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Association of fish intake with all-cause mortality according to CRP levels or inflammation in older adults: a prospective cohort study

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Abstract

Background The relationship between inflammatory response, fish consumption, and mortality risk in older individuals is unclear. We investigated whether C-reactive protein (CRP) levels ≥ 0.1 mg/dL, fish intake, and inflammatory responses are associated with all-cause mortality risk in older adults.

Methods This prospective cohort study included older adults aged 85–89 years from the Kawasaki Aging and Wellbeing Project, who did not require daily care. Cohort was recruited from March 2017 to December 2018 (follow-up ended on December 31, 2021). Dietary assessment was conducted using the Brief Self-Administered Diet History Questionnaire. Multivariate Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality in the CRP ≥ 0.1 mg/dL group; the CRP < 0.1 mg/dL group was used for reference. Within CRP ≥ 0.1 and < 0.1 mg/dL groups, participants were categorized into tertiles of fish intake. HRs and 95% CIs for all-cause mortality in the other groups were estimated using the lower tertile group as a reference.

Results The study included 996 participants (mean [standard deviation] age, 86.5 [1.37] years; 497 [49.9%] women) with a median CRP level of 0.08 (interquartile range [IQR] = 0.04–0.16). There were 162 deaths during 4,161 person-years of observation; the multivariable-adjusted HR for all-cause mortality in the CRP ≥ 0.1 mg/dL group was 1.86 (95% CI, 1.32–2.62); $P < 0.001$. In 577 individuals with median (IQR) fish intake of 39.3 g/1000 kcal (23.6–57.6) and CRP level of < 0.1 mg/dL, the multivariable-adjusted HR for all-cause mortality in the higher tertile group of fish intake was 1.15 (0.67–1.97); $P = 0.59$, non-linear $P = 0.84$. In 419 individuals with median (IQR) fish intake of 40.7 g/1000 kcal (25.0–60.1) and CRP level of ≥ 0.1 mg/dL, the multivariate-adjusted HR for all-cause mortality in the higher tertile group of fish intake was 0.49 (0.26–0.92); $P = 0.026$, non-linear $P = 0.38$, P-value for interaction = 0.040.

Conclusions A negative association between fish intake and all-cause mortality was seen in older adults with elevated CRP levels, which is a mortality risk factor. While the results may be limited owing to stringent methods ensuring impartiality, they offer valuable insights for future research.

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Keywords All-cause mortality, Fish intake, C-reactive protein

Background

The exploration of different food cultures facilitates the reconsideration of habitual foods. The low risk of coronary heart disease in the Inuit population in Greenland, who consume 400 g of fish, whale, and sea meat per day [1], triggered research into the modern health benefits of ω-3 fatty acids (FAs). Recent meta-analyses have reported associations between fish intake and all-cause mortality as well as contributions of ω-3 FA intake in reducing cardiovascular mortality [2–4]. Daily protein intake of 1–1.5 g/kg helps offset age-related inflammation and catabolism, especially in older people [5].

Inflammation mediates cardiovascular disease (CVD), plaque failure, and malignancy, and is an epidemiological risk factor for mortality [6–12]. The inflammatory marker C-reactive protein (CRP) demonstrates age- and ethnicity-related differences [13–15], and the risk of mortality associated with increasing CRP levels rises with age [16]. In older people, chronic inflammation is interrelated with several factors including immune-senescence and microvascular changes [17–21], and is associated with frailty, which is a mortality risk factor in older people [22, 23].

As the global population ages, research on inflammatory responses and fish consumption could boost life expectancy. Studies linking inflammation with fish intake and the efficacy of ω-3 FAs in modulating inflammatory responses are limited [24]. Furthermore, only few large-scale studies have investigated CRP and mortality risk in older people [25]; thus, there is a lack of comprehensive survey data on the association between fish intake and mortality, particularly focusing on the inflammatory response. Cross-sectional research has previously indicated a negative correlation between n-3 polyunsaturated FA intake and CRP levels [26]. Interventional studies suggest that inhibition of interleukin-6 signaling, which induces CRP production, decreases the risks of CVD and mortality [27, 28]. In trials such as JELIS and REDUCE-IT, ω-3 FA, particularly eicosapentaenoic acid (EPA; which is abundant in fish), has demonstrated efficacy against cardiovascular events and mortality; however, some reports question this efficacy [29–34]. The inflammatory response at recruitment and its subsequent trends in ω-3 FAs intervention studies have not been adequately evaluated; there is limited literature on the contribution of the anti-inflammatory effects of ω-3 FAs to the risk of CVD [30].

This study hypothesized that an elevated inflammatory response increases mortality risk in older people (≥85 years) without physical disability, and that fish consumption affects mortality risk differently in the presence and absence of inflammation. To this end, we examined the relationship between CRP levels, fish consumption, and all-cause mortality in older people.

Methods

Study population

This secondary analysis used data from the Kawasaki Aging and Wellbeing Project (KAWP), an ongoing longitudinal cohort study, which enrolled older people (aged 85–89 years) without physical disability at baseline who lived in Kawasaki City, Kanagawa Prefecture, a metropolitan area of Japan, between March 2017 and December 2018. The objectives, participation criteria, and basic research of the KAWP study were previously reported [35]. KAWP surveys were planned for 3 and 6 years after study commencement; however, the 3-year follow-up in 2020 was postponed because of the coronavirus pandemic and is now underway after a 1.5-year delay. Among the 1,026 KAWP participants, 30 were excluded due to missing blood tests, an incomplete self-administered brief dietary history questionnaire (BDHQ), or a BDHQ-estimated daily energy intake not in the range of 600–4,000 kcal/day. A total of 996 participants who provided written informed consent for participation were enrolled (Fig. 1). KAWP was approved by the Keio University School of Medicine Ethics Committee (ID: 20160297), registered in the University Hospital Medical Information Network Clinical Trials Registry (ID: UMIN000026053), and complied with the Strengthening the Reporting of Observational Studies in Epidemiology guideline for reporting observational studies [36].

Dietary assessment

The 4-page BDHQ could be completed in approximately 15–20 min, and comprises 90 sections on food and dietary habits for the preceding month [37, 38] under five categories, namely: (i) frequency of intake (food and non-alcoholic drinks); (ii) daily consumption of rice and miso soup; (iii) frequency of alcoholic beverage intake and quantity per meal; (iv) typical cooking methods; and (v) general eating behavior. Unlike the weighed food record method, the BDHQ primarily assesses the intake frequency of foods and dishes. Nutrient and food intakes were calculated using an ad hoc computer algorithm for BDHQ based on the Japanese Standard Tables of Food Composition [39] (Figure S1). As the Japanese diet includes diverse fish types, the BDHQ disaggregates fish into five categories: (1) fish eaten with the bones; (2) canned tuna; (3) dried fish (salted mackerel and salted fish); (4) oily fish such as sardines, mackerel, yellowtail,

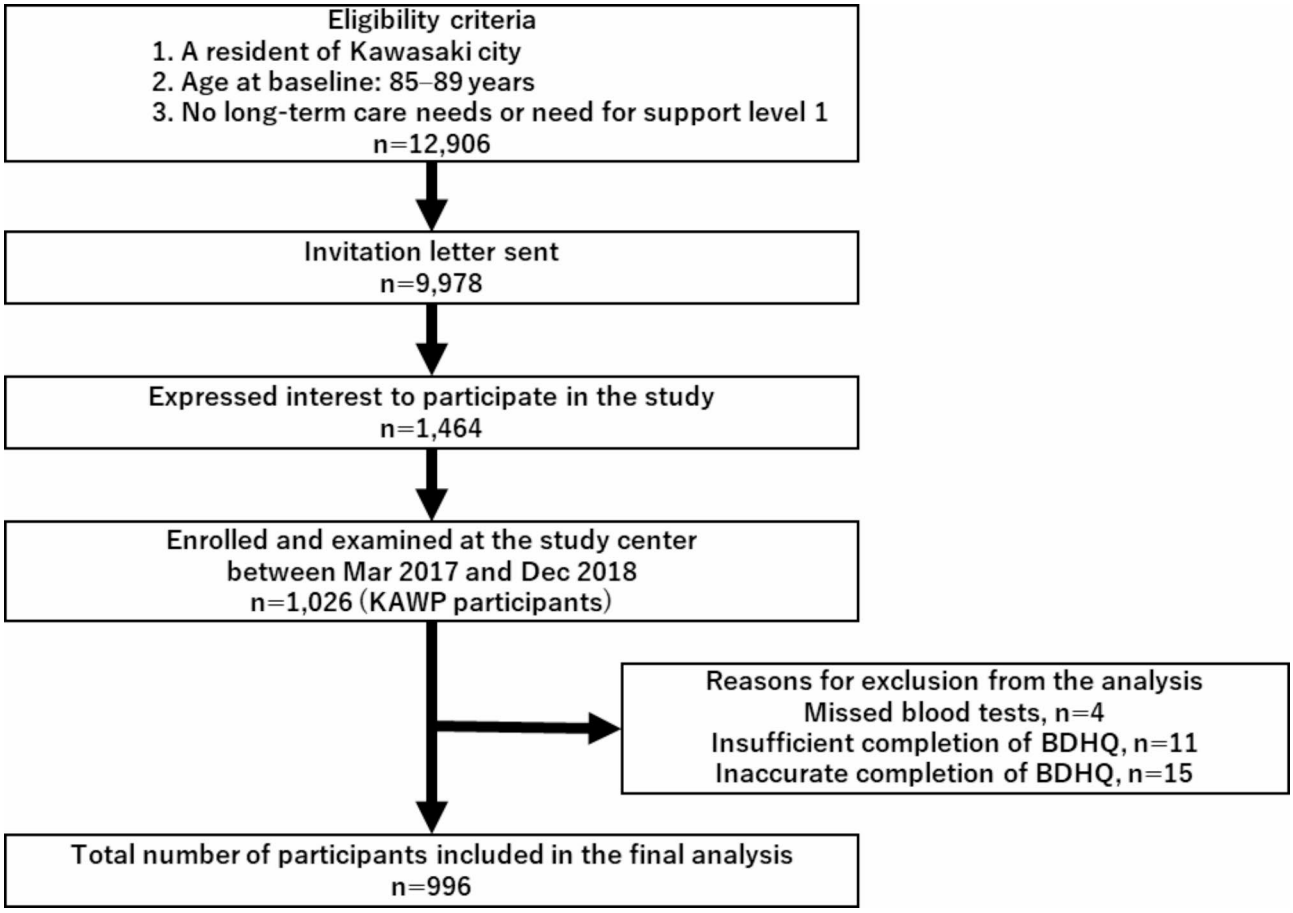

Fig. 1 Kawasaki aging and wellbeing project study population flowchart. The long-term care system in Japan includes seven categories: no certification (no need for long-term care certification), support levels 1 and 2 for preventive long-term care, as well as care levels 1–5 for long-term care. A higher care level indicates a greater functional decline in daily activities. Abbreviation: KAWP, Kawasaki Aging and Wellbeing Project

eel, tuna, saury, herring; and (5) fish with less fat. The BDHQ was previously validated in Japanese older adults aged≥80 years (Spearman's correlation with the 3-day semi-weighed dietary records of seafood or the sum of EPA, docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]: 0.38 and 0.36, respectively) [40]. The density method was used to estimate the intake per 1,000 kcal to analyze the nutritional data. The ratio of energy intake of energy-producing nutrients (protein, fat, and carbohydrate) (%Energy [%E]) was calculated using the formula energy intake from each nutrient/energy intake × 100. The nutritional survey, conducted using the BDHQ, was administered by trained staff.

Outcome variable: all-cause mortality

To evaluate the study outcome of all-cause mortality, survival status was determined from the database for the Long-Term Care Insurance Scheme, a national comprehensive welfare insurance scheme covering the majority of long-term care services for older people [41]. In the analysis timeline, the initial examination date was the entry point, and the date of loss to follow-up, defined as the date of migration outside Kanagawa Prefecture, commencement of welfare benefits, or death, was the endpoint. Information regarding outcomes was based on data up to December 31, 2021.

Predictor variables: CRP, fish intake, and Marine ω-3 FA

At enrollment in any of the three sites of the baseline study, all participants provided non-fasting blood samples, and the CRP level was measured using the latex agglutination immunoassay (SRL Inc., Tokyo, Japan) using the Nanopia CRP® reagent (Sekisui Medical Co.; range: 0.01–42 mg/dL). Using the BDHQ, fish intake was calculated by summing the intake of the five abovementioned categories of fish; the frequency of fish intake per category was tabulated under seven groups: at least twice daily, once daily, 4–6 times/week, 2–3 times/week, once a week, less than once a week, and none. The aggregate results were approximated to a weekly average and converted to 14/7, 7/7, 5/7, 2.5/7, 1/7, 0.333/7, and 0 times, and the total frequency in these seven categories was

subdivided into three groups: ≥7, 2–7, and <2 times/week. Marine ω-3 FAs intake was defined as the sum of EPA, DPA, and DHA, estimated based on the frequency of consuming fish and seafood, including squid, octopus, shrimp, clam, and the five abovementioned categories of fish. The contents used for these calculations were derived from the Japanese Standard of Food Composition Table [39].

Covariates

During the basic survey, age and sex information were provided by the local authorities; education level (university graduate or not), smoking status (current smoker or not), medical history (presence of coronary artery disease, stroke, or cancer), and medication use (statins, renin-angiotensin system inhibitors [RAI], and antithrombotic drugs) were assessed through a pre-filled questionnaire and a face-to-face interview, complemented by the pharmacy prescription records of the participants (Additional file 1: Table S1). CVD was defined based on the presence of coronary artery disease or stroke, diabetes mellitus was assessed from the prescription records of oral diabetes medication, insulin, or glycated hemoglobin ≥6.5% (National Glycohemoglobin Standardization Program), and hypertension was assessed from the prescription records of antihypertensive medications (calcium-channel blockers or angiotensin-receptor blockers) or systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively. The revised Japanese Cardiovascular Health Study criteria, including weight loss, muscle weakness, fatigue, walking speed, and physical activity, were used to diagnose frailty as follows: scores 0, 1–2, and ≥3 indicated robustness, pre-frailty, and frailty, respectively [42]. The use of dietary supplements was assessed based on the BDHQ results. These covariates were tabulated as categorical variables. Height and weight were measured after wearing light clothing and standing upright. The Barthel index (0–100 points) and Mini-Mental State Examination (MMSE; 0–30 points) were assessed by experienced staff [43, 44]. Using standard enzymatic methods, the plasma total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured at SRL Inc., Tokyo, Japan on the day the blood was drawn. In accordance with reports by Tabung et al. and Kaneuchi et al., the modified Empirical Dietary Inflammatory Index (modified EDII) was calculated, excluding fish intake [45, 46] (Additional file 1: Method S1).

Statistical analyses

The participants were categorized by the CRP cutoff value of 0.1 mg/dL [7]. The participants' characteristics are presented as continuous variables (mean with standard deviation or median with interquartile range) or categorical variables (frequency and proportions). Each CRP group (<0.1 and ≥0.1 mg/dL) was further sub-stratified by three fish-intake tertiles (CRP<0.1 mg/dL: T1 [<28.4 g/1,000 kcal], T2 [28.4≤fish<51.4 g/1,000 kcal], and T3 [51.4≤fish g/1,000 kcal]; CRP≥0.1 mg/dL: T1 [<30.3 g/1,000 kcal], T2 [30.3≤fish<52.5 g/1,000 kcal], and T3 [52.5≤fish g/1,000 kcal]). The results of the nutritional survey were disaggregated by the fish-intake tertiles. Using age, sex, smoking status, hypertension, diabetes, history of CVD, history of cancer, body mass index (BMI), and LDL-C as covariates, which were selected based on their mortality influence in older people, Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality in the CRP≥0.1 mg/dL group; HR (95% CI) were estimated in T2 and T3 using T1 as the reference in the study groups. Association trends in each tertile group were tested using Cox regression analysis that assigned scores to the independent variable levels (i.e., T1 of fish intake=1, T2=2, …etc.), with age, sex, history of CVD, history of cancer, diabetes, total energy intake, modified EDII, dietary supplements, and BMI as covariates. Restricted cubic spline models were depicted to examine the non-linear relationship between fish or Marine ω-3 FA intake and all-cause mortality. Effect modification was assessed using a Cox regression model by incorporating dummy variables for fish intake (T1–T3), Marine ω-3 FA intake (T1–T3), or fish intake frequency (<2 times, 2–7 times, ≥7 times), categorical CRP, and the interaction term between dummy variables for fish intake and categorical CRP before stratifying participants by CRP levels.

Sensitivity analyses for all-cause mortality were performed (estimated HR [95% CI]) for fish intake in the CRP≥0.1 mg/dL group, excluding participants with follow-up ≤180 days. To assess the potential heterogeneity, stratified analyses were conducted for the history of CVD, cancer, and pre-frailty or frailty with age, sex, and BMI as covariates.

All analyses were performed using SPSS Statistics (ver. 29.0; IBM SPSS Inc., Armonk, NY, USA) and R 4.3.3 (the R Foundation for Statistical Computing, Vienna, Austria), with statistical significance at a P-value<0.05, and two-sided tests were applied.

Results

In Table 1, the characteristics of 996 participants (497 [49.9%] women) with a mean (standard deviation) age of 86.5 (1.37) years, mean Barthel index of 98.5, and mean MMSE of 26.0 are shown. Hypertension, history of CVD, and history of cancer were noted in 54.0%, 32.7%, and 20.6% of the cohort, respectively; About 34.4%, 38.5%, and 27.3% of the cohort were on statins, RAI, and

Table 1 Participant characteristics stratified by the CRP category at baseline

Variables	Total, *n* = 996	CRP < 0.1 mg/dL, *n* = 577	CRP ≥ 0.1 mg/dL, *n* = 419
Age, years	86.5 (1.37)	86.6 (1.36)	86.5 (1.39)
Female sex, n (%)	497 (49.9)	301 (52.2)	196 (46.8)
Education, n (%)	196 (19.7)	109 (18.9)	87 (20.8)
Currently smoking, n (%)	417 (41.9)	211 (36.6)	206 (49.2)
Barthel index	98.5 (3.52)	98.7 (3.21)	98.2 (3.90)
MMSE	26.0 (2.73)	26.1 (2.77)	25.9 (2.67)
Height, cm	153 (8.83)	153 (8.66)	154 (9.07)
Weight, kg	55.1 (9.92)	53.6 (9.85)	57.3 (9.66)
Body mass index[a]	23.2 (3.10)	22.6 (3.06)	23.9 (3.00)
Hypertension, n (%)	538 (54.0)	306 (53.0)	232 (55.4)
Diabetes, n (%)	63 (6.32)	28 (4.85)	35 (8.35)
Pre-frailty or frailty, n (%)	828 (83.1)	476 (82.5)	352 (84.0)
History of CVD, n (%)	326 (32.7)	180 (31.2)	146 (34.8)
History of cancer, n (%)	205 (20.6)	114 (19.8)	91 (21.7)
Statins, n (%)	343 (34.4)	206 (35.7)	137 (32.7)
Renin-angiotensin inhibitors, n (%)	383 (38.5)	219 (38.0)	164 (39.2)
Anti-ischemic agents, n (%)	272 (27.3)	146 (25.3)	126 (30.1)
CRP, median (IQR), mg/dL	0.08 (0.04–0.16)	0.05 (0.03–0.07)	0.19 (0.14–0.37)
Total cholesterol, mg/dL	199 (34.1)	200 (33.4)	199 (35.1)
TG, median (IQR), mg/dL	113 (82.0–157)	105 (76.0–141)	130 (91.0–181)
LDL-C, mg/dL	111 (27.8)	109 (26.9)	113 (28.9)
HDL-C, mg/dL	60.7 (15.9)	64.2 (15.6)	55.9 (15.0)

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MMSE, Mini-Mental State Examination; TG, triglyceride

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared

antithrombotic drugs, respectively. The overall median CRP was 0.08 mg/dL; its values were 0.05 and 0.19 mg/dL in the CRP < 0.1 and ≥ 0.1 mg/dL groups, respectively. The maximum CRP value was 7.68 mg/dL. Compared with the CRP < 0.1 mg/dL group, the CRP ≥ 0.1 mg/dL group exhibited higher rates of smoking, BMI, and diabetes, but a lower proportion of women and HDL-C levels. Upon aggregating the participants' characteristics based on tertiles of fish intake, higher fish consumption was associated with a lower prevalence of CVD history, higher use of statins, and lower use of RAIs (Additional file 1: Table S2).

Table 2 presents the results of dietary assessment by fish-intake tertiles. The overall average total energy intake was approximately 2,000 kcal/day (carbohydrate, protein, and fat intake of 50%E, 17%E, and 29%E, respectively). The median fish intake was approximately 40 g/1,000 kcal, and the average Marine ω-3 FA was approximately 0.60%E. The median fish intake in T3 was approximately 3.5 times higher than that in T1, with 0% consuming fish less than twice a week. The mean intake of Marine ω-3 FA in T3 was 0.94%E. The median intake of meat in T1 to T3 was approximately 35–40 g/1,000 kcal. The CRP < 0.1 mg/dL group had a median overall fish intake of 39.3 g/1,000 kcal (T1, T2, and T3: 19.0, 39.3, and 67.3 g/1,000 kcal, respectively). About 14.9% of the whole group consumed fish less than twice a week; 47.0% and 38.1% consumed fish 2–7 and ≥7 times a week, respectively. In the CRP ≥ 0.1 mg/dL group, the overall median fish intake was 40.7 g/1,000 kcal (T1, T2, and T3: 20.9, 40.7, and 67.0 g/1,000 kcal, respectively). About 12.4% of the whole group consumed fish less than twice a week; 50.8% and 36.8% consumed fish 2–7 and ≥7 times a week, respectively. In the overall sample, 23 (2.30%) participants took EPA or EPA + DHA preparations.

The association between CRP and all-cause mortality (Table 3) during 4,161 person-years, with 162 deaths and 21 untraceable cases, was stratified by CRP < 0.1 and ≥ 0.1 mg/dL as follows: 2,428 person-years, 83 deaths, and 15 cases and 1,733 person-years, 79 deaths, and 6 cases, respectively. The estimated HR [95% CI] per 1 mg/dL increase in CRP was 1.31 [1.10–1.56] (P = 0.003) for all-cause mortality. With CRP < 0.1 mg/dL as the reference group, the all-cause mortality (HR [95% CI]) in the CRP ≥ 0.1 mg/dL group was 1.86 [1.32–2.62] (P < 0.001) after adjustment for various covariates.

The HR [95% CI] for all-cause mortality associated with continuous fish intake before stratification by CRP was 1.00 [95% CI: 0.99–1.00] (P = 0.44). For categorical fish intake before stratification, the HRs for T2 and T3 were 0.97 [95% CI: 0.67–1.41] (P = 0.90) and 0.79 [95% CI: 0.53–1.17] (P = 0.24), respectively.

Regarding the inflammatory response, the association of fish intake (g/1,000 kcal) with all-cause mortality is

Table 2 Dietary assessment by the tertiles of fish intake according to the CRP category

CRP < 0.1 mg/dL, Mean (SD)	**All, *n* = 577**	**T1 (< 28.4), *n* = 192**	**T2 (28.4–51.4), *n* = 192**	**T3 (≥ 51.4), *n* = 193**
Energy, kcal/day	2,060 (632)	1,950 (672)	2,032 (592)	2,196 (609)
Carbohydrate, %E	50.8 (7.48)	54.5 (7.72)	51.1 (6.27)	46.9 (6.37)
Protein, %E	17.0 (3.29)	14.6 (2.46)	16.6 (2.14)	19.9 (2.73)
Animal protein, %E	10.2 (3.50)	7.56 (2.60)	9.94 (2.07)	13.3 (2.95)
Plant protein, %E	6.79 (1.11)	7.05 (1.28)	6.75 (1.03)	6.58 (1.07)
Fish, median (IQR), g/1,000 kcal	39.3 (23.6–57.6)	19.0 (12.1–23.6)	39.3 (34.4–45.3)	67.3 (57.6–86.4)
Meat, median (IQR), g/1,000 kcal,	37.2 (26.1–50.3)	34.6 (22.6–45.8)	41.0 (27.4–51.0)	38.0 (26.7–54.2)
Egg, median (IQR), g/1,000 kcal	24.0 (13.5–33.7)	25.3 (11.4–36.3)	22.5 (13.7–32.5)	24.0 (13.9–32.3)
Dairy, median (IQR), g/1,000 kcal	94.6 (63.0–142)	98.1 (66.8–146)	98.3 (73.5–148)	84.8 (50.9–132)
Frequency per week, n (%)				
< 2 times	86 (14.9)	83 (43.2)	3 (1.56)	0 (0)
2–7 times	271 (47.0)	108 (56.3)	141 (73.4)	22 (11.4)
≥ 7 times	220 (38.1)	1 (0.52)	48 (25.0)	171 (88.6)
Fat, %E	29.3 (5.12)	27.9 (5.44)	29.3 (5.06)	30.6 (4.50)
SFA, %E	8.07 (1.82)	8.00 (2.13)	8.08 (1.74)	8.14 (1.55)
MUFA, %E	10.3 (2.06)	9.92 (2.19)	10.3 (2.07)	10.6 (1.85)
PUFA, %E	6.89 (1.44)	6.38 (1.41)	6.93 (1.36)	7.36 (1.39)
n–6PUFA, %E	5.37 (1.15)	5.24 (1.17)	5.45 (1.14)	5.42 (1.15)
n–3PUFA, %E	1.49 (0.45)	1.12 (0.27)	1.45 (0.27)	1.89 (0.42)
ω–3 FA, %E	0.58 (0.34)	0.27 (0.10)	0.53 (0.11)	0.94 (0.31)
EPA, %E	0.20 (0.10)	0.08 (0.03)	0.17 (0.04)	0.32 (0.11)
DHA, %E	0.32 (0.15)	0.16 (0.06)	0.30 (0.06)	0.52 (0.16)
DPA, %E	0.05 (0.02)	0.02 (0.01)	0.05 (0.01)	0.08 (0.03)
Dietary supplement, n (%)	144 (25.0)	42 (21.8)	53 (27.6)	49 (25.4)
Modified EDII	0.35 (2.32)	0.51 (2.45)	0.42 (2.15)	0.13 (2.35)
CRP ≥ 0.1 mg/dL, Mean (SD)	**All, *n* = 419**	**T1 (< 30.3), *n* = 140**	**T2 (30.3–52.5), *n* = 140**	**T3 (≥ 52.5), *n* = 139**
Energy, kcal/day	2,030 (611)	1,917 (575)	1,974 (524)	2,199 (691)
Carbohydrate, %E	50.7 (7.88)	54.3 (7.74)	51.1 (6.88)	46.6 (7.07)
Protein, %E	16.8 (3.09)	14.3 (2.05)	16.6 (2.23)	19.4 (2.60)
Animal protein, %E	10.2 (3.26)	7.63 (2.25)	9.98 (2.21)	13.0 (2.67)
Plant protein, %E	6.59 (1.12)	6.75 (1.17)	6.66 (1.07)	6.34 (1.10)
Fish, median (IQR), g/1,000 kcal	40.7 (25.0–60.1)	20.9 (14.0–25.2)	40.7 (35.1–46.6)	67.0 (60.1–80.4)
Meat, median (IQR), g/1,000 kcal	37.1 (25.9–50.0)	36.6 (24.3–47.7)	35.9 (26.1–49.1)	39.6 (28.5–53.9)
Egg, median (IQR), g/1,000 kcal	23.7 (13.7–33.9)	24.1 (12.8–34.2)	25.6 (14.3–35.5)	22.8 (13.7–33.5)
Dairy, median (IQR), g/1,000 kcal	88.6 (54.5–134)	90.3 (56.4–136)	104 (60.4–142)	78.5 (44.4–118)
Frequency per week, n (%)				
< 2 times	52 (12.4)	52 (37.1)	0 (0)	0 (0)
2–7 times	213 (50.8)	87 (62.1)	106 (75.7)	20 (14.4)
≥ 7 times	154 (36.8)	1 (0.71)	34 (24.3)	119 (85.6)
Fat, %E	29.1 (5.59)	27.5 (5.79)	29.2 (5.68)	30.6 (4.86)
SFA, %E	8.04 (1.93)	7.87 (1.96)	8.14 (2.13)	8.11 (1.68)
MUFA, %E	10.2 (2.26)	9.82 (2.40)	10.2 (2.28)	10.7 (1.99)
PUFA, %E	6.80 (1.45)	6.25 (1.47)	6.87 (1.42)	7.30 (1.26)
n–6PUFA, %E	5.29 (1.18)	5.12 (1.22)	5.39 (1.22)	5.36 (1.09)
n–3PUFA, %E	1.48 (0.43)	1.11 (0.29)	1.45 (0.26)	1.89 (0.32)
ω–3 FA, %E	0.60 (0.29)	0.29 (0.12)	0.55 (0.12)	0.94 (0.22)
EPA, %E	0.20 (0.10)	0.09 (0.04)	0.18 (0.04)	0.32 (0.08)
DHA, %E	0.33 (0.16)	0.17 (0.06)	0.31 (0.06)	0.52 (0.12)
DPA, %E	0.05 (0.02)	0.03 (0.01)	0.05 (0.01)	0.09 (0.02)
Dietary supplement, n (%)	108 (25.8)	32 (22.9)	43 (30.7)	33 (23.7)
Modified EDII	0.39 (2.30)	0.45 (2.64)	0.28 (2.07)	0.44 (2.17)

Abbreviations: %E, %Energy; CRP, C-reactive protein; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acid; IQR, interquartile range; Modified EDII, modified Empirical Dietary Inflammatory Index; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SD, standard deviation; SFA, saturated fatty acid

Table 3 Association between CRP and all-cause mortality

Mortality analysis models	CRP (continuous), mg/dL	CRP < 0.1 mg/dL	CRP ≥ 0.1 mg/dL
N	996	577	419
Person-years	4,161	2,428	1,733
Number of deaths	162	83	79
Model 1, HR (95% CI)	1.27 (1.08–1.49)	1 (Reference)	1.92 (1.37–2.69)
Model 2, HR (95% CI)	1.29 (1.08–1.54)	1 (Reference)	1.73 (1.23–2.43)
Model 3, HR (95% CI)	1.31 (1.10–1.56)	1 (Reference)	1.86 (1.32–2.62)

Model 1 is unadjusted, whereas Model 2 includes age, sex, smoking, hypertension, diabetes, history of cardiovascular disease, and cancer. Model 3 includes all variables in Model 2 in addition to body mass index and low-density lipoprotein cholesterol levels

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio

Table 4 Association between fish intake and all-cause mortality, stratified by CRP category

		Fish intake, g/1000 kcal			*P* for trend	*P* for interaction[a]
						0.040
CRP < 0.1 mg/dL	Continuous (10 g/1000 kcal)	T1 (< 28.4)	T2 (28.4–51.4)	T3 (≥ 51.4)		
N	577	192	192	193		
Person-years	2,425	799	817	808		
Number of deaths	83	26	28	29		
Unadjusted model, HR (95% CI)	1.02 (0.94–1.10)	1 (Reference)	1.00 (0.58–1.71)	1.08 (0.63–1.83)	0.76	
Adjusted model, HR (95% CI)	1.02 (0.95–1.10)	1 (Reference)	1.10 (0.64–1.90)	1.15 (0.67–1.97)	0.60	
CRP ≥ 0.1 mg/dL	Continuous (10 g/1000 kcal)	T1 (< 30.3)	T2 (30.3–52.5)	T3 (≥ 52.5)		
N	419	140	140	139		
Person-years	1,733	552	577	603		
Number of deaths	79	32	30	17		
Unadjusted model, HR (95% CI)	0.89 (0.81–0.98)	1 (Reference)	0.89 (0.54–1.46)	0.47 (0.26–0.85)	0.014	
Adjusted model, HR (95% CI)	0.90 (0.82–0.99)	1 (Reference)	0.88 (0.53–1.48)	0.49 (0.26–0.92)	0.029	

The adjusted model included age, sex, history of cardiovascular disease, cancer, diabetes, total energy intake, modified Empirical Dietary Inflammatory Index, dietary supplements, and body mass index

[a]Effect modification was assessed using a Cox regression model that included dummy variables for fish intake (T1–T3), categorical CRP, and the interaction term between dummy variables for fish intake and categorical CRP before stratifying participants by CRP levels. The p-value for the interaction term between the dummy variable representing T3 fish intake and categorical CRP was reported

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio

shown in Table 4. The effect modification of the interaction term between fish intake (T3 compared with T1) and categorical CRP was significant ($P=0.040$). In the CRP < 0.1 mg/dL group, the observation period and deaths in T1 ($n=192$), T2 ($n=192$), and T3 ($n=193$) were 799, 817, and 808 person-years and 26, 28, and 29, respectively (T3, all-cause mortality, HR [95% CI]: 1.15 [0.67–1.97]; $P=0.59$; P for trend = 0.60). The estimated HR [95% CI] for all-cause mortality per 10 g/1000 kcal increase in fish intake was 1.02 [0.95–1.10] ($P=0.54$). In the CRP ≥ 0.1 mg/dL group, the observation period and deaths in T1 ($n=140$), T2 ($n=140$), and T3 ($n=139$) were 552, 577, and 603 person-years and 32, 30, and 17 deaths, respectively (T3, all-cause mortality, HR [95% CI]: 0.49 [0.26–0.92]; $P=0.026$; P for trend = 0.029). The estimated HR [95% CI] for all-cause mortality per 10 g/1000 kcal increase in fish intake was 0.90 [0.82–0.99] ($P=0.042$).

The relationship between fish-intake frequency and all-cause mortality by inflammatory response is shown in Additional file 1: Table S3. The effect modification of the interaction term between the frequency of fish intake (≥7 times compared with < 2 times) and categorical CRP was significant ($P=0.030$). In the CRP < 0.1 and ≥ 0.1 mg/dL groups, the adjusted HR [95% CI] for all-cause mortality in the ≥7 times per week group (reference: less than twice a week) was 1.17 [0.56–2.46] ($P=0.66$) and 0.28 [0.12–0.65] ($P=0.003$), respectively. The HR [95% CI] for all-cause mortality associated with continuous Marine ω-3 FA intake before stratification by CRP was 0.79 [95% CI: 0.47–1.32] ($P=0.37$). For categorical Marine ω-3 FA intake before stratification, the HRs for T2 and T3 were 1.11 [95% CI: 0.77–1.61] ($P=0.56$) and 0.79 [95% CI: 0.53–1.18] ($P=0.26$), respectively. The relationship between Marine ω-3 FA intake and all-cause mortality by inflammatory response is shown in Additional file 1: Table S4. The effect modification of the interaction term between Marine ω-3 FA intake (T3 compared with T1) and categorical CRP was significant ($P=0.042$). In the CRP < 0.1 and ≥ 0.1 mg/dL groups, the adjusted HRs [95% CI] for all-cause mortality in the higher tertiles of Marine ω-3 FA intake (reference: lowest tertile) were 1.12 [0.66–1.91]; $P=0.82$; P for trend = 0.67 and 0.51 [0.27–0.97]; $P=0.040$; P for trend = 0.049, respectively. In the CRP < 0.1 mg/dL and CRP ≥ 0.1 mg/dL groups, the

estimated HR [95% CI] per 1%E increase in Marine ω-3 FA was 1.40 [0.75–2.62] (P=0.28) and 0.37 [0.17–0.82] (P=0.020) for all-cause mortality, respectively (Additional file 1: Table S4). Moreover, in the groups with CRP<0.1 mg/dL and CRP≥0.1 mg/dL, the relationship between fish intake and all-cause mortality, analyzed using restricted cubic spline models, yielded overall p-values of 0.71 and 0.17, respectively, and non-linear p-values of 0.84 and 0.38 (Fig. 2). Marine ω-3 FA intake had overall p-values of 0.58 and 0.05, respectively, and non-linear p-values of 0.98 and 0.11 (Figure S2).

A sub-analysis, excluding the participants with follow-up period≤180 days, in the CRP≥0.1 mg/dL group showed a significant negative association (HR [95% CI]: 0.53 [0.28–0.97], P=0.042; P for trend=0.047) between fish intake and all-cause mortality in T3 (Table 5). The association (HR [95% CI]) between fish intake and all-cause mortality in the T3 sub-analyses were as follows: with and without a history of CVD (0.29 [0.10–0.82], P=0.020 and 0.73 [0.34–1.53], P=0.40), with or without a history of cancer (0.63 [0.18–2.12], P=0.46 and 0.53 [0.27–1.06], P=0.07), with or without pre-frailty or frailty (0.45 [0.23–0.85], P=0.015 and 2.43 [0.35–9.17], P=0.36).

Discussion

In older people (aged≥85 years), CRP≥0.1 mg/dL was identified as a risk factor for all-cause mortality (Table 3), highlighting the clinical relevance of CRP measurement in this age group. This finding is supported by the positive correlation observed between interleukin-6 and all-cause mortality in the Japanese older adults, including supercentenarians (aged 85–110 years) [47]. Unlike the findings in the CRP<0.1 mg/dL group, a negative correlation between fish intake and all-cause mortality was observed in older people with CRP≥0.1 mg/dL (Table 4). In the sensitivity analyses, these results remained consistently significant in individuals with a history of CVD and pre-frailty/frailty, with similar findings for Marine ω-3 FA intake (Table 5, Additional file 1: Table S4). The fish-intake frequency, another covariate, was negatively associated with all-cause mortality (Additional file 1: Table S3). Our report offers valuable insights, emphasizing the importance of exploring the inflammatory response to understand the link between fish consumption and overall mortality.

In older people with CRP≥0.1 mg/dL, an inverse relationship was observed between fish intake and all-cause mortality. This result was supported within the same group by the comparison of categorical fish intake, the trend test, and the Cox regression analysis of continuous fish intake, as shown in Table 4. However, in the group with CRP≥0.1 mg/dL, the non-linear association (shown as a flat inverted J-curve in Fig. 2) did not support this finding. Additionally, the low number of events in the T3 group of fish intake may have led to an overestimation of its association with mortality. Long-term observations and replication of results in larger cohorts are warranted. Furthermore, the stratified analysis by history of cancer, as shown in Table 5, did not yield robust results. The lack of significant associations may be owing to insufficient

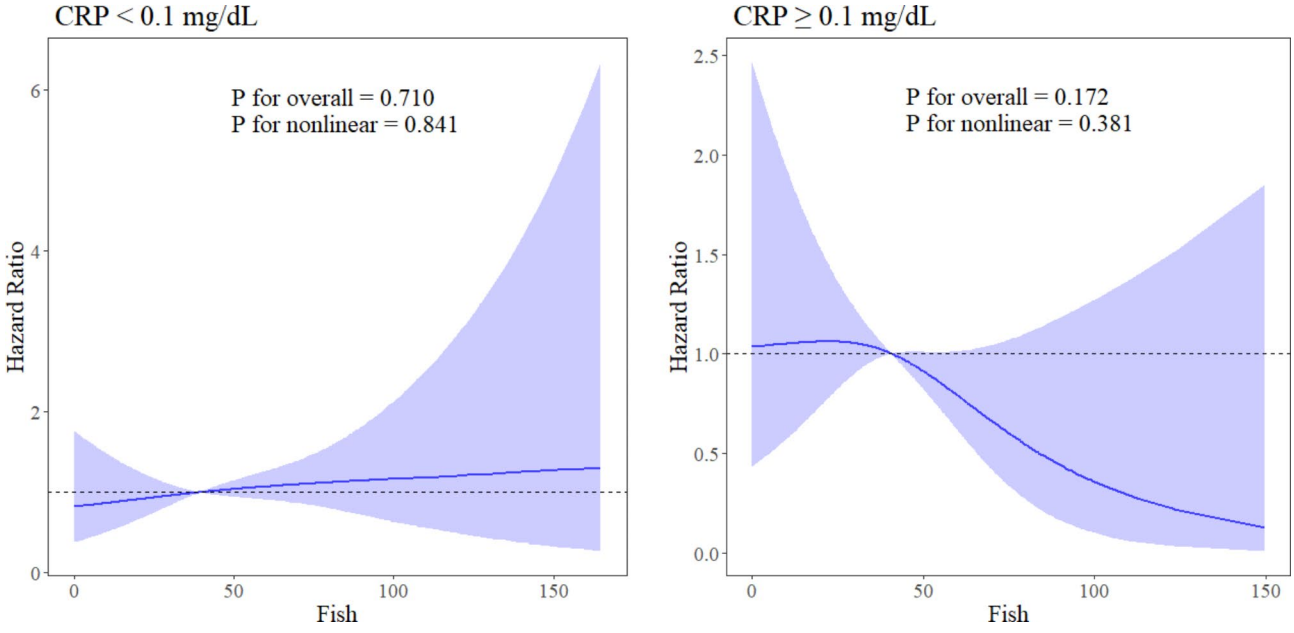

Fig. 2 Curve association of dietary fish intake with all-cause mortality. The X-axis shows fish intake, g/1000 kcal. The Y-axis shows the hazard ratio adjusted by age, sex, history of cardiovascular disease, cancer, diabetes, total energy intake, modified Empirical Dietary Inflammatory Index, dietary supplements, and body mass index. Abbreviation: CRP, C-reactive protein

Table 5 Adjusted HRs and 95% CIs of fish intake and all-cause mortality in participants with CRP < 0.1 mg/dL and CRP ≥ 0.1 mg/dL by subgroup

CRP < 0.1 mg/dL	**N**	**T1 (< 28.4)**	**T2 (28.4–51.4)**	**T3 (≥ 51.4)**	***P* for trend**
Excluded follow-up ≤ 180 days	573				0.86
Deaths	80	26	27	27	
		1 (Reference)	0.99 (0.58–1.71)	1.04 (0.61–1.79)	
History of CVD (+)	180				0.15
Deaths	39	10	15	14	
		1 (Reference)	1.67 (0.74–3.74)	1.80 (0.79–4.07)	
History of CVD (-)	397				0.59
Deaths	44	16	13	15	
		1 (Reference)	0.69 (0.33–1.45)	0.82 (0.40–1.66)	
History of cancer (+)	114				0.24
Deaths	26	8	5	13	
		1 (Reference)	0.67 (0.21–2.09)	1.63 (0.67–3.97	
History of cancer (-)	463				0.71
Deaths	57	18	23	16	
		1 (Reference)	1.18 (0.63–2.19)	0.87 (0.44–1.72)	
Pre-frailty or frailty (+)	476				0.48
Deaths	75	22	26	27	
		1 (Reference)	1.15 (0.65–2.04)	1.22 (0.69–2.15)	
Pre-frailty or frailty (-)	90				0.37
Deaths	8	4	2	2	
		1 (Reference)	0.25 (0.19–3.44)	0.31 (0.25–3.95)	
CRP ≥ 0.1 mg/dL		**T1 (< 30.3)**	**T2 (30.3–52.5)**	**T3 (≥ 52.5)**	***P* for trend**
Excluded follow-up ≤ 180 days	415				0.047
Deaths	75	30	29	16	
		1 (Reference)	0.99 (0.59–1.65)	0.53 (0.28–0.97)	
History of CVD (+)	146				0.023
Deaths	34	15	14	5	
		1 (Reference)	0.97 (0.46–2.03)	0.29 (0.10–0.82)	
History of CVD (-)	273				0.40
Deaths	45	17	16	12	
		1 (Reference)	0.86 (0.43–1.71)	0.73 (0.34–1.53)	
History of cancer (+)	91				0.42
Deaths	23	10	9	4	
		1 (Reference)	0.74 (0.29–1.87)	0.63 (0.18–2.12)	
History of cancer (-)	328				0.08
Deaths	56	22	21	13	
		1 (Reference)	1.01 (0.55–1.85)	0.53 (0.27–1.06)	
Pre-frailty or frailty (+)	352				0.019
Deaths	72	30	27	15	
		1 (Reference)	1.01 (0.59–1.72)	0.45 (0.23–0.85)	
Pre-frailty or frailty (-)	67				0.44
Deaths	7	2	2	3	
		1 (Reference)	0.46 (0.05–3.78)	2.43 (0.35–9.17)	

The covariates are age, sex, and body mass index

Abbreviations: CI, confidence interval, CRP, C-reactive protein; CVD, cardiovascular disease; HR, hazard ratio

statistical power in the stratified analysis, potential influence of a history of cancer on the relationship between fish intake and overall mortality risk, or the impact of other confounding factors.

The association between fish consumption and reduced risk of mortality is potentially mediated by the anti-inflammatory effects of nutrients found in fish, such as ω-3 FAs; vitamins D, E, and B; trace elements; and essential amino acids [48–55]. This mechanism receives credence from the anti-inflammatory effects of interleukin-1β inhibitors and the reduced incidence of CVD and mortality in individuals with stable

atherosclerosis [28], as well as the close association of inflammation with the pathology of CVD and frailty [6–10, 22]. In a stratified analysis, fish consumption was negatively associated with all-cause mortality for the same condition (Table 5), which supports the anti-inflammatory effects of fish intake.

The cultural peculiarities of the fish-eating study population should be considered when interpreting the results. First, regarding intake, the average combined EPA and DHA intake of 0.85%E in T3 with CRP ≥ 0.1 mg/dL (average energy intake: approximately 2,000 kcal, i.e., equivalent to approximately 1.8 g/day; Table 2) is comparable to the previously reported results with EPA and DHA supplementations in the interventional studies [31]. Second, regarding the intake frequency, 100% of the T3 cohort ate fish at least twice a week (the American Heart Association recommends fish intake at least twice a week), and more than 85% consumed fish at least seven times a week (Table 2) [56, 57]. High intake and increased intake frequency may have contributed to the negative association between fish intake and mortality risk in our study. Third, the Japanese custom of eating raw fish constitutes a difference in the cooking method [58] that possibly contributed to our results. Besides these distinctive features, our participants were older and had smaller stature, and their abundant blood levels of fish-derived nutrients such as ω-3 FA were more likely to be elevated than those in the general population (Table 1).

Our study has three main strengths. The first is the rarity of the study data, as we compiled valuable data on the dietary habits of approximately 1,000 older people who maintained activities of daily living up to the age of 85 years. Second, we found that the ease of implementation of fish intake was associated with a decreased risk of mortality; the Dietary Guidelines for Americans, 2020–2025, emphasizes practices and highlights of food intake rather than vague nutrients [59]. In contrast, despite the well-understood benefits of the Mediterranean diet, interventions to change culturally derived dietary patterns are required [60]. Third, the activities of daily living of the target population, which are associated with mortality in older people, indicated independence in all cohorts, which enables the results of the analysis to be interpreted without considering this effect [61].

Nonetheless, our study had several limitations. First, the unknown cause of death precludes assessment of the association of fish consumption with specific mortality. Second, reverse causality cannot be ruled out. However, the negative association of fish intake with mortality was robust in a sensitivity analysis that excluded follow-up within 180 days (Table 5). Third, only one blood sample and nutritional survey were conducted. Thus, changes in CRP levels and dietary behavior of the participants over time were unascertained for. Fourth, this study had some beta errors. Although stratified analyses were performed to assess the heterogeneity of effects, the small sample size contributed to unstable HRs in the estimated mortality (Table 5). Fifth, analyses adjusted for comorbidities such as osteoarthritis and chronic obstructive pulmonary disease could not be performed, but may have a stronger influence on the inflammatory response than dietary intake. Finally, unlike the detailed prescription records of EPA preparations, supplement intake data collection of was not conducted at baseline, potentially resulting in an insufficient consideration of ω-3FA intake.

Conclusions

Fish intake was associated with a reduced risk of mortality in older people aged ≥ 85 years with a culturally derived fish-eating lifestyle and no physical disability at baseline when accompanied by an increased inflammatory response, which is a mortality risk. Although the interpretation of our results is limited owing to the rigorous methods employed to ensure impartiality, our study provides valuable insights for future research. Further studies on the inflammatory response in the association between fish intake and mortality are warranted.

Abbreviations

%E	%Energy
BDHQ	Brief dietary history questionnaire
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
EPA	Eicosapentaenoic acid
FA	Fatty acid
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
IQR	Interquartile range
KAWP	Kawasaki Aging and Wellbeing Project
LDL-C	Low-density lipoprotein cholesterol
MMSE	Mini-Mental State Examination
Modified EDII	Modified Empirical Dietary Inflammatory Index
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
RAI	Renin-angiotensin system inhibitors
SD	Standard deviation
SFA	Saturated fatty acid
TG	Triglyceride

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20162-z.

Supplementary Material 1

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Author contributions

YA and YAbe conceived the study design. HK, YA, and YAbe participated in data collection. HK, SM, and YA participated in data analysis and interpretation. HK performed the final statistical analysis. TS, YA, and YAbe assisted with the

preparation of the data. HK drafted the report. KH, SM, and YA critically revised the draft. All the authors approved the final version of the report.

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Data availability
The data will be available upon reasonable request from the corresponding author, following an appropriate research arrangement and approval of the Research Ethics Committee of Keio University School of Medicine for Clinical Research. Thus, to request the data, please contact Dr. Yasumichi Arai (PI of the KAWP) via e-mail: yasumich@keio.jp.

Declarations

Ethics approval and consent to participate
We have complied with all relevant regulations and guidelines for work with humans. The KAWP study was approved by the ethics committee of the Keio University School of Medicine (ID: 20160297) and was registered in the University Hospital Medical Information Network Clinical Trial Registry as an observational study (ID: UMIN000026053). Written informed consent to participate in the study KAWP was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Feskens EJ, Kromhout D. Epidemiologic studies on eskimos and fish intake. Ann N Y Acad Sci. 1993;683:9–15.
2. Khan SU, Lone AN, Khan MS, Virani SS, Blumenthal RS, Nasir K, et al. Effect of omega-3 fatty acids on cardiovascular outcomes: a systematic review and meta-analysis. EClinicalMedicine. 2021;38:100997.
3. Jiang H, Wang L, Wang D, Yan N, Li C, Wu M, et al. Omega-3 polyunsaturated fatty acid biomarkers and risk of type 2 diabetes, cardiovascular disease, cancer, and mortality. Clin Nutr. 2022;41:1798–807.
4. Giosuè A, Calabrese I, Lupoli R, Riccardi G, Vaccaro O, Vitale M. Relations between the consumption of fatty or lean fish and risk of cardiovascular disease and all-cause mortality: a systematic review and meta-analysis. Adv Nutr. 2022;13:1554–65.
5. Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE Study Group. J Am Med Dir Assoc. 2013;14:542–59.
6. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350:1387–97.
7. Möhlenkamp S, Lehmann N, Moebus S, Schmermund A, Dragano N, Stang A, et al. Quantification of coronary atherosclerosis and inflammation to predict coronary events and all-cause mortality. J Am Coll Cardiol. 2011;57:1455–64.
8. Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. Stroke. 2003;34:2518–32.
9. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375:132–40.
10. Tanaka A, Shimada K, Sano T, Namba M, Sakamoto T, Nishida Y, et al. Multiple plaque rupture and C-reactive protein in acute myocardial infarction. J Am Coll Cardiol. 2005;45:1594–9.
11. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–7.
12. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
13. Ford ES, Giles WH, Mokdad AH, Myers GL. Distribution and correlates of C-reactive protein concentrations among adult US women. Clin Chem. 2004;50:574–81.
14. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, et al. The origins of age-related proinflammatory state. Blood. 2005;105:2294–9.
15. Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. Am J Epidemiol. 2001;153:1183–90.
16. Watson J, Whiting P, Salisbury C, Banks J, Hamilton W. Raised inflammatory markers as a predictor of one-year mortality: a cohort study in primary care in the UK using electronic health record data. BMJ Open. 2020;10:e036027.
17. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol. 2013;14:428–36.
18. Salminen A, Ojala J, Kaarniranta K. Apoptosis and aging: increased resistance to apoptosis enhances the aging process. Cell Mol Life Sci. 2011;68:1021–31.
19. An P, Wei LL, Zhao S, Sverdlov DY, Vaid KA, Miyamoto M, et al. Hepatocyte mitochondria-derived danger signals directly activate hepatic stellate cells and drive progression of liver fibrosis. Nat Commun. 2020;11:2362.
20. Novak ML, Thorp EB. Shedding light on impaired efferocytosis and nonresolving inflammation. Circ Res. 2013;113:9–12.
21. Arnardottir HH, Dalli J, Colas RA, Shinohara M, Serhan CN. Aging delays resolution of acute inflammation in mice: reprogramming the host response with novel nano-proresolving medicines. J Immunol. 2014;193:4235–44.
22. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15:505–22.
23. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018;3:e323–32.
24. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr. 2012;107:S171–84.
25. Shinkai S, Chaves PH, Fujiwara Y, Watanabe S, Shibata H, Yoshida H, et al. β2-microglobulin for risk stratification of total mortality in the elderly population: comparison with cystatin C and C-reactive protein. Arch Intern Med. 2008;168:200–6.
26. Niu K, Hozawa A, Kuriyama S, Ohmori-Matsuda K, Shimazu T, Nakaya N, et al. Dietary long-chain n-3 fatty acids of marine origin and serum C-reactive protein concentrations are associated in a population with a diet rich in marine products. Am J Clin Nutr. 2006;84:223–9.
27. Ngwa DN, Pathak A, Agrawal A. IL-6 regulates induction of C-reactive protein gene expression by activating STAT3 isoforms. Mol Immunol. 2022;146:50–6.
28. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab anti-inflammatory thrombosis outcomes study (CANTOS). Eur Heart J. 2018;39:3499–507.
29. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.
30. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11–22.
31. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH Randomized Clinical Trial. JAMA. 2020;324:2268–80.
32. Kalstad AA, Myhre PL, Laake K, Tveit SH, Schmidt EB, Smith P, et al. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized, controlled trial. Circulation. 2021;143:528–39.

33. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med. 2018;379:1540–50.
34. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. N Engl J Med. 2019;380:23–32.
35. Arai Y, Oguma Y, Abe Y, Takayama M, Hara A, Urushihara H, et al. Behavioral changes and hygiene practices of older adults in Japan during the first wave of COVID-19 emergency. BMC Geriatr. 2021;21:137.
36. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the reporting of Observational studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335:806–8.
37. Kobayashi S, Honda S, Murakami K, Sasaki S, Okubo H, Hirota N, et al. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J Epidemiol. 2012;22:151–9.
38. Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, et al. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. Public Health Nutr. 2011;14:1200–11.
39. Ministry of Education, Culture, Sports, Science and Technology. Standard Tables of Food Composition in Japan (5th rev ed.). Tokyo: Printing Bureau of the Ministry of Finance. 2005. (In Japanese).
40. Kobayashi S, Yuan X, Sasaki S, Osawa Y, Hirata T, Abe Y, et al. Relative validity of brief-type self-administered diet history questionnaire among very old Japanese aged 80 years or older. Public Health Nutr. 2019;22:212–22.
41. Tamiya N, Noguchi H, Nishi A, Reich MR, Ikegami N, Hashimoto H, et al. Population ageing and wellbeing: lessons from Japan's long-term care insurance policy. Lancet. 2011;378:1183–92.
42. Satake S, Arai H. The revised Japanese version of the Cardiovascular Health Study criteria (revised J-CHS criteria). Geriatr Gerontol Int rev Japanese Version. 2020;20:992.
43. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J. 1965;14:61–5.
44. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
45. Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs CS, Hu FB, et al. Development and validation of an empirical dietary inflammatory index. J Nutr. 2016;146:1560–70.
46. Kaneuchi M. Paradigm shift in dietary therapy: dietary inflammatory potential and dietary acid load. J Clin Physiol. 2019;49:59–63.
47. Hirata T, Arai Y, Yuasa S, Abe Y, Takayama M, Sasaki T, et al. Associations of cardiovascular biomarkers and plasma albumin with exceptional survival to the highest ages. Nat Commun. 2020;11:3820.
48. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011;58:2047–67.
49. Bäck M, Yurdagul A Jr, Tabas I, Öörni K, Kovanen PT. Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. Nat Rev Cardiol. 2019;16:389–406.
50. Zhou A, Hyppönen E. Vitamin D deficiency and C-reactive protein: a bidirectional mendelian randomization study. Int J Epidemiol. 2023;52:260–71.
51. Rimbach G, Minihane AM, Majewicz J, Fischer A, Pallauf J, Virgli F, et al. Regulation of cell signalling by vitamin E. Proc Nutr Soc. 2002;61:415–25.
52. Ueland PM, McCann A, Midttun Ø, Ulvik A. Inflammation, vitamin B6 and related pathways. Mol Aspects Med. 2017;53:10–27.
53. Tripathi M, Singh BK, Zhou J, Tikno K, Widjaja A, Sandireddy R, et al. Vitamin B12 and folate decrease inflammation and fibrosis in NASH by preventing syntaxin 17 homocysteinylation. J Hepatol. 2022;77:1246–55.
54. Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2012;16:705–43.
55. Qaradakhi T, Gadanec LK, McSweeney KR, Abraham JR, Apostolopoulos V, Zulli A. The anti-inflammatory effect of taurine on cardiovascular disease. Nutrients. 2020;12:2847.
56. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. Circulation. 2019;140:e563–95.
57. Rimm EB, Appel LJ, Chiuve SE, Djoussé L, Engler MB, Kris-Etherton PM, et al. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. Circulation. 2018;138:e35–47.
58. Mekonnen MF, Desta DT, Alemayehu FR, Kelikay GN, Daba AK. Evaluation of fatty acid-related nutritional quality indices in fried and raw nile tilapia, (Oreochromis niloticus), fish muscles. Food Sci Nutr. 2020;8:4814–21.
59. Phillips JA. Dietary guidelines for americans, 2020–2025. Workplace Health Saf. 2021;69:395.
60. Woodside J, Young IS, McKinley MC. Culturally adapting the Mediterranean diet pattern - a way of promoting more 'sustainable' dietary change? Br J Nutr. 2022;128:693–703.
61. He S, Craig BA, Xu H, Covinsky KE, Stallard E, Thomas J 3rd, et al. Unmet need for ADL assistance is associated with mortality among older adults with mild disability. J Gerontol Biol Sci Med Sci. 2015;70:1128–32.

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