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Original article

Fish intake and risk of mortality due to aortic dissection and aneurysm: A pooled analysis of the Japan cohort consortium☆

Kazumasa Yamagishi [a, *], Hiroyasu Iso [b], Taichi Shimazu [c], Akiko Tamakoshi [d], Norie Sawada [c], Keitaro Matsuo [e, f], Hidemi Ito [f, g], Kenji Wakai [h], Tomio Nakayama [i], Yuri Kitamura [j], Junya Sado [j], Ichiro Tsuji [k], Yumi Sugawara [k], Tetsuya Mizoue [l], Manami Inoue [c], Chisato Nagata [m], Atsuko Sadakane [n], Keitaro Tanaka [o], Shoichiro Tsugane [c], Shizuka Sasazuki [c], for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

[a] Department of Public Health Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[b] Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Suita, Japan
[c] Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan
[d] Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[e] Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan
[f] Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[g] Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
[h] Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
[i] Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan
[j] Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, Suita, Japan
[k] Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[l] Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan
[m] Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan
[n] Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan
[o] Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga, Japan

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SUMMARY

Background & aims: Many studies have suggested that fish intake is associated with protection from risk of atherosclerotic diseases; however, this association with aortic diseases has not been elucidated worldwide. We hypothesized that fish intake is inversely associated with mortality from aortic diseases (aortic dissection and aneurysm).

Methods: The study was conducted as a pooled analysis of original data from a maximum of 8 cohort studies, comprising a total of 366,048 community-based men and women who had no history of cardiovascular disease or cancer. In each cohort, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality from aortic dissection, aneurysm and total aortic disease according to the frequency of fish intake and estimated summary HRs derived from each study.

Results: Nonlinear inverse associations were found between fish intake and total aortic disease. Compared with persons who ate fish 1–2 times/week, persons who seldom ate fish had higher mortality from total aortic disease (multivariable-adjusted pooled HR = 1.93; 95% CI, 1.13–3.31). Higher mortality was not seen in those who ate fish 1–2 times/month. A similar pattern was observed for aortic dissection. Regarding aortic aneurysm, both persons who seldom ate fish and those who ate fish 1–2 times/month had higher mortality (HR = 1.99; 95% CI, 0.90–4.40 and HR = 1.86; 95% CI, 0.87–3.98, respectively).

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author. Department of Public Health Medicine, Faculty of Medicine, University of Tsukuba, Tennodai 1-1-1, Tsukuba, 305-8575, Japan. Fax: +81 29 853 2695

E-mail address: yamagishi.kazumas.ge@u.tsukuba.ac.jp (K. Yamagishi).

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Conclusions: Persons who seldom ate fish had higher mortality from aortic dissection, aneurysm, and total aortic diseases.

1. Introduction

Aortic diseases (dissection and aneurysm) are regarded as significant causes of death in developed countries, and their resulting mortality is increasing worldwide. The Global Burden of Disease project [1] reported that the estimates of overall global death rate from aortic diseases increased from 2.49 per 100,000 persons/year in 1990 to 2.78 in 2010, but that the age-specific death rates decreased between 1990 and 2010. According to the national vital statistics, the crude mortality from these diseases has increased more steeply in Japan, from 5.0 in 1995 to 14.5 in 2016, likely due to the rapid aging of the population. In contrast, crude mortality has decreased in the United States, from 14.6 in 1999 to 7.8 in 2016.

Several mechanisms play a role in the development of aortic diseases, including inflammation, platelet aggregation, proteolysis, and smooth muscle cell apoptosis [2]. Some of these also occur in coronary disease. In particular, the findings that inflammation [3], platelet aggregation [4], and triglycerides [5] are suppressed by fish intake led us to hypothesize that fish intake would be protective against mortality from aortic diseases. To our knowledge, however, no study has yet elucidated this hypothesis worldwide. The Japanese population is unique in its high consumption of a wide range of fish and seafood products [6] and traditionally low mortality from aortic disease. This has prevented Japanese cohort studies from analyzing this association due to the small number of cases of aortic disease in individual cohort studies.

One way of overcoming this limitation is by using pooled analyses to increase the power and precision of estimates. Unlike meta-analyses, which integrate published data, pooled analyses allow the unification of methods of adjustments and definitions of exposure across studies. To date, however, no pooled analysis of the association of fish consumption with aortic disease risk has yet appeared.

Here, to test this hypothesis in the Japanese population, we conducted a pooled analysis of 8 prospective studies that involved more than 350,000 Japanese individuals.

2. Methods

2.1. Study cohorts

The Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been conducting pooled analyses (the Japan Cohort Consortium) using original data from 10 major cohort studies to examine the association of lifestyle factors with major cancers in Japanese people [7]. The following inclusion criteria were defined *a priori* for the present analysis: population-based cohort studies conducted in Japan; initiation between the mid-1980s and mid-1990s; inclusion of more than 30,000 participants; availability of dietary information, including fish intake, from a baseline survey with a validated questionnaire; and collection of mortality data for aortic diseases during a follow-up period. Based on these criteria, we included 8 cohort studies: (1) the Japan Collaborative Cohort Study (JACC) [8]; (2) the Japan Public Health Center-based Prospective Study Cohort I (JPHC-I); (3) the Japan Public Health Center-based Prospective Study Cohort II (JPHC-II) [9]; (4) the Miyagi Cohort Study (MIYAGI) [10]; (5) the Ohsaki National Health Insurance Cohort Study (OHSAKI) [11]; (6) the Three Prefecture Study Aichi portion (3Pref-Aichi); (7) the Three Prefecture Study Osaka portion (3Pref-Osaka); and (8) the Three Prefecture Study Miyagi portion (3Pref-Miyagi) [12]. Because some of the Three Prefecture Studies (3Prefs) involved no aortic disease cases in either the seldom or 1–2 times/month categories of fish consumption, the three 3Prefs portions were combined as one cohort. From a total of 454,235 subjects from the 8 cohorts, we excluded 25,628 subjects with histories of cancer, stroke or myocardial infarction at baseline, 58,165 subjects with missing fish intake at baseline, and 4394 subjects meeting cohort-specific exclusion criteria. Finally, we included 366,048 subjects from all 8 studies in this pooled analysis. Selected characteristics of these studies are summarized in Table 1. Each study was approved by the relevant institutional review boards.

2.2. Assessment of fish intake

In each study, dietary fish intake was assessed using a self-administered food frequency questionnaire (FFQ). The FFQ slightly differed by study, but the query regarding fish intake was similar across the studies. The provided item was “fresh fish” for JPHC-I; “fresh fish (raw, boiled, or broiled)” for JACC and JPHC-II; “fresh seafood (raw, boiled, or broiled)” for OSAKI and MIYAGI; and “seafood (including processed seafood)” for 3Prefs. Each study typically provided five choices for frequency of fish intake: “seldom,” “1–2 days/month,” “1–2 days/week,” “3–4 days/week,” and “almost every day.” Some exceptions included the following: JPHC-I had no “1–2 days/month” category and therefore involved only four categories; JPHC-II had the choices “never” instead of “seldom” and “occasionally” instead of “1–2 days/month”; and JACC, MIYAGI, and OSAKI used “times/month” and “times/week” units instead of “days/month” and “days/week” units.

2.3. Mortality surveillance

Participants were followed from the baseline survey until the last date of follow-up in each study. Vital status was confirmed through the residential registry and death certificates. We used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems (ICD)-9 or ICD-10 to identify mortality endpoints of aortic diseases. Aortic dissection was defined as 441.0 in ICD-9 or I710 in ICD-10; aortic aneurysm was defined as 441.1–441.6 in ICD-9 or I711-719 in ICD-10; and total aortic disease was defined as 441.0–441.6 in ICD-9 or I710-719 in ICD-10.

2.4. Statistical analysis

The follow-up period was calculated from the date of the baseline survey until the last date of follow-up (in most cases the date of death, migration from the study area, or end of follow-up, whichever came first) defined in each study. Losses to follow-up due to migration and deaths not due to aortic disease were treated as censored cases. Each cohort study performed the analysis using a proportional hazards model to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs) for mortality from aortic diseases by consumption level of the five or four (the first-

Table 1
Characteristics of the 8 cohort studies included in a pooled analysis of fish intake and mortality from aortic disease.

Study	Population	Age range at baseline, y	Year of baseline survey	Population size	Response rate for baseline questionnaire	Method of follow-up	For the present pooled analysis						
							Age range, y	Last follow −up	Mean follow-up period, y	Size of cohort		No. of aortic disease cases	
										Men	Women	Men	Women
JPHC-I	Japanese residents of 5 public health center areas in Japan	40–59	1990	61,595	82%	Death certificate	40–59	2009–2014	22.1	22,523	25,230	68	34
JPHC-II	Japanese residents of 6 public health center areas in Japan	40–69	1993–1994	78,825	80%	Death certificate	40–69	2012–2014	19.3	28,045	31,457	91	67
JACC	Residents from 45 areas throughout Japan	40–79	1988–1990	110,585	83%	Death certificate	40–79	2009	16.3	37,908	52,883	137	93
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47,605	92%	Death certificate	40–64	2013	20.4	20,312	21,839	50	28
OHSAKI	Beneficiaries of National Health Insurance among residents of 14 municipalities in Miyagi Prefecture, Japan	40–79	1994	54,996	95%	Death certificate	40–79	2008	10.9	20,920	22,715	52	20
3Pref-Miyagi	Residents of 3 municipalities in Miyagi Prefecture, Japan	40–98	1984	31,345	94%	Death certificate	40–98	1998	11.6	11,193	12,845	25	6
3Pref-Aichi	Residents of 2 municipalities in Aichi Prefecture, Japan	40–103	1985	33,529	90%	Death certificate	40–99	2000	11.6	13,468	14,630	19	13
3Pref-Osaka	Residents of 4 municipalities in Osaka Prefecture, Japan	40–97	1983–1985	35,755	85%	Death certificate	40–97	1998–2000	12.4	14,279	15,801	27	9
Total				454,235						168,648	197,400	469	270

Abbreviations: y, year; JPHC, Japan Public Health Center-based prospective Study; JACC, The Japan Collaborative Cohort Study; MIYAGI, The Miyagi Cohort Study; OHSAKI: The Ohsaki National Health Insurance Cohort Study; 3Pref-Miyagi, The Three Prefecture Study - Miyagi portion; 3Pref-Aichi, The Three Prefecture Study - Aichi portion; and 3Pref-Osaka, The Three Prefecture Study - Osaka portion.

least and second-least group pooled, respectively) groups for fish intake. For JPHC-I, only a four-group analysis was performed because of the different cutpoint. We defined 1–2 days/week as the reference group for comparability with most western studies, which have distributions ranging from never to 1–2 days/week. All of the studies estimated two types of HR: age-, sex- and area-adjusted HR and multivariate-adjusted HR. Area adjustment was performed for the JACC, JPHC-I, JPHC-II and 3Prefs studies, which comprised multiple communities. The multivariate model further included smoking (never smokers, ex-smokers, current smokers of <20 and $\geq$ 20 cigarettes/day), body mass index (cohort-specific quintile), and alcohol intake (never drinkers, ex-drinkers, current drinkers of <46 and $\geq$ 46 g ethanol/day). SAS version 9.3 (SAS Institute, Cary, NC, USA) or STATA version 11.2 (Stata Corporation, College Station, TX, USA) statistical software was used for these estimations.

Our pooled analysis was conducted by two steps which have been frequently applied in pooled analyses, namely study-specific analysis by a Cox proportional hazards model and summary estimates of the study-specific HRs for each category by a random effects model. Studies with at least one case in each category were included in the analyses. For analyses with subtype analyses (aortic dissection and aneurysm), a few studies had no cases in the seldom category. To maintain a sufficient number of cases, we first performed the analysis by combining the seldom and 1–2 times/month categories. JPHC-I, which had four categories ("seldom", "1–2 days/week", "3–4 days/week" and "almost every day"), was also included. However, this inclusion might have been inappropriate because the impact of the seldom category cannot be estimated by this approach. To cope with this limitation, we also performed five-category analyses which excluded studies with no cases in the seldom category and also JPHC-I, because those in the very low fish intake group are expected to be at excess risk for aortic diseases. The extent of heterogeneity among studies for each category was evaluated using Cochran's Q statistics. The dose–response relationship (p for trend) was examined by models in which the lowest to highest categories were scored as 0, 0.05, 0.214, 0.5, and 1, respectively, and were incorporated as explanatory variables in individual studies. The resulting HR values from all of the available cohorts were combined using a fixed-effects model.

Summary HR estimates were done using the "meta" command of STATA (http://www.stata.com/stb/stb44).

3. Results

As shown in Table 2, HRs for aortic dissection, aneurysm, and total aortic disease (aortic dissection and aneurysm) for those in the seldom and/or 1–2 times/month fish intake categories were generally higher than the HRs for those in the 1–2 times/week category, albeit that statistical significance was low. Using this approach, the test for heterogeneities were statistically significant in the 3–4 times/week category for aortic dissection ($p = 0.04$ for Cochran's Q statistics) and in the seldom and 1–2 times/week categories for aortic aneurysm ($p = 0.007$).

When we performed the five-category analysis (Table 3 and Fig. 1), heterogeneities remained in the 3–4 times/week category for aortic dissection ($p = 0.03$), but disappeared for aortic aneurysm. Persons who seldom ate fish had higher mortality from total aortic disease (multivariable-adjusted pooled HR = 1.93; 95% CI, 1.13–3.31) compared to those who ate fish 1–2 times/week. Those who ate fish 1–2 times/month, 3–4 times/week, or almost every day did not have such higher mortality from total aortic disease. A similar pattern was observed for aortic dissection. For aortic aneurysm, both persons who seldom ate fish and those who ate fish 1–2 times/month had higher mortality (HR = 1.99; 95% CI,

Table 2
Summary hazard ratios of the associations between frequency of fish intake and mortality from aortic diseases in 4 categories of consumption.

Fish intake	Seldom or 1–2 times/month	1–2 times/week	3–4 times/week	Almost every day	p for trend
Total aortic diseases (8 studies)	81	205	253	200	
Number of subjects	33,802	115,368	124,917	91,961	
Person-years	561,772	1,926,564	2,045,099	1,461,064	
Model 1[a]	1.25 (0.96–1.62)	1.0	1.12 (0.93–1.35)	1.10 (0.87–1.37)	0.75
Model 2[a]	1.20 (0.92–1.57)	1.0	1.15 (0.95–1.39)	1.12 (0.90–1.40)	0.53
Aortic dissection (5 studies[b])	37	87	124	80	
Number of subjects	27,746	90,275	95,297	70,514	
Person-years	490,890	1,627,973	1,692,722	1,206,714	
Model 1[a]	1.36 (0.90–2.04)	1.0	1.44 (0.88–2.35)[d]	1.09 (0.67–1.78)	0.91
Model 2[a]	1.32 (0.88–1.99)	1.0	1.46 (0.89–2.41)[d]	1.10 (0.67–1.80)	0.85
Aortic aneurysm (7 studies[c])	44	104	114	98	
Number of subjects	31,114	103,927	110,409	78,447	
Person-years	507,766	1,692,655	1,747,287	1,185,135	
Model 1[a]	1.20 (0.58–2.48)[d]	1.0	0.96 (0.73–1.26)	1.03 (0.77–1.38)	0.68
Model 2[a]	1.18 (0.56–2.47)[d]	1.0	1.00 (0.76–1.31)	1.07 (0.80–1.43)	0.95

Studies with at least one case in each category were included in the analyses.
[a] Model 1: Adjusted for age, sex (and community for JACC, JPHC-I, JPHC-II and 3Prefs). Model 2: Further adjusted for body mass index, smoking status, and alcohol intake.
[b] JACC, JPHC-I, JPHC-II, OHSAKI and MIYAGI.
[c] JACC, JPHC-I, JPHC-II, OHSAKI and 3Prefs.
[d] Statistically significant heterogeneity indicated by Cochran's Q test.

Table 3
Summary hazard ratios of the associations between frequency of fish intake and mortality from aortic diseases in 5 categories of consumption.

Fish intake	Seldom	1–2 times/month	1–2 times/week	3–4 times/week	Almost every day	p for trend
Total aortic diseases (7 studies[b])	15	58	164	211	189	
Number of subjects	3971	26,207	95,574	108,145	84,398	
Person-years	57,750	424,081	1,492,380	1,675,317	1,289,609	
Age and sex-adjusted	1.98 (1.16–3.39)	1.17 (0.82–1.68)	1.0	1.13 (0.92–1.39)	1.17 (0.94–1.45)	0.41
	└ 1.27 (0.94–1.72) ┘					
Multivariate adjusted[a]	1.93 (1.13–3.31)	1.13 (0.79–1.61)	1.0	1.16 (0.94–1.42)	1.20 (0.96–1.49)	0.25
	└ 1.23 (0.92–1.64) ┘					
Aortic dissection (3 studies[c])	7	24	62	91	63	
Number of subjects	2466	18,994	60,771	63,383	46,830	
Person-years	41,506	341,847	1,088,831	1,156,668	858,995	
Age and sex-adjusted	2.59 (1.17–5.70)	1.20 (0.65–2.21)	1.0	1.45 (0.76–2.76)[e]	1.12 (0.78–1.61)	0.89
	└ 1.40 (0.89–2.20) ┘					
Multivariate adjusted[a]	2.48 (1.12–5.46)	1.15 (0.60–2.20)	1.0	1.47 (0.76–2.81)[e]	1.12 (0.78–1.61)	0.82
	└ 1.35 (0.86–2.13) ┘					
Aortic aneurysm (5 studies[d])	7	25	59	74	73	
	3086	13,247	63,617	75,387	61,305	
Person-years	40,909	175,773	862,598	1,023,529	828,679	
Age and sex-adjusted	1.97 (0.89–4.33)	1.88 (0.87–4.04)	1.0	1.03 (0.73–1.46)	1.13 (0.79–1.60)	0.53
	└ 1.81 (0.87–3.77) ┘					
Multivariate adjusted[a]	1.99 (0.90–4.40)	1.86 (0.87–3.98)	1.0	1.07 (0.76–1.51)	1.17 (0.83–1.67)	0.71
	└ 1.82 (0.90–3.70) ┘					

Studies with at least one case in each category were included in the analyses.
[a] Model 1: Adjusted for age, sex (and community for JACC, JPHC-I, JPHC-II and 3Prefs). Model 2: Further adjusted for body mass index, smoking status, and alcohol intake.
[b] JACC, JPHC-II, OHSAKI, MIYAGI, and 3Prefs.
[c] JACC, JPHC-II and MIYAGI.
[d] JACC, OHSAKI and 3Prefs.
[e] Statistically significant heterogeneity indicated by Cochran's Q test.

0.90–4.40, and HR = 1.86; 95% CI, 0.87–3.98). When these two categories were combined, the association was attenuated (HR = 1.82; 95% CI, 0.90–3.70) for aortic aneurysm. Such associations were not statistically significant for aortic dissection or total aortic disease.

4. Discussion

We found significantly higher mortality from aortic dissection, aneurysm, and total aortic disease among persons who seldom ate fish. A threshold was suggested between those who ate fish seldom versus 1–2 times/month. To date, this is the first study to show an inverse association between fish intake and aortic disease. Aortic diseases are considered atherosclerotic disease, and studies have shown that fish consumption has anti-atherosclerotic effects, including reducing inflammation [3], reducing platelet count and aggregation [4], decreasing triglycerides [5], and improving endothelial dysfunction [13]. Fish consumption also has an impact on endocardiac hemodynamics [14]. Animal studies suggest that fish oil has a preventive effect on abdominal aneurysm development [15], in part via suppression of the tissue remodeling process [16–19]. Our present results are in line with these previous studies.

The non-linearity of the association was not surprising given that a similar threshold effect is observed in coronary heart disease [20], in which a significant threshold effect was evident at intake of 250 mg/day of ω-3 polyunsaturated fatty acids (eicosapentaenoic and docosahexaenoic acids). This threshold effect [21] may be applicable to aortic disease as well, which motivated us to test it in a Japanese population because these individuals are unique in their consumption of a large amount of fish. The mode of fish intake in

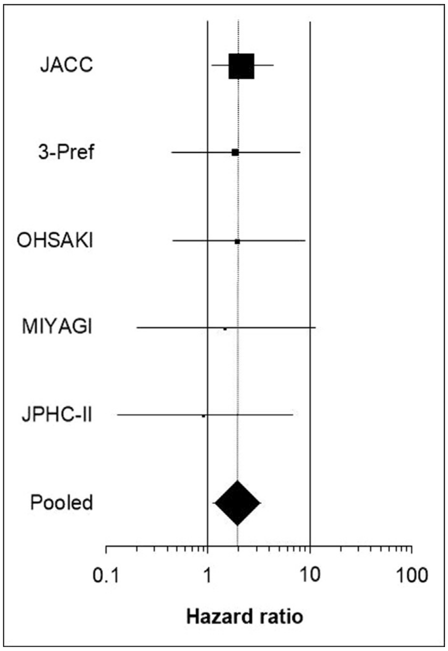

Fig. 1. Forest plot showing hazard ratios of seldom versus 1–2 times/week categories of fish intake in relation to risk of mortality from aortic disease in each study.

the present population was 3–4 times/week, and approximately 60% of people consumed fish more than 3–4 times/week. This is far different to consumption reported in western studies. For example, in the Nurses' Health Study [22], the mode was once per week and more than 80% of people consumed fish once per week or less. The large fish consumption of the individuals is a strength of this study and allowed us to detect a threshold effect.

A recent epidemiological study in 26,133 Swedes reported that persons with fruit and vegetables intake of 400 g/day or more had a significantly lower risk of abdominal aortic aneurysm (HR = 0.59; 95% CI, 0.46–0.76) than those consuming less than 400 g/day. In contrast, they did not find any association with fish/shellfish intake (HR = 0.89; 95% CI, 0.72–1.11 for persons with the intake of 300 g/week versus those with less than 300 g/week). One possible reason for this inconsistency is that the cut-point they used may be higher than the threshold we presented above, since their focus of interest was adherence to dietary recommendations. The inflection point of the non-linear curve in the present study was 1–2 times/month, which corresponded to 24 g/week (assuming a single portion size of 63 g) of fish. This was much lower than their cutpoint, which may have masked the real associations. Of note, the inflection point of the present study was much lower than that in a coronary heart disease study (250 mg/day of ω-3 polyunsaturated fatty acids, corresponding to approximately 8 ounce (227 g)/week of fish intake) [20], which corresponds to the recommended fish intake in the Dietary Guidelines for Americans 2015–2020 [1].

4.1. Study limitations

First, even when we involved more than 350,000 people, the numbers at risk in the seldom category were quite limited. To retain a sufficient number of cases, we first combined seldom and 1–2 times/month into one category (Table 2). However, this approach might have been inappropriate because it does not allow for estimation of the impact of the seldom category. To cope with this limitation, we subsequently performed five-category analyses and found a significant excess risk in the seldom category, although 1 or 2 studies had no cases in the seldom category (Table 3). A threshold was suggested between the seldom versus 1–2 times/month categories. Second, we only adjusted for major covariates (age, sex, community, body mass index, smoking and alcohol intake), because the number of cases in each cohort was quite small. Some other important covariates, such as fruit, vegetable or diet score, were not included in the present analyses. Instead, when we performed the analysis in the single largest cohort, the JACC Study, which accounted for 37% of the total number of aortic disease decedents from the 8 studies, the results did not alter substantially: HR of total aortic disease in the 'seldom' vs '1–2 times/week' categories were 2.18 (1.08–4.41) in the multivariable-adjusted model and 2.23 (1.10–4.51) with further adjustment for fruit and vegetable intakes. When histories of diabetes and hypertension were adjusted further, the corresponding HR did not change materially: 2.23 (1.11–4.52). Further, when we excluded persons with diabetes mellitus in the JACC Study (n = 4188 excluded), the results did not alter materially: the multivariable HR was 2.24 (1.11–4.52). Third, the information on fish intake was obtained at baseline survey only, and thus any later changes in fish intake were not reflected in the present study.

In conclusion, we found that persons who seldom eat fish had higher mortality rates from aortic dissection, aneurysm, and total aortic disease. Confirming this finding warrants further studies in western populations that can differentiate between the seldom and 1–2/month categories.

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Disclosures

None.

Conflicts of interest

None declared.

Appendix

Research group members are listed at the following site (as of August 2018): http://epi.ncc.go.jp/en/can_prev/796/7955.html

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