

# Fish Consumption and Risk of Stroke in Men

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**E**COLOGICAL DATA PROMPTED THE hypothesis that fish consumption might reduce the risk of ischemic stroke and increase the risk of hemorrhagic stroke.<sup>1-5</sup> Long-chain omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are almost exclusively derived from marine sources and inhibit platelet aggregation, might play an important role in this effect.<sup>6-11</sup>

Epidemiological data on these associations are sparse because most studies did not separate ischemic from hemorrhagic stroke, due to either small numbers of hemorrhagic events or incomplete clinical information.<sup>12-15</sup> In the Nurses' Health Study, Iso and colleagues<sup>16</sup> found a significant inverse association between fish intake and risk of thrombotic stroke but not hemorrhagic stroke. In a randomized trial among patients with coronary heart disease, supplementation with omega-3 PUFAs at 1 g/d significantly reduced the risk of acute myocardial infarction but was associated with a nonsignificant increase in risk of stroke.<sup>17</sup> However, the amount of omega-3 PUFAs used in this trial exceeded those consumed typically in diet, and fish oil supplementation may have different effects than fish consumption.

**Context** The effect of fish consumption or long-chain omega-3 polyunsaturated fatty acid (PUFA) intake on risk of stroke remains uncertain.

**Objective** To examine the relation of fish consumption and long-chain omega-3 PUFA intake and risk of stroke in men.

**Design and Setting** The Health Professional Follow-up Study, a US prospective cohort study with 12 years of follow-up.

**Participants** A total of 43 671 men aged 40 to 75 years who completed a detailed and validated semiquantitative food frequency questionnaire and who were free of cardiovascular disease at baseline in 1986.

**Main Outcome Measure** Relative risk (RR) of stroke by subtype based on cumulative average fish consumption or long-chain omega-3 PUFA intake, ascertained in 1986, 1990, and 1994.

**Results** We documented 608 strokes during the 12-year follow-up period, including 377 ischemic, 106 hemorrhagic, and 125 unclassified strokes. Compared with men who consumed fish less than once per month, the multivariate RR of ischemic stroke was significantly lower among those who ate fish 1 to 3 times per month (RR, 0.57; 95% confidence interval [CI], 0.35-0.95). However, a higher frequency of fish intake was not associated with further risk reduction; the RR was 0.54 (95% CI, 0.31-0.94) for men who consumed fish 5 or more times per week. This lack of linearity was confirmed by spline analyses. By dichotomized fish intake, the multivariate RR for men who consumed fish at least once per month compared with those who ate fish less than once per month was 0.56 (95% CI, 0.38-0.83) for ischemic stroke and 1.36 (95% CI, 0.48-3.82) for hemorrhagic stroke. The inverse association between fish intake and risk of ischemic stroke was not materially modified by use of aspirin. No significant associations were found between fish or long-chain omega-3 PUFA intake and risk of hemorrhagic stroke.

**Conclusion** Our findings suggest that eating fish once per month or more can reduce the risk of ischemic stroke in men.

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Therefore, we prospectively examined the relation between fish intake and risk of stroke in the Health Professional Follow-up Study (HPFS), a large cohort of men who periodically completed dietary measurements during 12 years of follow-up. We hypothesized that fish consumption or long-chain omega-3 PUFA intake reduces the risk of ischemic stroke but not hemorrhagic stroke.

## METHODS

### Study Population

The details of the HPFS have been described elsewhere.<sup>18</sup> This cohort was es-

tablished in 1986, when 51 529 male health care professionals aged 40 to 75 years responded to a mailed questionnaire that included a comprehensive survey of diet, lifestyle characteristics,

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and medical history.<sup>19</sup> Nondietary variables were updated every other year and diet every 4 years. The follow-up rates averaged 94% in each 2- or 4-year cycle. Men with certain diseases, such as diabetes mellitus or transient ischemic attack, may change their diets and are more likely to develop stroke. To eliminate the possible prognostic bias, we excluded men at baseline with previously diagnosed stroke (n=205), myocardial infarction (n=2221), coronary artery surgery (n=967), angina pectoris (n=732), peripheral arterial disease (n=517), diabetes mellitus (n=1181), transient ischemic attack (n=276), or other cardiovascular disease (n=24). Furthermore, we excluded men whose baseline questionnaires had more than 70 instances of missing data of 131 listed food items, those with daily total energy intake of less than 800 or greater than 4200 calories (n=1676),<sup>20</sup> and those who did not provide information on fish intake at baseline (n=59). A total of 43 671 men were followed up from 1986 to 1998. The study design, data collection, and analysis plan were approved by the Harvard School of Public Health Institutional Review Board.

### Dietary Assessment

Dietary information was collected through a semiquantitative food frequency questionnaire<sup>19</sup> in 1986, 1990, and 1994. Participants were asked to indicate their average consumption of specified portions of each selected food during the previous year, with 9 frequency options, ranging from never or less than once per month to 6 or more times per day. Nutrient intakes were calculated by multiplying the consumption frequency of each food by the nutrient content of the specified portion according to composition values from US Department of Agriculture (USDA) sources,<sup>21</sup> manufacturers, or published reports.<sup>19</sup> Total nutrient intake was the sum of the nutrients derived from different foods. With respect to fish consumption, participants were asked about consumption of the following amounts of 4 different items: canned tuna fish (3-4

oz [84-112 g]); dark-meat fish such as mackerel, salmon, sardines, bluefish, and swordfish (3-5 oz [84-140 g]); other fish (3-5 oz [84-140 g]); and shrimp, lobster, or scallops as a main dish (3.5 oz [98 g]). In this study, fish consumption was defined as fish and other seafood intake. Therefore, total fish consumption was computed as the sum of the frequencies of the above 4 items.<sup>22</sup> Participants were also asked about use of fish oil supplements in 1988, 1992, and 1996.

The estimation of long-chain omega-3 PUFA intake has been previously described.<sup>16</sup> Briefly, we obtained EPA and DHA contents among each specific type of fish from the USDA nutrient database.<sup>21</sup> Then, we weighted the values of long-chain omega-3 PUFAs for the most common types of fish according to US landing data (US Department of Commerce).<sup>23</sup> For example, in the 1994 questionnaire, we weighted dark-meat fish as 58% salmon, 19% herring, 5% mackerel, 4% sardines, 1% bluefish, 1% swordfish, and 12% other dark-meat fish. The derived values of long-chain omega-3 PUFA in 1 serving size were 0.41 g for canned tuna fish, 1.60 g for dark-meat fish, 0.56 g for other fish, and 0.26 g for shrimp, lobster, or scallops as a main dish.

The reproducibility and validity of the questionnaire were evaluated in a subset of 127 participants selected from the HPFS cohort.<sup>24</sup> The reproducibility was assessed by examining the correlations between 2 administrations of the food frequency questionnaire 1 year apart. Correlations were 0.54 for canned tuna, 0.63 for dark-meat fish, 0.48 for other fish, and 0.67 for shrimp, lobster, or scallops as a main dish. In addition, comparing the food frequency questionnaire to diet records, the correlations were 0.56 for canned tuna, 0.42 for dark-meat fish, 0.39 for other fish, and 0.23 for shrimp, lobster, or scallops as a main dish.<sup>25</sup> Moreover, long-chain omega-3 PUFA intake from fish was compared with its concentration in participants' adipose tissues. The Spearman correlation coefficient for intake of EPA and percentage of EPA in adipose tissue was 0.49 ( $P<.001$ ).<sup>26</sup>

### Outcome Assessment

End points were incident fatal and non-fatal strokes occurring between the return of the baseline questionnaire and January 31, 1998. Stroke was defined as sudden or rapid onset of a typical neurological defect of more than 24-hour duration or leading to death that was attributable to a cerebrovascular event. We wrote to participants who reported an incident stroke on a follow-up questionnaire to request permission to review the medical records. The medical records were reviewed by a physician blinded to risk factor status. Strokes were classified as ischemic (embolism or thrombosis), hemorrhagic (subarachnoid and intracerebral), or unknown according to the criteria of the National Survey of Stroke.<sup>27</sup> Information on fatal cases was based on the report of next of kin, colleagues, postal authorities, or the National Death Index. All cases of fatal stroke were confirmed by checking medical records, autopsy reports, or death certificates.<sup>28</sup>

### Statistical Analyses

Each participant contributed person-time from the date of return of the first questionnaire until the date of occurrence of stroke, death, or the end of the follow-up period. Only the first event of interest was included in the analysis. Incidence rates were calculated as number of stroke events divided by person-time of follow-up in each category. Because a few men consumed more than 5 servings of fish per week, we categorized participants into 5 groups: less than once per month, 1 to 3 times per month, once per week, 2 to 4 times per week, and 5 or more times per week. To account for changes in diet during the follow-up and to best represent long-term intake, we related the incidence of stroke between 1986 and 1990 to fish consumption reported in 1986; the incidence of stroke between 1990 and 1994 to the average of fish consumption reported in 1986 and 1990; and the incidence of stroke between 1994 and 1998 to the average consumption in 1986, 1990, and 1994. To determine whether there were different effects of long-

term and most recent fish consumption, we also used baseline diet report and most recent diet report, respectively, in relation to incidence of stroke. For example, when using the most recent diet, we related the incidence of stroke between 1990 and 1994 to fish consumption reported in 1990.

Relative risks (RRs) were computed by dividing the incidence rate of stroke among men in a particular fish intake category by the incidence rate among men in the lowest fish consumption group with adjustment for age (5-year categories) and smoking status (never, past, or current smoker with 1-14, 15-24, or  $\geq 25$

cigarettes/d). The Mantel extension test was used to test for linear trends.<sup>29</sup> We also divided participants into 5 categories according to their long-chain omega-3 PUFA intake ( $<0.05$ ,  $0.05$ - $<0.2$ ,  $0.2$ - $<0.4$ ,  $0.4$ - $<0.6$ , or  $\geq 0.6$  g/d). The reference group ( $<0.05$  g/d) was set to have similar level of long-chain omega-3 PUFA intake to the reference category of fish consumption. Relative risks with adjustment for age and smoking were calculated in a similar way for fish consumption. Since  $\alpha$ -linolenic acid intake may compensate for the effect of low long-chain omega-3 PUFA intake,<sup>30</sup> we also examined the modifica-

tion of  $\alpha$ -linolenic acid and its joint classification with long-chain omega-3 PUFAs on stroke.

Multivariate RRs were estimated by using Cox proportional hazards models with age (months) as the time variable. The RRs for total stroke and stroke subtypes were examined separately. Some dietary and nondietary variables were considered potential confounders and adjusted in the multivariate analyses. Hypercholesterolemia was considered an intermediate variable so we adjusted for it only at baseline. Since men were likely to change their diets after development of diabetes mellitus, coronary heart disease, transient ischemic attack, or peripheral arterial disease or diagnosis of hypercholesterolemia, we stopped updating individual diet information after the occurrence of any of these events. All nutrient intakes were energy adjusted, and total energy intake was included in all regression models.<sup>20</sup> The median fish consumption or long-chain omega-3 PUFA intake in each category was used as a continuous variable to test for linear trends. In addition, propensity scores were used to further ensure that the comparison groups are comparable with multivariate adjustment.<sup>31,32</sup>

The continuous measure of cumulative average fish consumption (servings per week) was used to fit a restricted cubic spline model and to obtain a smooth representation of the RR as a function of fish intake with adjustment for the effects of potential confounders.<sup>33-35</sup> We used 4 knots to divide continuous fish intake into 5 intervals. To make the graph more stable and meaningful, we deleted the observations with fish intake higher than the 95th percentile when we fitted the spline model. All reported *P* values are 2-sided and  $P < .05$  is considered statistically significant. Analyses were performed using SAS software, version 8.0 (SAS Institute Inc, Cary, NC).

## RESULTS

The age-adjusted baseline characteristics of the study population by frequency of fish consumption are shown in TABLE 1. Men with high fish con-

**Table 1.** Age-Adjusted Baseline Characteristics of Study Population (N = 43 671 Men) by Frequency of Fish Consumption in 1986\*

Characteristics	Fish Consumption†				
	<1 per Month	1-3 per Month	1 per Week	2-4 per Week	$\geq 5$ per Week
No. of participants	2616	4512	20 789	12 351	3403
Mean (SD) age, y	53 (9.7)	53 (9.6)	53 (9.6)	54 (9.4)	55 (9.5)
Risk factors					
Current smoking, No. (%)	298 (11.4)	546 (12.1)	2287 (11.0)	1037 (8.4)	211 (6.2)
Overweight, No. (%) with BMI $>25$	1418 (54.2)	2418 (53.6)	10 831 (52.1)	6200 (50.2)	1681 (49.4)
Hypertension, No. (%)‡	471 (18.0)	794 (17.6)	4012 (19.3)	2544 (20.6)	701 (20.6)
Physical activity, mean (SD), MET/wk	17.7 (32.3)	17.5 (29.0)	19.9 (28.4)	24.3 (30.8)	27.1 (33.5)
Aspirin use, No. (%)	641 (24.5)	1128 (25.0)	5488 (26.4)	3310 (26.8)	963 (28.3)
Hypercholesterolemia, No. (%)‡	175 (6.7)	320 (7.1)	1892 (9.1)	1569 (12.7)	531 (15.6)
Alcohol, mean (SD), g/d	9.2 (15.5)	10.6 (16.0)	11.9 (15.7)	11.8 (15.1)	11.2 (14.5)
Dietary daily intake, mean (SD)					
Total, kcal	1856 (616)	1865 (594)	1966 (609)	2068 (621)	2191 (660)
Total fat, energy %	33.6 (7.00)	33.9 (6.25)	32.8 (5.91)	30.9 (6.08)	29.1 (6.37)
Saturated fat, energy %	11.9 (3.26)	12.1 (2.75)	11.4 (2.59)	10.3 (2.56)	9.3 (2.58)
Trans-unsaturated fat, g§	3.2 (1.32)	3.3 (1.21)	3.0 (1.09)	2.6 (1.03)	2.2 (1.00)
Long-chain omega-3 PUFAs, g§	0.04 (0.03)	0.09 (0.04)	0.21 (0.09)	0.43 (0.16)	0.85 (0.41)
Linoleic acid, g§	11.5 (3.75)	11.4 (3.44)	11.4 (3.13)	11.4 (3.27)	11.0 (3.50)
$\alpha$ -Linolenic acid, g§	1.07 (0.43)	1.08 (0.41)	1.07 (0.35)	1.08 (0.35)	1.08 (0.38)
Potassium, mg§	3200 (779)	3183 (689)	3331 (663)	3568 (691)	3835 (752)
Magnesium, mg§	328 (89.9)	325 (79.8)	342 (77.1)	370 (80.6)	401 (89.6)
Vitamin E, mg§	77 (185)	76 (182)	86 (191)	111 (214)	129 (229)
Fish, servings	0.00 (0.00)	0.07 (0.00)	0.20 (0.06)	0.50 (0.12)	1.07 (0.29)
Fruits, servings	1.96 (1.59)	1.83 (1.34)	2.17 (1.43)	2.68 (1.65)	3.14 (1.93)
Vegetables, servings	2.43 (1.61)	2.37 (1.38)	2.83 (1.47)	3.50 (1.77)	4.22 (2.14)
Supplements, No. (%)					
Multivitamins	973 (37.2)	1687 (37.4)	8399 (40.4)	5595 (45.3)	1623 (47.7)
Vitamin E	395 (15.1)	641 (14.2)	3555 (17.1)	2767 (22.4)	885 (26.0)

\*Body mass index (BMI) is calculated as weight in kilograms divided by the square of height in meters. MET indicates metabolic equivalent; PUFA, polyunsaturated fatty acid.

†Includes dark-meat fish (eg, mackerel, salmon, sardines, bluefish, swordfish; 3-5 oz); canned tuna fish (3-4 oz); other fish (3-5 oz); and shrimp, lobster, or scallops as a main dish (3.5 oz).

‡Hypertension and hypercholesterolemia were defined by self-report.

§Adjusted for total energy intake.

sumption were less likely to be current smokers or overweight and more likely to have a history of hypertension and hypercholesterolemia, to be physically active, and to use aspirin or multivitamin supplements. To account for these differences, we adjusted for the corresponding variables in multivariate analyses.

A total of 608 participants developed stroke during the 12-year follow-up. Among these cases, 377 were confirmed as ischemic stroke, 106 were identified as hemorrhagic stroke, and the remainder could not be classified from the available medical documentation. The RRs of total stroke and stroke subtypes according to cumulative average and most recent fish consumption or cumulative average long-chain omega-3 PUFA intake are shown in TABLE 2. For cumulative average fish consumption,

the risk of ischemic stroke was lower among men in each category of fish consumption compared with those who ate fish less than once per month. Even a small amount of fish consumption (1-3 times per month) was associated with a significant reduction in risk of ischemic stroke (RR, 0.57; 95% confidence interval [CI], 0.35-0.95), and no further benefit was observed at higher levels of fish intake. The RR for those who ate fish 5 or more times per week was 0.54 (95% CI, 0.31-0.94). The test for trend was nonsignificant in both the age- and smoking-adjusted model ( $P = .08$ ) and the multivariate model ( $P = .28$ ). Risk of hemorrhagic stroke was not significantly associated with fish intake. These associations remained after controlling for propensity scores. For instance, the RR for men in the highest fish intake group was 0.51 (95% CI, 0.26-

0.98) with adjustment for propensity scores, which were derived from the same covariates in the multivariate analyses. With most recent fish consumption, the RRs showed an overall pattern similar to that of using cumulative average intake. However, they were somewhat attenuated with respect to risk reduction of ischemic stroke. For example, the RR of ischemic stroke for men who ate fish 5 or more times per week was 0.81 (95% CI, 0.50-1.32) compared with men who ate fish less than once per month. Results of analyses using baseline diet were similar to those obtained using cumulative average diet (data not shown). The inverse association between fish consumption and risk of ischemic stroke did not materially change after further adjusting for use of antihypertensive medications.

**Table 2.** Relative Risk of Stroke Based on Fish Consumption and Omega-3 Polyunsaturated Fatty Acid Intake

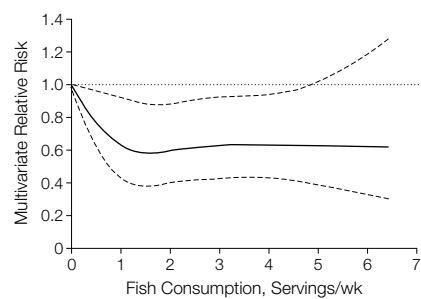
Intake*	Person-Years	Relative Risk (95% Confidence Interval)								
		Total Stroke			Ischemic Stroke			Hemorrhagic Stroke		
		Age/Smoking Adjusted†	Multivariate‡	No. of Cases	Age/Smoking Adjusted†	Multivariate‡	No. of Cases	Age/Smoking Adjusted†	Multivariate‡	No. of Cases
<b>Cumulative Fish Intake</b>										
<1/mo	22 883	1.00	1.00	40	1.00	1.00	30	1.00	1.00	4
1-3/mo	44 629	0.70 (0.47-1.06)	0.73 (0.48-1.10)	57	0.56 (0.35-0.92)	0.57 (0.35-0.95)	34	1.83 (0.56-6.03)	1.81 (0.58-5.66)	14
1/wk	214 851	0.78 (0.56-1.08)	0.74 (0.52-1.04)	282	0.62 (0.42-0.91)	0.56 (0.37-0.84)	169	1.48 (0.52-4.20)	1.40 (0.49-3.99)	53
2-4/wk	143 507	0.69 (0.49-0.97)	0.67 (0.46-0.96)	174	0.61 (0.41-0.91)	0.55 (0.36-0.85)	115	1.05 (0.34-3.21)	0.96 (0.32-2.89)	25
≥5/wk	36 154	0.76 (0.50-1.14)	0.83 (0.53-1.29)	55	0.54 (0.33-0.91)	0.54 (0.31-0.94)	29	1.50 (0.42-5.35)	1.55 (0.45-5.35)	10
<i>P</i> for trend		.19	.81		.08	.28		.42	.70	
<b>Most Recent Fish Intake</b>										
<1/mo	25 863	1.00	1.00	50	1.00	1.00	34	1.00	1.00	8
1-3/mo	44 046	0.64 (0.44-0.94)	0.79 (0.55-1.13)	55	0.56 (0.34-0.90)	0.74 (0.48-1.16)	33	0.75 (0.30-1.84)	0.99 (0.37-2.61)	10
1/wk	201 769	0.72 (0.53-0.97)	0.78 (0.58-1.05)	267	0.65 (0.45-0.95)	0.67 (0.46-0.97)	165	0.75 (0.34-1.53)	1.08 (0.47-2.47)	44
2-4/wk	148 380	0.61 (0.45-0.84)	0.66 (0.48-0.92)	174	0.56 (0.38-0.82)	0.55 (0.37-0.82)	108	0.76 (0.35-1.64)	0.86 (0.36-2.05)	35
≥5/wk	41 965	0.71 (0.49-1.03)	0.89 (0.60-1.32)	62	0.66 (0.41-1.06)	0.81 (0.50-1.32)	37	0.64 (0.24-1.68)	0.74 (0.25-2.20)	9
<i>P</i> for trend		.07	.20		.06	.55		.61	.35	
<b>Cumulative Omega-3 Polyunsaturated Fatty Acids Intake, g/d</b>										
<0.05	19 741	1.00	1.00	31	1.00	1.00	24	1.00	1.00	4
0.05-<0.2	155 579	0.84 (0.58-1.23)	0.77 (0.52-1.14)	197	0.62 (0.40-0.95)	0.56 (0.35-0.88)	112	1.38 (0.48-4.00)	1.29 (0.45-3.75)	41
0.2-<0.4	175 161	0.83 (0.57-1.21)	0.77 (0.52-1.14)	228	0.69 (0.45-1.07)	0.63 (0.40-0.98)	147	1.08 (0.37-3.15)	1.02 (0.35-3.00)	37
0.4-<0.6	68 003	0.71 (0.47-1.09)	0.71 (0.46-1.10)	84	0.55 (0.33-0.90)	0.54 (0.32-0.91)	51	0.95 (0.28-3.21)	0.89 (0.27-2.87)	13
≥0.6	43 539	0.86 (0.56-1.34)	0.87 (0.56-1.37)	68	0.72 (0.43-1.20)	0.73 (0.43-1.25)	43	1.13 (0.31-4.07)	1.14 (0.34-3.84)	11
<i>P</i> for trend		.54	.71		.69	.73		.35	.87	

\*See the "Methods" section of the text for descriptions of cumulative and most recent intakes.

†Adjusted for age (5-year categories) and smoking status (never, past, or current with 1-14 cigarettes/d, 15-24 cigarettes/d, or ≥25 cigarettes/d).

‡Adjusted for body mass index (calculated as weight in kilograms divided by the square of height in meters; <21, 21-22.9, 23-24.9, 25-29.9, or ≥30); physical activity (quintiles); history of hypertension (yes or no); smoking status (same as age/smoking-adjusted model); use of aspirin (yes or no), fish oil (yes or no), and multivitamins (yes or no); intake of total calories (quintiles), total fat (quintiles), saturated fat (quintiles), trans-unsaturated fat (quintiles), alcohol (0, 0.1-9.9, 10-19.9, 20-29.9, or ≥30 g/d), potassium (quintiles), and magnesium (quintiles); total servings of fruits and vegetables (quintiles); and hypercholesterolemia (yes or no) at baseline.

**Figure.** Multivariate Relative Risk of Ischemic Stroke as a Function of Fish Consumption



Data were fitted by a restricted cubic spline Cox proportional hazards model. The 95% confidence intervals are indicated by the dashed lines. See "Methods" section of text for explanation of serving sizes.

**Table 3.** Relative Risk (RR) of Ischemic Stroke According to Cumulative Fish Consumption Stratified by Aspirin Use and Vitamin E Intake\*

	Fish Consumption	
	<1 per Month	≥1 per Month
<b>Total Cohort</b>		
RR (95% CI)	1.00	0.56 (0.38-0.83)
No. of cases	30	347
<b>Aspirin Use</b>		
Users		
RR (95% CI)	1.00	0.59 (0.28-1.23)
No. of cases	9	150
Nonusers		
RR (95% CI)	1.00	0.50 (0.30-0.82)
No. of cases	20	181
<b>Vitamin E Intake, mg/d†</b>		
>11.4		
RR (95% CI)	1.00	0.48 (0.28-0.84)
No. of cases	16	187
≤11.4		
RR (95% CI)	1.00	0.57 (0.31-1.03)
No. of cases	14	160

\*Adjusted for the covariates listed in Table 2 multivariate model. CI indicates confidence interval.  
†Median intake was 11.4 mg/d.

For long-chain omega-3 PUFA intake, the RR of ischemic stroke was significantly reduced for men in each category except the highest category compared with those in the lowest one. The RR was attenuated to 0.73 (95% CI, 0.43-1.25) among men in the highest category. No significant association was observed between long-chain omega-3 PUFA intake and risk of hemorrhagic stroke (Table 2). Approximately 2.7% of participants in this cohort used fish oil

supplements. Among them, 19 men developed strokes (12 ischemic and 7 of unknown type); the RR for fish oil users compared with nonusers was 1.01 (95% CI, 0.55-1.86) for ischemic stroke. We also examined the relation between cumulative average  $\alpha$ -linolenic acid intake and risk of stroke. There was no apparent or statistically significant overall association between  $\alpha$ -linolenic acid intake and risk of stroke (data not shown).

By visual inspection, the restricted cubic spline curve (FIGURE) confirms the impression of a threshold of fish consumption in relation to risk of ischemic stroke, in concordance with the categorical analysis in Table 2. Therefore, we dichotomized fish intake as less than once per month vs at least once per month. The multivariate RRs for men who consumed fish at least once per month compared with those who ate fish less than once per month were 0.72 (95% CI, 0.52-1.01) for total stroke, 0.56 (95% CI, 0.38-0.83) for ischemic stroke, and 1.36 (95% CI, 0.48-3.82) for hemorrhagic stroke.

To determine whether and to what extent aspirin use or vitamin E intake modifies the relation between fish consumption and risk of stroke, we stratified the study population according to use of aspirin or vitamin E intake. The number of hemorrhagic strokes was too small to be analyzed in the stratification studies so only the multivariate RRs of ischemic strokes were investigated. The overall inverse association between fish intake and risk of ischemic stroke persisted in each subgroup and was not materially modified by use of aspirin or vitamin E intake (TABLE 3). Tests for interaction were not statistically significant.

To examine whether intake of  $\alpha$ -linolenic acid modifies the association between intake of long-chain omega-3 PUFAs and ischemic stroke, we created 3 equal categories of  $\alpha$ -linolenic acid intake. We categorized the long-chain omega-3 PUFA intake into 3 groups, making the lowest category of long-chain omega-3 PUFA intake the same as the reference group for the omega-3 PUFA categorical variable in Table 2, then equally divided the remaining into 2 other categories. The inverse associa-

tion between long-chain omega-3 PUFA intake and risk of ischemic stroke was attenuated among men in the highest tertile of  $\alpha$ -linolenic acid intake (TABLE 4). None of the tests for interaction, however, were significant.

**COMMENT**

In this large prospective study among male health care professionals, we observed a 40% lower risk of ischemic stroke in men who consumed fish once per month or more compared with those who ate fish less often. The cubic spline curve leveled off at approximately 1 serving of fish per week, suggesting that the beneficial effect of fish intake on risk of ischemic stroke might be maximal at a relatively low level of consumption. No significant associations were found between fish consumption or long-chain omega-3 PUFA intake and risk of hemorrhagic stroke.

The prospective nature of the study design minimized the likelihood of recall and selection biases, and the high follow-up rates largely reduced the concern that the results have been affected by differential follow-up rates. Also, our results were unlikely to be explained by confounding, since the RR estimates did not materially change after simultaneous controlling for potential confounding variables, including major lifestyle and dietary risk factors. The similar results after adjustment for propensity scores further supported our findings. However, the possibility of residual confounding by unknown risk factors could not be excluded. In addition, our dietary assessments were based on the previously validated semiquantitative food frequency questionnaires. The range of exposure was wide, and we reduced error in dietary assessment by using repeated measurements and cumulative average dietary intakes. To estimate long-chain omega-3 PUFA intake, we assigned a value to each fish item. Although these values were reasonably derived from the USDA database, they should be considered approximations. Moreover, there was inevitable error in estimating fish consumption, and we ignored the small amounts of long-chain

omega-3 PUFAs contributed by intake of poultry and other animal organs.<sup>36</sup> However, the error in both fish and long-chain omega-3 PUFA intake would be mostly random and tend to dilute their associations with stroke. Furthermore, our study focused on men without history of diabetes and cardiovascular diseases. The generalizability may be limited by the unique study base.

Inverse associations between fish intake and risk of stroke have been previously reported. In the Zutphen study,<sup>12</sup> men who ate more than 20 g/d of fish had a 50% (RR, 0.49; 95% CI, 0.24-0.99) lower risk of total stroke compared with those who consumed less than 20 g/d of fish. In the National Health and Nutrition Examination Survey I Epidemiological Follow-up Study,<sup>13</sup> a modest and nonsignificant risk reduction was observed in men who ate fish more than once per week compared with those who never ate fish (RR, 0.85; 95% CI, 0.49-1.46). In the Physicians' Health Study,<sup>14</sup> compared with men whose fish consumption was less than 1 meal per week, the adjusted RRs of stroke for those who consumed 1 meal, 2 to 4 meals, and 5 or more meals per week were 0.9 (95% CI, 0.6-1.3), 0.8 (95% CI, 0.5-1.2), and 0.6 (95% CI, 0.3-1.6), respectively (*P* for trend = .13). These studies did not separate ischemic and hemorrhagic strokes<sup>12-14</sup>; however, the results probably reflect the beneficial effects of fish intake on risk of ischemic stroke, as it is more common than hemorrhagic stroke in most populations. Iso et al<sup>16</sup> found nonsignificant inverse associations between fish intake and total or ischemic stroke in a large cohort of women. The multivariate RR of ischemic stroke was 0.38 (95% CI, 0.12-1.19; *P* for trend = .09) among women in the highest fish intake category ( $\geq 5$  times/wk) compared with women who ate fish less than once per month. In addition, they found that the inverse association was stronger and significant in analyses restricted to thrombotic stroke; no excess risk of hemorrhagic stroke was found with high fish intake. Furthermore, Albert et al<sup>17</sup> found a threshold effect on sudden cardiac death in the Physicians'

**Table 4.** Relation of Long-Chain Omega-3 Polyunsaturated Fatty Acid Intake and Risk of Ischemic Stroke Stratified and Jointly Classified by  $\alpha$ -Linolenic Acid Intake

Category	Median, g/d	Relative Risk (95% Confidence Interval) by $\alpha$ -Linolenic Acid Intake†		
		Tertile 1 (0.23-0.91 g/d)	Tertile 2 (0.91-1.14 g/d)	Tertile 3 (1.14-5.82 g/d)
		1.00	0.94 (0.73-1.21)	0.98 (0.74-1.29)
Stratification				
1	0.03	1.00	1.00	1.00
2	0.16	0.61 (0.29-1.30)	0.38 (0.18-0.83)	0.82 (0.30-2.29)
3	0.40	0.70 (0.32-1.54)	0.29 (0.13-0.64)	0.89 (0.32-2.50)
Joint Classification				
1	0.03	1.00	1.69 (0.67-4.25)	0.68 (0.22-2.07)
2	0.16	0.63 (0.31-1.29)	0.67 (0.33-1.39)	0.62 (0.30-1.29)
3	0.40	0.68 (0.33-1.40)	0.53 (0.25-1.10)	0.69 (0.33-1.45)

\*For category 1, omega-3 polyunsaturated fatty acid intake was less than 0.05 g/d (the reference group for the omega-3 polyunsaturated fatty acid categorical variable in Table 2); the remaining participants were equally divided into categories 2 and 3. Relative risks (95% confidence intervals) for the total cohort were as follows: for category 1, 1.00; category 2, 0.60 (0.38-0.93); and category 3, 0.59 (0.37-0.93).

†Adjusted for covariates cited in the multivariate model in Table 2.

Health Study. For men who ate fish at least once per week, the multivariate RR of sudden death was 0.48 (95% CI, 0.24-0.96) compared with men who consumed fish less than once per month.

Since both aspirin and long-chain omega-3 PUFAs decrease platelet aggregability through the inhibition of thromboxane A<sub>2</sub> synthesis, fish intake may not provide any additional benefit among men using aspirin. However, we did not find that aspirin use materially modified the apparent beneficial effect of fish consumption on risk of ischemic stroke. Although the inverse association was slightly strengthened among men with high vitamin E intake, tests for interaction were nonsignificant between fish or long-chain omega-3 PUFA intake and use of vitamin E, a fat-soluble vitamin presumed to improve the beneficial effect of fish on atherosclerosis and thrombosis by preventing the auto-oxidation and peroxidation of omega-3 PUFAs.<sup>38-40</sup> This result is consistent with that of the GISSI prevention trial, in which the effect of combined treatment with vitamin E and omega-3 PUFAs was similar to that of omega-3 PUFAs alone with respect to risk of total stroke (mainly ischemic stroke).<sup>17</sup> In addition, the inverse association between long-chain omega-3 PUFA intake and risk of ischemic stroke was attenuated among men in the high-

est tertile of  $\alpha$ -linolenic acid intake. These results support the hypothesis that high  $\alpha$ -linolenic acid may compensate for the effect of low long-chain omega-3 PUFA intake because  $\alpha$ -linolenic acid can be converted to EPA.<sup>30</sup> We did not find an association between fish oil intake and risk of stroke, but the number of men taking fish oil supplements was small.

A beneficial effect of fish consumption on ischemic stroke could be related to the overall favorable effects of long-chain omega-3 PUFAs on lipid profiles,<sup>41-44</sup> platelet activity,<sup>6,45,46</sup> threshold for arrhythmias,<sup>47</sup> and endothelial function.<sup>48,49</sup> In our study, even rather low fish consumption was associated with a significantly lower risk of ischemic stroke. The biological mechanism of the apparent beneficial effects of such a small amount of fish intake and the lack of a dose response remain unclear. It is of interest, however, that in a clinical trial, platelet aggregation was reduced by supplementation with only 150 mg/d of EPA for 4 weeks.<sup>50</sup> Conversely, the antiplatelet effect and the observation of high incidence of hemorrhagic stroke in native Alaskans, who consume a diet rich in long-chain omega-3 PUFA, have raised concerns about possible adverse effects of high fish intake on risk of hemorrhagic stroke. Although we did not find a significant association between fish or long-chain

omega-3 PUFA intake and risk of hemorrhagic stroke, the 95% CIs of our RR estimates were wide due to a relatively small number of cases. Therefore, further investigations are needed to address this question.

In summary, in this large cohort of men without history of cardiovascular disease or diabetes, we observed a significantly lower risk of ischemic stroke in men who consumed fish once per month or more compared with men who ate fish less often. The possibility that high fish consumption increases risk of hemorrhagic stroke could not be ruled out and needs further exploration.

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