Title page

Fish intake and risk of mortality due to aortic dissection and aneurysm: A pooled analysis of the Japan Cohort Consortium

Fish intake and aortic diseases

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All authors take responsibility for all aspects of the reliability and freedom from bias of

the data presented and their discussed interpretation.

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1   **Abstract**

2   ***Background & Aims.*** Many studies have suggested that fish intake is associated with

3   protection from risk of atherosclerotic diseases; however, this association with aortic

4   diseases has not been elucidated worldwide. We hypothesized that fish intake is inversely

5   associated with mortality from aortic diseases (aortic dissection and aneurysm).

6   ***Methods.*** The study was conducted as a pooled analysis of original data from a maximum

7   of 8 cohort studies, comprising a total of 366,048 community-based men and women who

8   had no history of cardiovascular disease or cancer. In each cohort, we used Cox

9   proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence

10   intervals (CIs) for mortality from aortic dissection, aneurysm and total aortic disease

11   according to the frequency of fish intake and estimated summary HRs derived from each

12   study.

13   ***Results.*** Nonlinear inverse associations were found between fish intake and total aortic

14   disease. Compared with persons who ate fish 1-2 times/week, persons who seldom ate fish

15   had higher mortality from total aortic disease (multivariable-adjusted pooled HR=1.93;

16   95% CI, 1.13-3.31). Higher mortality was not seen in those who ate fish 1-2 times/month. A

17   similar pattern was observed for aortic dissection. Regarding aortic aneurysm, both persons

18   who seldom ate fish and those who ate fish 1-2 times/month had higher mortality

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19   (HR=1.99; 95% CI, 0.90-4.40 and HR=1.86; 95% CI, 0.87-3.98, respectively).

20   ***Conclusions.*** Persons who seldom ate fish had higher mortality from aortic dissection,

21   aneurysm, and total aortic diseases.

22

23   **Key words**: epidemiology; diet; fatty acids; prospective cohort study; meta-analysis

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

42   cohort studies from analyzing this association due to the small number of cases of aortic

43   disease in individual cohort studies.

44   One way of overcoming this limitation is by using pooled analyses to increase the

45   power and precision of estimates. Unlike meta-analyses, which integrate published data,

46   pooled analyses allow the unification of methods of adjustments and definitions of

47   exposure across studies. To date, however, no pooled analysis of the association of fish

48   consumption with aortic disease risk has yet appeared.

49   Here, to test this hypothesis in the Japanese population, we conducted a pooled

50   analysis of 8 prospective studies that involved more than 350,000 Japanese individuals.

51

Methods

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 4,394 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.

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

88   "occasionally" instead of "1-2 days/month"; and JACC, MIYAGI, and OSAKI used

89   "times/month" and "times/week" units instead of "days/month" and "days/week" units.

90

91   **Mortality Surveillance**

92   Participants were followed from the baseline survey until the last date of follow-up in each

93   study. Vital status was confirmed through the residential registry and death certificates. We

94   used the underlying cause of death coded by the International Statistical Classification of

95   Diseases and Related Health Problems (ICD)-9 or ICD-10 to identify mortality endpoints of

96   aortic diseases. Aortic dissection was defined as 441.0 in ICD-9 or I710 in ICD-10; aortic

97   aneurysm was defined as 441.1-441.6 in ICD-9 or I711-719 in ICD-10; and total aortic

98   disease was defined as 441.0-441.6 in ICD-9 or I710-719 in ICD-10.

99

100   **Statistical Analysis**

101   The follow-up period was calculated from the date of the baseline survey until the last date

102   of follow-up (in most cases the date of death, migration from the study area, or end of

103   follow-up, whichever came first) defined in each study. Losses to follow-up due to

104   migration and deaths not due to aortic disease were treated as censored cases. Each cohort

105   study performed the analysis using a proportional hazards model to estimate the hazard

106   ratios (HRs) and their 95% confidence intervals (CIs) for mortality from aortic diseases by

107   consumption level of the five or four (the first-least and second-least group pooled,

108   respectively) groups for fish intake. For JPHC-I, only a four-group analysis was performed

109   because of the different cutpoint. We defined 1-2 days/week as the reference group for

110   comparability with most western studies, which have distributions ranging from never to 1-

111   2 days/week. All of the studies estimated two types of HR: age-, sex- and area-adjusted HR

112   and multivariate-adjusted HR. Area adjustment was performed for the JACC, JPHC-I,

113   JPHC-II and 3Prefs studies, which comprised multiple communities. The multivariate

114   model further included smoking (never smokers, ex-smokers, current smokers of <20 and

115   ≥20 cigarettes/day), body mass index (cohort-specific quintile), and alcohol intake (never

116   drinkers, ex-drinkers, current drinkers of <46 and ≥46 g ethanol/day). SAS version 9.3

117   (SAS Institute, Cary, NC, USA) or STATA version 11.2 (Stata Corporation, College

118   Station, TX, USA) statistical software was used for these estimations.

119   Our pooled analysis was conducted by two steps which have been frequently

120   applied in pooled analyses, namely study-specific analysis by a Cox proportional hazards

121   model and summary estimates of the study-specific hazard ratios for each category by a

122   random effects model. Studies with at least one case in each category were included in the

123   analyses. For analyses with subtype analyses (aortic dissection and aneurysm), a few

8

124   studies had no cases in the seldom category. To maintain a sufficient number of cases, we

125   first performed the analysis by combining the seldom and 1-2 times/month categories.

126   JPHC-I, which had four categories ("seldom", "1-2 days/week", "3-4 days/week" and

127   "almost every day"), was also included. However, this inclusion might have been

128   inappropriate because the impact of the seldom category cannot be estimated by this

129   approach. To cope with this limitation, we also performed five-category analyses which

130   excluded studies with no cases in the seldom category and also JPHC-I, because those in

131   the very low fish intake group are expected to be at excess risk for aortic diseases. The

132   extent of heterogeneity among studies for each category was evaluated using Cochran's Q

133   statistics. The dose-response relationship (p for trend) was examined by models in which

134   the lowest to highest categories were scored as 0, 0.05, 0.214, 0.5, and 1, respectively, and

135   were incorporated as explanatory variables in individual studies. The resulting HR values

136   from all of the available cohorts were combined using a fixed-effects model.

137   Summary HR estimates were done using the "meta" command of STATA

138   (http://www.stata.com/stb/stb44).

139

Results

140 **Results**

141 As shown in Table 2, HRs for aortic dissection, aneurysm, and total aortic disease (aortic

142 dissection and aneurysm) for those in the seldom and/or 1-2 times/month fish intake

143 categories were generally higher than the HRs for those in the 1-2 times/week category,

144 albeit that statistical significance was low. Using this approach, the test for heterogeneities

145 were statistically significant in the 3-4 times/week category for aortic dissection (p=0.04 for

146 Cochran's Q statistics) and in the seldom and 1-2 times/week categories for aortic

147 aneurysm (p=0.007).

148   When we performed the five-category analysis (Table 3 and Figure 1),

149 heterogeneities remained in the 3-4 times/week category for aortic dissection (p=0.03), but

150 disappeared for aortic aneurysm. Persons who seldom ate fish had higher mortality from

151 total aortic disease (multivariable-adjusted pooled HR=1.93; 95% CI, 1.13-3.31) compared

152 to those who ate fish 1-2 times/week. Those who ate fish 1-2 times/month, 3-4 times/week,

153 or almost every day did not have such higher mortality from total aortic disease. A similar

154 pattern was observed for aortic dissection. For aortic aneurysm, both persons who seldom

155 ate fish and those who ate fish 1-2 times/month had higher mortality (HR=1.99; 95% CI,

156 0.90-4.40, and HR= 1.86; 95% CI, 0.87-3.98). When these two categories were combined,

157 the association was attenuated (HR=1.82; 95% CI, 0.90-3.70) for aortic aneurysm. Such

158   associations were not statistically significant for aortic dissection or total aortic disease.

159

Discussion

160

161 We found significantly higher mortality from aortic dissection, aneurysm, and total aortic

162 disease among persons who seldom ate fish. A threshold was suggested between those who

163 ate fish seldom versus 1-2 times/month. To date, this is the first study to show an inverse

164 association between fish intake and aortic disease. Aortic diseases are considered

165 atherosclerotic disease, and studies have shown that fish consumption has anti-

166 atherosclerotic effects, including reducing inflammation[3], reducing platelet count and

167 aggregation[4], decreasing triglycerides[5], and improving endothelial dysfunction[13].

168 Fish consumption also has an impact on endocardiac hemodynamics[14]. Animal studies

169 suggest that fish oil has a preventive effect on abdominal aneurysm development[15], in

170 part via suppression of the tissue remodeling process[16-19]. Our present results are in line

171 with these previous studies.

172 　　　　The non-linearity of the association was not surprising given that a similar

173 threshold effect is observed in coronary heart disease[20], in which a significant threshold

174 effect was evident at intake of 250 mg/day of ω-3 polyunsaturated fatty acids

175 (eicosapentaenoic and docosahexaenoic acids). This threshold effect[21] may be applicable

176 to aortic disease as well, which motivated us to test it in a Japanese population because

177 these individuals are unique in their consumption of a large amount of fish. The mode of

12

178 fish intake in the present population was 3-4 times/week, and approximately 60% of people

179 consumed fish more than 3-4 times/week. This is far different to consumption reported in

180 western studies. For example, in the Nurses' Health Study[22], the mode was once per

181 week and more than 80% of people consumed fish once per week or less. The large fish

182 consumption of the individuals is a strength of this study and allowed us to detect a

183 threshold effect.

184   A recent epidemiological study in 26,133 Swedes reported that persons with fruit

185 and vegetables intake of 400 g/day or more had a significantly lower risk of abdominal

186 aortic aneurysm (HR=0.59; 95% CI, 0.46-0.76) than those consuming less than 400 g/day.

187 In contrast, they did not find any association with fish/shellfish intake (HR=0.89; 95% CI,

188 0.72-1.11 for persons with the intake of 300g/week versus those with less than 300g/week).

189 One possible reason for this inconsistency is that the cut-point they used may be higher

190 than the threshold we presented above, since their focus of interest was adherence to dietary

191 recommendations. The inflection point of the non-linear curve in the present study was 1-2

192 times/month, which corresponded to 24 g/week (assuming a single portion size of 63g) of

193 fish. This was much lower than their cutpoint, which may have masked the real

194 associations. Of note, the inflection point of the present study was much lower than that in a

195 coronary heart disease study (250mg/day of ω-3 polyunsaturated fatty acids, corresponding

196   to approximately 8 ounce (227g)/week of fish intake)[20], which corresponds to the

197   recommended fish intake in the Dietary Guidelines for Americans 2015-2020[1].

198

199   *Study limitations*

200   First, even when we involved more than 350,000 people, the numbers at risk in the seldom

201   category were quite limited. To retain a sufficient number of cases, we first combined

202   seldom and 1-2 times/month into one category (Table 2). However, this approach might

203   have been inappropriate because it does not allow for estimation of the impact of the

204   seldom category. To cope with this limitation, we subsequently performed five-category

205   analyses and found a significant excess risk in the seldom category, although 1 or 2 studies

206   had no cases in the seldom category (Table 3). A threshold was suggested between the

207   seldom versus 1-2 times/month categories. Second, we only adjusted for major covariates

208   (age, sex, community, body mass index, smoking and alcohol intake), because the number

209   of cases in each cohort was quite small. Some other important covariates, such as fruit,

210   vegetable or diet score, were not included in the present analyses. Instead, when we

211   performed the analysis in the single largest cohort, the JACC Study, which accounted for

212   37% of the total number of aortic disease decedents from the 8 studies, the results did not

213   alter substantially: HR of total aortic disease in the 'seldom' vs '1-2 times/week' categories

214 were 2.18 (1.08-4.41) in the multivariable-adjusted model and 2.23 (1.10-4.51) with further

215 adjustment for fruit and vegetable intakes. When histories of diabetes and hypertension

216 were adjusted further, the corresponding HR did not change materially: 2.23 (1.11-4.52).

217 Further, when we excluded persons with diabetes mellitus in the JACC Study (n=4188

218 excluded), the results did not alter materially: the multivariable HR was 2.24 (1.11-4.52).

219 Third, the information on fish intake was obtained at baseline survey only, and thus any

220 later changes in fish intake were not reflected in the present study.

221 In conclusion, we found that persons who seldom eat fish had higher mortality

222 rates from aortic dissection, aneurysm, and total aortic disease. Confirming this finding

223 warrants further studies in western populations that can differentiate between the seldom

224 and 1-2/month categories.

225

226 **Source of funding**

229

230 **Disclosures**

231 None

15

232

Figure legend

Figure 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.

236

Appendix

Research group members are listed at the following site (as of August 2018):

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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	40-97	1983 -1985	35,755	85%	Death certificate	40-97	1998 -2000	12.4	14,279	15,801	27	9

	Osaka Prefecture, Japan				
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.

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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‡	1.25 (0.96-1.62)	1.0	1.12 (0.93-1.35)	1.10 (0.87-1.37)	0.75
Model 2‡	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‖)	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‡	1.36 (0.90-2.04)	1.0	1.44 (0.88-2.35)§	1.09 (0.67-1.78)	0.91
Model 2‡	1.32 (0.88-1.99)	1.0	1.46 (0.89-2.41)§	1.10 (0.67-1.80)	0.85
Aortic aneurysm (7 studies*)	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‡	1.20 (0.58-2.48)§	1.0	0.96 (0.73-1.26)	1.03 (0.77-1.38)	0.68
Model 2‡	1.18 (0.56-2.47)§	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.

‡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.

‖ JACC, JPHC-I, JPHC-II, OHSAKI and MIYAGI

* JACC, JPHC-I, JPHC-II, OHSAKI and 3Prefs

§ Statistically significant heterogeneity indicated by Cochran's Q test.

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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†)	15	58	164	211	189	
Number of subjects	3,971	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‡	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¶)	7	24	62	91	63	
Number of subjects	2,466	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)§	1.12 (0.78-1.61)	0.89
	└ 1.40 (0.89-2.20) ┘					
Multivariate adjusted‡	2.48 (1.12-5.46)	1.15 (0.60-2.20)	1.0	1.47 (0.76-2.81)§	1.12 (0.78-1.61)	0.82
	└ 1.35 (0.86-2.13) ┘					
Aortic aneurysm (5 studies#)	7	25	59	74	73	
	3,086	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‡	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.

‡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.

† JACC, JPHC-II, OHSAKI, MIYAGI, and 3Prefs

¶ JACC, JPHC-II and MIYAGI

JACC, OHSAKI and 3Prefs

§ Statistically significant heterogeneity indicated by Cochran's Q test.

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