77). The criteria of dementia in these studies were based on long-term care
321 insurance under which their criteria have been validated (78). A cross-sectional study of
322 Japanese elderly persons showed that those with high serum EPA and EPA + DHA
323 levels had higher J-MMSE scores (24 points or more) (79).
324 A meta-analysis showed that increment of dietary fish and DHA intake was
325 associated with lower risks of dementia and Alzheimer disease (80). On the other hand,
326 a meta-analysis of interventional studies showed that supplementation of n-3 PUFA was

not associated with cognitive decline among patients with Alzheimer disease (81).

DHA is an important constituent of the brain and is involved in the regulation of brain function (82). Results from observational and interventional studies have been inconsistent. To date, the higher intake of LC n-3 PUFA has been associated with reduced risk of dementia among the general population, but the treatment effect of LC n-3 PUFA among dementia patients has not been established.

J. Autoimmune disease

As for inflammatory bowel disease, a recent meta-analysis showed an inverse association between fish intake and risk of Crohn disease and between dietary LC n-3 PUFA (EPA and DHA) intake and risk of ulcerative colitis (83).

As for allergic disease, a series of observational studies consisting of pregnant women and their babies examined the association between dietary intake and risk of asthma and eczema. A cross-sectional study of pregnant women showed that fish intake during the previous month was inversely associated with the prevalence of current asthma and asthma after the age of 18 years, and n-3/n-6 intake ratio during the previous month was inversely associated with the prevalence of current asthma (84). Two prospective studies showed that maternal fish intake during pregnancy was not

345 associated with risk of suspected atopic eczema in infants aged 3 to 4 months or with
346 risk of wheeze and eczema in infants aged 16 to 24 months (85, 86), whilst maternal
347 DHA intake, but not EPA intake, during pregnancy was inversely associated with risk of
348 wheeze in infants aged 16 to 24 months (85). Maternal LC n-3 PUFA intake during
349 pregnancy was not associated with risk of suspected atopic eczema in infants aged 3 to
350 4 months (86). A prospective study of Japanese mothers and their children showed that
351 maternal EPA intake and EPA + DHA intake in the preceding month of delivery was
352 inversely associated with risk of wheeze in infants aged 24 months, but fish intake was
353 not (87). This study showed no association between fish, EPA, and EPA + DHA intake
354 and risk of eczema. A cross-sectional study of Japanese boys and girls aged 10 to 11 or
355 13 to 14 years showed that patients with eczema or asthma had lower levels of fish
356 intake as compared with the control group (88). On the other hand, a pooled-analysis of
357 18 European and US prospective cohorts showed no evidence to support a protective
358 effect of fish and seafood consumption during pregnancy on symptoms of wheeze,
359 asthma, and allergic rhinitis in children (89), probably owing to the low intake of fish
360 and seafood.
361
362 **K. Other diseases and symptoms**

As shown in Table 2, some epidemiological studies carried out in Japanese populations examined the association between fish/n-3 PUFA intake and diseases and/or symptoms such as impaired glucose tolerance (90), hypertension (91, 92), serum lipid abnormality (93), pulmonary embolism (94), depressive symptoms (95-99), suicide (100), sleep quality (101), activities of daily living (102), and hyposalivation (103).

Conclusions

According to epidemiological studies carried out in Japanese, fish or LC n-3 PUFA intake may be beneficial for prevention of noncommunicable diseases, especially coronary heart disease and heart failure.

The beneficial effects of fish or LC n-3 PUFA intake seems to be cross-cultural—not only for Westerners but also for Asians, but the association seemed nonlinear and most Japanese consumed fish at higher than the threshold levels (12). The impact of the effect may be different across cultures. For example, the amount and way of consuming fish may affect the association between fish and/or LC n-3 PUFA intakes and risk of CHD.

Further studies are needed to clarify more comprehensively the health benefits of fish or LC n-3 PUFA intake.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

M.U. and K.Y. designed the review; M.U. wrote the first draft; and K.Y. and H.I. revised the draft.

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726

727 Table legends

728 Table 1.

729 Summary of Japanese studies that examined the association between fish and/or n-3

730 polyunsaturated fatty acids and coronary heart disease, heart failure, stroke,

731 cardiovascular disease, aortic disease and atherosclerosis

732

733 Table 2.

734 Summary of Japanese studies that examined the association between fish and/or n-3

735 polyunsaturated fatty acids and all-cause death, cancer, dementia, cognitive dysfunction,

736 chronic inflammatory diseases, allergy and others

Table 1. Summary of Japanese studies that examined the association between fish and/or n-3 polyunsaturated fatty acids and coronary heart disease, heart failure, stroke, cardiovascular disease, aortic disease and atherosclerosis

Exposure	Endpoint	Reference (study name)	Study design	Participants, N	Evaluation for intake	Summary	Reference no.
Fish							
	Coronary heart disease						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (0–27 g/day), the highest quintile (72–229 g/day) showed no significant association with mortality from ischemic heart disease, myocardial infarction, or cardiac arrest.	23
		Iso et al. (JPHC study, cohort I) 2006	Prospective cohort study	41,578 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (23 g/day, median), the highest quintile (180 g/day, median) showed a 53% lower risk of myocardial infarction. This association was evident for nonfatal events (HR = 0.43, 95% CI: 0.23–0.81), but not for fatal events. For total coronary heart disease, the association was marginally significant (HR = 0.63, 95% CI: 0.38–1.04).	24
		Eshak et al. (JPHC study, cohorts I and II) 2014	Prospective cohort study	72,012 men and women	Food frequency questionnaire	The impact of smoking on coronary heart disease was evident among the low seafood/fish intake group (<86 g/day), compared with the high intake group (≥86 g/day). Multivariable-adjusted hazard ratios of coronary heart disease of heavy smokers (30+ cigarettes/day), compared with nonsmokers, were 3.24 in the low seafood/fish intake group and 2.00 in the high seafood/fish intake group.	25
		Nakamura et al. (NIPPON DATA80) 2005	Prospective cohort study	8,879 men and women	Self-administered questionnaire	Compared with participants who consumed fish 1–2 times/week, participants who consumed it twice or more every day showed no significant association with mortality from coronary heart disease.	26
		Sasazuki et al. (Fukuoka Heart Study)	Case-control study	660 cases and 1,277 controls	Interview	Male participants who consumed fish 4 times or more per week showed an almost 40% lower risk of nonfatal myocardial infarction than did male participants who consumed fish less than twice per week; however, this association was not observed in women.	27
		Takachi et al. (JPHC study, cohorts I and II) 2010	Prospective cohort study	77,500 men and women	Food frequency questionnaire	Compared with the lowest quintile of dried and salted fish intake (0.5 g/day, median), the highest quintile (43 g/day) showed a 34% lower risk of myocardial infarction.	31
	Heart failure						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (0–27 g/day), the middle quintile (39–53 g/day) showed a 37% lower mortality from heart failure, but the highest quintile (72–229 g/day) did not show a significant association.	23
	Stroke						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (0–27 g/day), the highest quintile (72–229 g/day) showed no significant association with mortality from total stroke or its subtypes.	23
		Nakamura et al. (NIPPON DATA80) 2005	Prospective cohort study	8,879 men and women	Self-administered questionnaire	Compared with participants who consumed fish 1–2 times/week, those who consumed fish twice or more every day showed no significant association with mortality from stroke, cerebral hemorrhage, or cerebral infarction.	26
		Sauvaget et al. (Hiroshima/Nagasaki Life Span Study) 2003	Prospective cohort study	37,130 men and women	Food frequency questionnaire	Participants whose fish product intake, as fish and broiled fish intake, was moderate or high (30 g/day and 46 g/day, median) showed 15% and 15% lower mortality from total stroke and 30% and 30% lower mortality from intracerebral hemorrhage, compared with participants whose fish product intake was low (18 g/day, median).	43
		Kinjo et al. (Six-Prefecture cohort) 1999	Prospective cohort study	223,170 men and women	Questionnaire	Compared with participants who consumed fish less than 1 time/week, participants who consumed fish 4 times/week or more showed a 14% lower mortality from all cerebrovascular death and a 13% lower mortality from cerebral hemorrhage. This association was not observed for cerebral embolism or thrombosis.	44
	Cardiovascular disease						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (0–27 g/day), the highest quintile (72–229 g/day) showed a 18% lower mortality from total cardiovascular disease.	23
		Nagata et al. (Takayama Study) 2002	Prospective cohort study	29,079 men and women	Semiquantitative food frequency questionnaire	For women, compared with the lowest quintile of fish oil (LC n-3 PUFA) intake (332 mg/day, median), the highest quintile (1,253 mg/day, median) showed a marginally significant inverse association with mortality from cardiovascular disease: HR = 0.77 (95% CI: 0.55–1.00). However, this association was not observed in men.	47
		Takachi et al. (JPHC study, cohorts I and II) 2010	Prospective cohort study	77,500 men and women	Food frequency questionnaire	Compared with the lowest quintile of dried and salted fish intake (0.5 g/day, median), the highest quintile (43 g/day) showed a 14% lower risk of myocardial infarction.	31
	Aortic disease						
		Yamagishi et al. (Japan Cohort Consortium) 2019	Prospective cohort study (pooled analysis)	366,048 men and women	Questionnaire	Compared with participants who consumed fish 1–2 times/week, participants who seldom consumed fish showed a 93% higher mortality from total aortic disease.	50
	Atherosclerosis						
		Nakamura et al. 2007	Cross-sectional study	250 men	Self-administered questionnaire	Compared with the 147 men who consumed fish fewer than 4 times per week, the 103 men who consumed fish 4 or more times per week showed a lower average intima-media thickness. However, this association was weakened after adjustment for serum lipids (P = 0.064).	53
		Tada et al. (SONIC study) 2017	Cross-sectional study	468 men and women	Brief-type self-administered diet history questionnaire	Fish and shellfish intake (g/100 kcal) did not show a signficant inverse association with atherosclerosis diagnosed with carotid ultrasonography (P = 0.085).	54
n-3 polyunsaturated fatty acids							
	Coronary heart disease						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.05–1.18 g/day), the highest quintile (2.11–5.06 g/day) showed no significant association with mortality from ischemic heart disease, myocardial infarction, or cardiac arrest.	23
		Iso et al. (JPHC study, cohort I) 2006	Prospective cohort study	41,578 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.3 g/day, median), the highest quintile (2.1 g/day, median) showed a 42% lower risk of coronary heart disease and a 57% lower risk of myocardial infarction.	24

Miyagawa et al. (NIPPON DATA80) 2014	Prospective cohort study	9,190 men and women	Household weighed food record, 3 days	Mortality from coronary heart disease did not differ between the lowest quartile of LC n-3 PUFA intake (0.18% kcal in men and 0.19% kcal in women, median) and the highest quartile (0.65% kcal in men and 0.70% kcal in women, median).	28
Hamazaki et al. (JPHC study, cohorts I and II) 2018	Nested case-control study	209 cases and 418 controls	Blood sample	Compared with participants with the lowest percentage of plasma LC n-3 PUFA of total fatty acids (6.7%, median for control), the highest (13.5%, median for control) showed 88% and 92% lower risks of fatal coronary events and sudden cardiac death, but not of total coronary heart disease.	29
Chei et al. (CIRCS) 2018	Nested case-control study	152 cases and 456 controls	Blood sample	Serum EPA, DPA, and DHA levels were not associated with risk of coronary artery disease.	30
Yokoyama et al. (JELIS) 2007	Intervention study	18,645 men and women (hypercholesterolemia patients)	Intervention: 1800 mg EPA intake/day with statin Control: statin	Compared with the control group, the participants who received the intervention showed a 19% lower risk of non-fatal coronary events (including unstable angina) (P = 0.011), but not coronary death or fatal/non-fatal MI.	38
Heart failure					
Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.05–1.18 g/day), the highest quintile (2.11–5.06 g/day) showed a 42% lower mortality from heart failure.	23
Stroke					
Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.05–1.18 g/day), the highest quintile (2.11–5.06 g/day) showed no significant association with mortality from total stroke and its subtypes.	23
Miyagawa et al. (NIPPON DATA80) 2014	Prospective cohort study	9,190 men and women	Household weighed food record, 3 days	Mortality from stroke did not differ between the lowest quartile of LC n-3 PUFA intake (0.18% kcal in men and 0.19% kcal in women, median) and the highest quartile (0.65% kcal in men and 0.70% kcal in women, median).	28
Iso et al. (CIRCS) 2002	Nested case-control study	197 cases and 591 controls	Blood sample	Compared with the controls, the stroke cases had similar serum proportions of n-3 polyunsaturated fatty acids.	45
Cardiovascular disease					
Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.05–1.18 g/day), the highest quintile (2.11–5.06 g/day) showed a 19% lower mortality from cardiovascular disease.	23
Miyagawa et al. (NIPPON DATA80) 2014	Prospective cohort study	9,190 men and women	Household weighed food record, 3 days	Mortality from cardiovascular disease was 20% lower in the highest quartile of LC n-3 PUFA intake (0.65% kcal in men and 0.70% kcal in women, median), compared withthe lowest (0.18% kcal in men and 0.19% kcal in women, median): HR = 0.80 (95% CI: 0.66–0.96).	29
Atherosclerosis					
Tada et al. (SONIC study) 2017	Cross-sectional study	468 men and women	Brief-type self-administered diet history questionnaire	n-3 PUFA intake (g/100 kcal) showed a signficant inverse association with atherosclerosis diagnosed with carotid ultrasonography (P = 0.014).	54
Hino et al. 2004	Cross-sectional study	1,902 men and women	Food frequency questionnaire	EPA, DHA, and DPA intakes were inversely associated with carotid intima-media thickness (all P < 0.05).	55
Sekikawa et al. (The Shiga Epidemiological Study of Subclinical Atherosclerosis) 2019	Cross-sectional study	1,086 men	Blood sample	Serum level of DHA was inversely associated with coronary artery calcification score measured by computed-tomography (P=0.03), but not EPA and total marine n-3 fatty acids.	56
Sekikawa et al. 2008	Cross-sectional study	281 men	Blood sample	Compared with the lowest tertile of proportion of marine derived n-3 fatty acids of serum fatty acids (6.51%, median), the highest tertile (12.30%, median) showed lower thickness of intima-media thickness (P=0.004).	16
Yano et al. 2011	Cross-sectional (Ecological study)	263 essential hypertensives in a fishing village and 333 in a farming village	Blood sample	Indexes of hypertensive cardiovascular remodeling, such as left ventricular mass index and intima-media thickness of common-carotid artery and internal-carotid artery, were significantly lower in essential hypertensive patients in a fishing village compared to those in a farming village (all P<0.01). Corresponding mean values of serum EPA and DHA composition were 70.9 μg/ml and 157.8 μg/ml in a fishing village and 63.2 μg/ml and 137.2 μg/ml in a farming village.	51
Yamada et al. 2000	Cross-sectional (Ecological study)	261 inhabitants in a fishing village and 209 in a farming village	Semi-quantitative item-frequency questionnaire	Copared with inhavitants in a farming village, inhabitants in a fishing village showed thinner intima-media thickness and lower number of plaques in common carotid arteries both men and women. The corresponding mean value of fish, EPA, DHA and DPA intake in a fishing village were 186 g/day, 799 mg/day, 1,454 mg/day and 245 g/day in men and 120 g/day, 523 mg/day, 930 mg/day and 157 mg/day in women. Those in a farming village were 103 g/day, 451 mg/day, 842 mg/day and 137 mg/day in men and 76 g/day, 339 mg/day, 625 mg/day and 101 mg/day in women.	52

LC n-3 PUFA: long-chain n-3 polyunsaturated fatty acids
EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid
DPA: docosapentaenoic acid
CIRCS: Circulatory Risk in Communities Study
INTERMAP: International Study of Macro-/Micronutrients and Blood Pressure
JACC: Japan Collaborative Cohort
JPHC: Japan Public Health Center
NIPPON DATA: National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged
SONIC: Septuagenarians, Octogenarians, NonagenariansInvestigation with Centenarians

Table 2. Summary of Japanese studies that examined the association between fish and/or n-3 polyunsaturated fatty acids and all-cause death, cancer, dementia, cognitive dysfunction, chronic inflammatory diseases, allergy and others

Exposure	Endpoint	Reference (study name)	Study design	Participants, N	Evaluation for intake	Summary	Reference no.
Fish							
	All death						
		Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of fish intake (0–27 g/day), the highest quintile (72–229 g/day) showed a marginally significant association with all-cause mortality: HR = 0.92 (95% CI: 0.85–1.00).	23
		Nakamura et al. (NIPPON DATA80) 2005	Prospective cohort study	8,879 men and women	Self-administered questionnaire	Compared with participants who consumed fish 1–2 times/week, participants who consumed fish twice or more every day showed no significant association with all-cause mortality.	26
		Nagata et al. (Takayama Study) 2002	Prospective cohort study	29,079 men and women	Semiquantitative food frequency questionnaire	Compared with the lowest quintile of fish oil (LC n-3 PUFA) intake (332 mg/day, median), the highest quintile (1,253 mg/day, median) showed a 23% lower all-cause mortality in women, but not in men.	47
		Otsuka et al. (NILS-LSA) 2019	Prospective cohort study	1,054 men and women	24-hour dietary recalls, 3 days	Compared with the lowest tertile of fish intake (55.0 g/day), the highest tertile (141.4 g/day) showed no significant association with risk of all-cause death.	59
	Cancer						
	All cancers	Takachi et al. (JPHC study, cohorts I and II) 2010	Prospective cohort study	77,500 men and women	Food frequency questionnaire	Compared with the lowest quintile of dried and salted fish intake (0.5 g/day, median), the highest quintile (43 g/day) showed a 11% higher risk of total cancer.	31
	Subtypes						
	Breast	Kiyabu et al. (JPHC study, cohorts I and II) 2015	Prospective cohort study	38,234 women	Food frequency questionnaire	Compared with the lowest quartile of fish intake (22.4 g/day, median), the highest quartile (124 g/day, median) showed no significant difference in breast cancer risk.	60
	Breast	Kuriki et al. (HERPACC) 2007	Case-control study	103 cases and 309 controls (women)	Semiquantitative food frequency questionnaire	Total seafood intake and fish intake were not associated with breast cancer risk. Seafood and fish intake values were <23.91 g/1,000 kcal and <12.77 g/1,000 kcal in the lowest tertile and >38.76 g/1,000 kcal and >26.10 g/1,000 kcal in the highest tertile.	61
	Breast	Hirose et al. (HERPACC) 2003	Case-control study	2385 cases and 19,013 controls (women)	Semiquantitative food frequency questionnaire	For postmenopausal women, the highest cooked/raw fish intake group (5+ times/week) showed a 25% lower breast cancer risk, compared with the lowest group (1–3 times/month or less). For premenopausal women, frequent dried/salted fish intake was positively associated with breast cancer risk (*P* for trend = 0.03), although the odds ratios of the highest intake group were not significant.	62
	Prostate	Sonoda et al. 2004	Case-control study	140 cases and 140 controls	Semiquantitative food frequency questionnaire	Compared with the lowest fish intake group (≤47.3 g/day, the highest group (≥130.7 g/day) showed a marginally lower risk of prostate cancer: OR = 0.45 (95% CI: 0.20–1.02) and *P* for trend = 0.04.	64
	Prostate	Sato et al. (Ohsaki study) 2008	Prospective cohort study	18,866 men	Food frequency questionnaire	For participants aged 70 years or older at baseline, fish intake showed a marginally significant inverse association with incidence of prostate cancer *(P* for trend = 0.08), whilst the association was null among participants aged 40–69 years.	65 (in Japanese)
	Gastric	Tsugane et al. (JPHC study, cohort I) 2004	Prospective cohort study	39,065 men and women	Food frequency questionnaire	For men, participants who consumed preserved salted fish almost every day showed a 133% higher risk of gastric cancer than did participants who consumed almost none. For women, this association was not observed.	66
	Gastric and Colorectal	Takachi et al. (JPHC study, cohorts I and II) 2010	Prospective cohort study	77,500 men and women	Food frequency questionnaire	Compared with the lowest quintile of dried and salted fish intake (0.5 g/day, median), the highest quintile (43 g/day) showed a 46% higher risk of gastric cancer and a 40% higher risk of colorectal cancer.	31
	Liver	Sawada et al. (JPHC study, cohorts I and II) 2012	Prospective cohort study	90,296 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA-rich fish intake (9.6 g/day, median), the highest quintile (70.6 g/day, median) showed a 36% lower risk of hepatocelluler carcinoma. However, total fish intake was not inversely associated with risk of hepatocelluler carcinoma.	67
	Uterus	Takayama et al. 2013	Case-control study	161 cases and 380 controls	Food frequency questionnaire	Compared with the lowest quartile of fish intake (8.25g/1000kcal), the highest quartile (16.02g/1000kcal) showed lower risk of endometrial endometrioid adenocarcinoma: OR = 0.53 (95% CI: 0.30–0.94).	68
	Malignant lymphoma	Matsuo et al. (HERPACC) 2001	Case-control study	333 cases and 55,904 controls	Semiquantitative food frequency questionnaire	Compared with participants whose frequency of fish dish intake was occasional or less, women, but not men, who took fish dishes ≥3–4 times/week showed a 33% lower risk of malignant lymphoma. Salty fish intake was not associated with risk of malignant lymphoma in either men or women.	69
	Dementia and cognitive dysfunction						
		Tsurumaki et al. (Ohsaki cohort 2006 study) 2019	Prospective cohort study	13,102 men and women	Food frequency questionnaire	Compared with the lowest quartile of fish intake (20.4 g/day, mean), the highest quartile (96.9 g/day, mean) showed a 16% lower incidence of disabling dementia.	76
	Autoimmune disease						
		Miyamoto et al. (Osaka Maternal and Child Health Study) 2007	Cross-sectional study	1,002 pregnant women	Self-administered diet history questionnaire	Compared with the lowest tertile of fish intake (<36.14 g/day), the highest tertile (>54.44 g/day) showed an 81% lower risk of current asthma and a 74% lower risk of asthma after the age of 18 years.	84
		Miyake et al. (Osaka Maternal and Child Health Study) 2009	Prospective cohort study	763 mother-child pairs	Self-administered diet history questionnaire	Maternal fish intake during pregnancy was not associated with wheeze or eczema in infants aged 16–24 months. The median value of maternal fish intake in the lowest quartile was 23.4 g/day, whilst in the highest quartile, it was 73.2 g/day.	85
		Saito et al. (Osaka Maternal and Child Health Study) 2010	Prospective cohort study	771 mother–child pairs	Self-administered diet history questionnaire	Maternal fish intake during pregnancy was not associated with suspected atopic eczema in infants aged 3–4 months. The median value of maternal fish intake in the lowest quartile was 23.0 g/day, whilst in the highest quartile, it was 73.1 g/day .	86
		Miyake et al. (the Kyushu Okinawa Maternal and Child Health Study) 2012	Prospective cohort study	1,354 mother-child pairs	Self-administered diet history questionnaire	Maternal fish intake in the preceding month of delivery was not associated with risk of wheeze and eczema in infants aged 24 months. The median values of fish intake in the lowest quartile and the highest quartile were 23.4 g/day and 71.3 g/day.	87
		Kunitsugu et al. (Shunan Child Health cohort study) 2012	Cross-sectional study	357 boys and girls	Brief-type, self-administered diet history questionnaire	Participants with eczema and those with asthma showed a significantly lower intake of all fish products than did the controls. The median values were 16.7 g/4218 J in the eczema group, 18.7 g/4218 J in the asthma group, and 21.8 g/4218 J in the control group.	88
	Impaired glucose tolerance						

	Nanri et al. (JPHC study, cohorts I and II)	Prospective cohort study	52,680 men and women	Food frequency questionnaire	Total fish/seafood intake was inversely associated with type 2 diabetes mellitus after 5 years in men (*P* for trend = 0.04), but not in women. The median values of total fish/seafood intake in the lowest and highest quartiles were 36.6 g/day and 171.7 g/day in men and 35.3 g/day and 163.1 g/day in women.	90
Blood pressure						
	Gibson et al. (INTERMAP study)	Cross-sectional study	1,145 men and women	24-hour dietary recalls, 4 days	No significant difference in blood pressure levels was found between the low fish consumers group (>0.0 g/1,000 kcal –28.4 g/1,000 kcal) and the high fish consumers group (45.3 g/1,000 kcal –165.5 g/1,000 kcal).	91
Serum lipids						
	Tani et al. 2019	Cross-sectional study	1,270 men	Lifestyle questionnaire	Compared with participants who consumed fish 0–1 day/week, those who consumed fish 6–7 days/week showed significantly lower serum non-HDL-cholesterol levels: 149 mg/dL vs 134 mg/dL.	93
Pulmonary embolism						
	Ohira et al. (JACC study) 2018	Prospective cohort study	58,086 men and women	Food frequency questionnaire	Compared with the participants who consumed fresh fish rarely, those who took fresh fish every day showed a 83% lower risk of death due to pulmonary embolism.	94
Depressive symptoms						
	Matsuoka et al. (JPHC study, Saku area) 2017	Prospective cohort study	1,121 men and women	Food frequency questionnaire	Compared with the lowest quartile of fish intake (57.2 g/day, median), the third quartile of fish intake (111.1 g/day) showed a 56% lower risk of depression; however, the association was not significant in the highest quartile.	96
	Miyake et al. (the Kyushu Okinawa Maternal and Child Health Study) 2013	Cross-sectional study	1,754 pregnant women	Self-administered diet history questionnaire	Compared with the lowest quartile of fish intake (22.8 g/day, median), the highest quartile (71.7 g/day, median) showed a 39% lower risk of depressive symptoms.	99
	Miyake et al. (Osaka Maternal and Child Health Study) 2006	Prospective cohort study	865 pregnant women	Self-administered diet history questionnaire	No association was found between fish intake and risk of postpartum depression. The amount of fish intake in the lowest quartile was 23.1 g/day (median), whilst in the highest quartile, it was 72.9 g/day (median) .	98
Suicide						
	Poudel-Tandukar et al. (JPHC study, cohorts I and II) 2011	Prospective cohort study	101,507 men and women	Food frequency questionnaire	Fish intake was not associated with suicide in men or women. The median value of fish intake in the lowest and highest quintiles in men were 32.50 g/day and 152.84 g/day, and in women, 32.29 g/day and 142.09 g/day.	100
Sleep quality						
	Katagiri et al. (Three-Generation Study of Women on Diets and Health) 2014	Cross-sectional study	3,129 men and women	Self-administered diet history questionnaires	Compared with the lowest quintile of fish intake (<17.8 g/1,000 kcal), the highest quintile (41.1< g/1000 kcal) showed 28% lower odds ratios of poor sleep quality evaluated by the Pittsburgh Sleep Quality Index.	101
Activities of daily living (ADLs)						
	Nakamura et al. (NIPPON DATA80) 2009	Prospective cohort study	2,316 men and women	Self-administered questionnaire	Dietary fish intake, ≥1/day, was not associated with impaired ADLs.	102
Hyposalivation						
	Iwasaki et al. (Niigata Study) 2016	Cross-sectional study	352 men and women	Brief-type self-administered diet history questionnaire	Participants without hyposalivation consumed a higher amount of fish and shellfish than did those with hyposalivation: 110 g/day vs 83 g/day (*P* = 0.03).	103
n-3 polyunsaturated fatty acids						
All death						
	Yamagishi et al. (JACC study) 2008	Prospective cohort study	57,972 men and women	Food frequency questionnaire	Compared with the lowest quintile of n-3 PUFA intake (0.05–1.18 g/day), the highest quintile (2.11–5.06 g/day) showed a marginally significant association with all-cause mortality: HR = 0.92 (95% CI: 0.84–1.02).	23
	Otsuka et al. (NILS-LSA) 2019	Prospective cohort study	1,054 men and women	Blood sample, 24-hour dietary recalls, 3 days	Compared with the lowest tertile of serum DHA and EPA/ARA ratio (111.6 μg/mL and 0.3), the highest tertile (191.0 μg/mL and 0.7) showed 27% and 29% lower risks of all-cause death. Dietary n-3 PUFA, EPA, and DHA intake were not significantly associated with risk of all-cause death.	59
Cancer						
All cancers	Nagata et al. (Takayama Study) 2002	Prospective cohort study	29,079 men and women	Semiquantitative food frequency questionnaire	Fish oil (LC n-3 PUFA) intake was not significantly associated with all-cancer mortality in either men or women. The values of fish oil intake in the lowest and highest quintiles were 410 mg/day and 1582 mg/day in men and 332 mg/day and 1253 mg/day in women.	47
Subtypes						
Breast	Kiyabu et al. (JPHC study, cohorts I and II) 2015	Prospective cohort study	38,234 women	Food frequency questionnaire	Compared with the lowest quartile of total n-3 PUFA intake (1.7 g/day, median), the highest quartile (5.2 g/day, median) showed no significant difference in breast cancer risk. EPA, DHA and DPA intake were not associated with risk of breast cancer.	60
Breast	Kuriki et al. (HERPACC) 2007	Case-control study	103 cases and 309 controls	Semiquantitative food frequency questionnaire, blood sample	n-3 PUFA, EPA, and DHA intakes were not associated with breast cancer risk. EPA and DHA in erythrocyte membranes were inversely associated with breast cancer risk (P for trend <0.0001 and <0.0001, respectively)	61
Liver	Sawada et al. (JPHC study, cohorts I and II) 2012	Prospective cohort study	90,296 men and women	Food frequency questionnaire	Compared with the lowest quintile of EPA, DPA and DHA intake (0.14 g/day, 0.04 g/day and 0.28 g/day, median), the highest quintile (0.74 g/day, 0.19 g/day and 1.19 g/day, median) showed a 44%, 36% and 44% lower risk of hepatocelluler carcinoma.	67
Pancreas	Hidaka et al. (JPHC study, cohorts I and II) 2015	Prospective cohort study	82,024 men and women	Food frequency questionnaire	Participants with the highest quartile of marine n-3 PUFA and DHA intakes (1.83 g/day and 1.04 g/day, median) showed 30% and 31% lower risks of pancreatic cancer excluding cases that were found in the 3 years from the baseline survey, compared with participants with the lowest quartile (0.45 g/day and 0.28 g/day, median).	63
Dementia, cognitive dysfunction						
	Yamagishi et al. (CIRCS study) 2017	Nested case-control study	315 cases and 630 controls	Blood sample	Serum EPA and DHA levels were not associated with risk of disabling dementia.	77
	Nishihira et al. (KOCOA study) 2016	Cross-sectional study	2,011 men and women	Blood sample	Compared with participants whose serum EPA and serum EPA+DHA levels were in the lowest 25%, those with levels in the highest 25% showed 138% and 131% higher ratios of having higher J-MMSE scores.	79
Autoimmune disease						
	Miyamoto et al. (Osaka Maternal and Child Health Study) 2007	Cross-sectional study	1,002 pregnant women	Self-administered diet history questionnaire	Compared with the lowest tertile of n-3/n-6 intake ratio (<0.1914), the highest tertile (>0.2218) showed a 74% lower risk of current asthma, but not of asthma after the age of 18 years. n-3 PUFA, EPA ,and DHA intakes were not significantly associated with either outcome of asthma.	84

Miyake et al. (Osaka Maternal and Child Health Study) 2009	Prospective cohort study	763 mother-child pairs	Self-administered diet history questionnaire	Compared with the lowest quartile of DHA intake during pregnancy (0.15 g/day, median), the highest quartile (0.46 g/day, median) showed a 63% lower risk of wheeze in infants aged 16–24 months. However, the associations between n-3 PUFA and EPA and risk of wheeze were null. The median values of the maternal intakes of n-3 PUFA and EPA in the lowest quartile were 1.7 g/day and 0.08 g/day, whilst in the highest quartile they were 3.0 g/day and 0.28 g/day, respectively. The associations of maternal intakes of n-3 PUFA, EPA, and DHA during pregnancy with risk of eczema in infants aged 16–24 months were null.	85
Saito et al. (Osaka Maternal and Child Health Study) 2010	Prospective cohort study	771 mother–child pairs	Self-administered diet history questionnaire	Maternal n-3 PUFA, EPA, and DHA intakes during pregnancy were not associated with suspected atopic eczema in infants aged 3–4 months. The median values of the maternal intakes in the lowest quartile were 1.7 g/day, 0.07 g/day, and 0.15 g/day, whilst they were 3.0 g/day, 0.27 g/day, and 0.46 g/day in the highest quartile.	86
Miyake et al. (the Kyushu Okinawa Maternal and Child Health Study) 2012	Prospective cohort study	1,354 mother-child pairs	Self-administered diet history questionnaire	Maternal EPA intake and EPA + DHA intake in the preceding month of delivery were inversely associated with risk of wheeze in infants aged 24 months (P for trend= 0.02 and 0.02). However, the risk of wheeze in the highest quartile of EPA or EPA +DHA was not significantly low compared with the lowest quartile of them. The median values of EPA and EPA +DHA intake in the lowest quartile were 0.07 g/day and 0.22 g/day, those in the highest quartile were 0.28 g/day and 0.73 g/day.	87
Kunitsugu et al. (Shunan Child Health cohort study) 2012	Cross-sectional study	357 boys and girls	Blood sample	EPA in erythrocyte membranes was inversely associated with atopic eczema symptoms (P = 0.048).	88
Blood pressure					
Umemura et al. 2005	Cross-sectional study	421 men and women (university students)	Blood sample	The proportion of n-3 PUFA of serum fatty acids was inversely associated with systolic, but not diastolic, blood pressure level among women. For men, this association was not significant.	92
Pulmonary embolism					
Ohira et al. (JACC study) 2018	Prospective cohort study	58,086 men and women	Food frequency questionnaire	Compared with the participants whose n-3 PUFA intake was low (0.8 g/day, median), those whose n-3 PUFA intake was high (2.4 g/day, median) showed a 74% lower risk of death due to pulmonary embolism.	94
Depressive symptoms					
Shibata et al. (Hisayama Study) 2018	Cross-sectional study	2,529 men and women	Blood sample	Compared with the participants with the lowest quartile of serum AA/EPA ratios (range, 0.30–1.65), those with the highest quartile (range, 3.28–13.3) showed 4.10 times higher odds ratios for the presence of depressive symptoms.	95
Matsuoka et al. (JPHC study, Saku area) 2017	Prospective cohort study	1,121 men and women	Food frequency questionnaire	Compared with the lowest quartile of DPA intake (67.1 mg/day, median), the third quartile of DPA intake (123.1 mg/day, median) showed a 56% lower risk of depression; however, the association was not significant in the highest quartile.	96
Horikawa et al. (NILS-LSA) 2016	Cross-sectional study	2,123 men and women	Blood sample	Compared with the lowest quintile of serum n-3 PUFA concentration (range, 77.5–210.5 μg/mL), the highest quintile (range, 379.9–1197.5 μg/mL) showed 43% lower odds ratios of depressive symptoms. The same associations were observed for DHA and EPA.	97
Miyake et al. (the Kyushu Okinawa Maternal and Child Health Study) 2013	Cross-sectional study	1,754 pregnant women	Self-administered diet history questionnaire	Compared with the lowest quartile of EPA and DHA intake (0.07 g/day and 0.14 g/day, median), the highest quartile (0.29 g/day and 0.46 g/day, median) showed a 34% and a 36% lower risk of depressive symptoms.	99
Miyake et al. (Osaka Maternal and Child Health Study) 2006	Prospective cohort study	865 pregnant women	Self-administered diet history questionnaire	Compared with the lowest quartile of n-3 PUFA and DHA intakes (1.6 g/day and 0.16 g/day, median), the third quartile (2.4 g/day and 0.34 g/day, median) was marginally inversely associated with risk of postpartam depression: OR = 0.58 (95% CI: 0.33–1.02) and OR = 0.62 (95% CI: 0.34–1.09), respectively. However, the highest tertile was not significantly associated with risk of postpartum depression	98
Suicide					
Poudel-Tandukar et al. (JPHC study, cohorts I and II) 2011	Prospective cohort study	101,507 men and women	Food frequency questionnaire	EPA and DHA intakes were not associated with suicide in men or women. The median values of EPA intake in the lowest and highest quintiles in men were 0.10 g/day and 0.67 g/day, and 0.10 g/day and 0.64 g/day in women. For DHA, the corresponding values were 0.22 g/day and 1.10 g/day in men and 0.21 g/day and 1.03 g/day in women.	100
Hyposalivation					
Iwasaki et al. (Niigata Study) 2016	Cross-sectional study	352 men and women	Brief-type self-administered diet history questionnaire	Participants without hyposalivation consumed higher amounts of n-3 PUFA, compared with participants with hyposalivation: 3.7 g/day vs 3.1 g/day (P = 0.04).	103

LC n-3 PUFA: long-chain n-3 polyunsaturated fatty acids
EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid
DPA: docosapentaenoic acid
HERPACC: Hospital-Based Epidemiologic Research Program at Aichi Cancer Center
JACC: Japan Collaborative Cohort
JPHC: Japan Public Health Center
KOCOA: Keys to Optimal Cognitive Aging
NIPPON DATA: National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged
NILS-LSA: National Institute for LongevitySciences-Longitudinal Study of Aging