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**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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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

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

24 **Introduction**

25 Aortic diseases (dissection and aneurysm) are regarded as significant causes of death in  
26 developed countries, and their resulting mortality is increasing worldwide. The Global  
27 Burden of Disease project[1] reported that the estimates of overall global death rate from  
28 aortic diseases increased from 2.49 per 100,000 persons/year in 1990 to 2.78 in 2010, but  
29 that the age-specific death rates decreased between 1990 and 2010. According to the  
30 national vital statistics, the crude mortality from these diseases has increased more steeply  
31 in Japan, from 5.0 in 1995 to 14.5 in 2016, likely due to the rapid aging of the population.  
32 In contrast, crude mortality has decreased in the United States, from 14.6 in 1999 to 7.8 in  
33 2016.

34 Several mechanisms play a role in the development of aortic diseases, including  
35 inflammation, platelet aggregation, proteolysis, and smooth muscle cell apoptosis [2]. Some  
36 of these also occur in coronary disease. In particular, the findings that inflammation[3],  
37 platelet aggregation[4], and triglycerides[5] are suppressed by fish intake led us to  
38 hypothesize that fish intake would be protective against mortality from aortic diseases. To  
39 our knowledge, however, no study has yet elucidated this hypothesis worldwide. The  
40 Japanese population is unique in its high consumption of a wide range of fish and seafood  
41 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



52 **Methods**

53 **Study cohorts**

54 The Research Group for the Development and Evaluation of Cancer Prevention Strategies  
55 in Japan has been conducting pooled analyses (the Japan Cohort Consortium) using original  
56 data from 10 major cohort studies to examine the association of lifestyle factors with major  
57 cancers in Japanese people[7]. The following inclusion criteria were defined *a priori* for the  
58 present analysis: population-based cohort studies conducted in Japan; initiation between the  
59 mid-1980s and mid-1990s; inclusion of more than 30,000 participants; availability of  
60 dietary information, including fish intake, from a baseline survey with a validated  
61 questionnaire; and collection of mortality data for aortic diseases during a follow-up period.  
62 Based on these criteria, we included 8 cohort studies: (1) the Japan Collaborative Cohort  
63 Study (JACC)[8]; (2) the Japan Public Health Center-based Prospective Study Cohort I  
64 (JPHC-I); (3) the Japan Public Health Center-based Prospective Study Cohort II (JPHC-  
65 II)[9]; (4) the Miyagi Cohort Study (MIYAGI)[10]; (5) the Ohsaki National Health  
66 Insurance Cohort Study (OHSAKI)[11]; (6) the Three Prefecture Study Aichi portion  
67 (3Pref-Aichi); (7) the Three Prefecture Study Osaka portion (3Pref-Osaka); and (8) the  
68 Three Prefecture Study Miyagi portion (3Pref-Miyagi)[12]. Because some of the Three  
69 Prefecture Studies (3Prefs) involved no aortic disease cases in either the seldom or 1-2

70 times/month categories of fish consumption, the three 3Prefs portions were combined as  
71 one cohort. From a total of 454,235 subjects from the 8 cohorts, we excluded 25,628  
72 subjects with histories of cancer, stroke or myocardial infarction at baseline, 58,165  
73 subjects with missing fish intake at baseline, and 4,394 subjects meeting cohort-specific  
74 exclusion criteria. Finally, we included 366,048 subjects from all 8 studies in this pooled  
75 analysis. Selected characteristics of these studies are summarized in Table 1. Each study  
76 was approved by the relevant institutional review boards.

77

#### 78 **Assessment of fish intake**

79 In each study, dietary fish intake was assessed using a self-administered food frequency  
80 questionnaire (FFQ). The FFQ slightly differed by study, but the query regarding fish  
81 intake was similar across the studies. The provided item was "fresh fish" for JPHC-I; "fresh  
82 fish (raw, boiled, or broiled)" for JACC and JPHC-II; "fresh seafood (raw, boiled, or  
83 broiled)" for OSAKI and MIYAGI; and "seafood (including processed seafood)" for 3Prefs.  
84 Each study typically provided five choices for frequency of fish intake: "seldom," "1-2  
85 days/month," "1-2 days/week," "3-4 days/week," and "almost every day." Some exceptions  
86 included the following: JPHC-I had no "1-2 days/month" category and therefore involved  
87 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  $\geq 20$  cigarettes/day), body mass index (cohort-specific quintile), and alcohol intake (never  
116 drinkers, ex-drinkers, current drinkers of <46 and  $\geq 46$  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

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

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

160 **Discussion**

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  $\omega$ -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



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  $\omega$ -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

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229

#### 230 **Disclosures**

231 None

232

233 **Figure legend**

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

236

237 **Appendix**

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

239 [http://epi.ncc.go.jp/en/can\\_prev/796/7955.html](http://epi.ncc.go.jp/en/can_prev/796/7955.html)

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300



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

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Total	454,235	168,648	197,400	469	270
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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.

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.

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 <sup>†</sup> )	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 <sup>‡</sup>	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 <sup>¶</sup> )	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) <sup>§</sup>	1.12 (0.78-1.61)	0.89
	└ 1.40 (0.89-2.20) ─┘					
Multivariate adjusted <sup>‡</sup>	2.48 (1.12-5.46)	1.15 (0.60-2.20)	1.0	1.47 (0.76-2.81) <sup>§</sup>	1.12 (0.78-1.61)	0.82
	└ 1.35 (0.86-2.13) ─┘					
Aortic aneurysm (5 studies <sup>#</sup> )	7	25	59	74	73	
Number of subjects	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 <sup>‡</sup>	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) ─┘					

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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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