Fish Consumption and Incidence of Stroke
A Meta-Analysis of Cohort Studies

Ka He, MD, ScD; Yiqing Song, MD; Martha L. Daviglus, MD, PhD; Kiang Liu, PhD; Linda Van Horn, PhD; Alan R. Dyer, PhD; Uri Goldbourt, PhD; Philip Greenland, MD

Background and Purpose—Results from observational studies on fish consumption and risk of stroke are inconsistent. We quantitatively assessed the relationship between fish intake and incidence of stroke using a meta-analysis of cohort studies.

Methods—We searched the Medline and Embase databases (1966 through October 2003) and identified 9 independent cohorts (from 8 studies) that provided a relative risk (RR) and corresponding 95% CI for total or any type of stroke in relation to fish consumption. Pooled RR and 95% CI of stroke were estimated by variance-based meta-analysis.

Results—Compared with those who never consumed fish or ate fish less than once per month, the pooled RRs for total stroke were 0.91 (95% CI, 0.79 to 1.06) for individuals with fish intake 1 to 3 times per month, 0.87 (95% CI, 0.77 to 0.98) for once per week, 0.82 (95% CI, 0.72 to 0.94) for 2 to 4 times per week, and 0.69 (95% CI, 0.54 to 0.88) for ≥5 times per week (P for trend=0.06). In stratified analyses of 3 large cohort studies with data on stroke subtypes, the pooled RRs across 5 categories of fish intake were 1.0, 0.69 (95% CI, 0.48 to 0.99), 0.68 (95% CI, 0.52 to 0.88), 0.66 (95% CI, 0.51 to 0.87), and 0.65 (95% CI, 0.46 to 0.93) for ischemic stroke (P for trend=0.24); and 1.0, 1.47 (95% CI, 0.81 to 2.69), 1.21 (95% CI, 0.78 to 1.85), 0.89 (95% CI, 0.56 to 1.40), and 0.80 (95% CI, 0.44 to 1.47) for hemorrhagic stroke (P for trend=0.31).

Conclusions—These results suggest that intake of fish is inversely related to risk of stroke, particularly ischemic stroke. Fish consumption as seldom as 1 to 3 times per month may protect against the incidence of ischemic stroke. (Stroke. 2004;35:1538-1542.)

Key Words: cerebrovascular accident • fishes • meta-analysis

Ecological data indicate that fish consumption may be associated inversely with ischemic stroke and positively with hemorrhagic stroke.1,2 Data from the World Health Organization on 36 countries showed an inverse association between fish intake and stroke mortality.3 Long-chain omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid and docosahexaenoic acid, which are derived from marine foods, were thought to be the potent nutrients in fish responsible for the low rate of ischemic stroke and high rate of hemorrhagic stroke among those who consumed large amounts of fish.4,5

A number of epidemiological studies have also examined the relationship between fish intake and risk of stroke. The preponderance of data derives from prospective cohort studies, but findings are conflicting. Some but not all cohort studies reported an inverse association between fish consumption and risk of stroke after adjustment for potential confounders.6–13 Differences in study populations, sample size, assessment of fish intake, and stroke end point, as well as adjustment for covariates, coupled with the fact that most studies did not separate ischemic from hemorrhagic stroke, may account for differences in assessing the effects of fish consumption on stroke risk. To provide a reliable quantitative assessment of the relationship of fish intake with stroke risk, we conducted a meta-analysis of all prospective cohort studies with relevant data. We also attempted to explore the major sources of heterogeneity among the reported studies.

Materials and Methods

Study Selection
All relevant cohort studies published in English-language journals from 1966 to October 2003, which reported the association between fish consumption and stroke, were identified by searching Medline and Embase using the terms “fish,” “seafood,” “animal products,” “omega-3 fatty acids,” “n-3 fatty acids,” “stroke,” “cerebrovascular event,” and “cardiovascular disease.” Additional information was retrieved through a hand search of references from relevant articles and recent reviews. Two of our investigators (K.H., Y.S.) independently reviewed all relevant articles and identified eligible studies.
Discrepancies were resolved by group discussion. In general, articles were included if the studies were cohort studies, and the relative risks (RRs) and their corresponding 95% CIs of stroke relating to each category of fish consumption were reported. We identified 8 studies that provided an RR and corresponding 95% CI for total or type of stroke in relation to the amount or frequency of fish consumption. One study, which estimated RR and 95% CI for men and women separately, was counted as 2 separate cohorts in the meta-analysis.

**Data Extraction**

The data we collected included the first author’s name, year of publication, country of origin, duration of follow-up, range or mean of participants’ age, sample size, proportion of men, number of events, categories of fish intake, the amount of fish intake for each category, methods for measurement of fish intake, and adjusted covariates, as well as RRs and 95% CIs of total stroke and stroke subtypes in the corresponding categories. RRs transformed to their natural logarithms (ln), and the 95% CIs were used to calculate the corresponding SEs.

To standardize fish intake, we first converted frequency into grams per day. The amount of fish consumption (grams per day) was estimated by multiplying the frequency of consumption (servings per day) by the corresponding portion size (grams per serving). For example, the derived average portion size in the Health Professional Follow-Up Study was 105 g/serving. The range of fish consumption for 1 to 3 times per month was converted to 3.5 g/day (105/30) to 10.5 g/day. When the portion size of fish intake in an individual study was not available from the published article, the value was determined on the basis of data from the 2 largest cohort studies (the Nurses’ Health Study and the Health Professional Follow-Up Study), considering that the food frequency questionnaire (FFQ) used in these 2 studies has been validated.14,15 If the uppermost amount of the highest fish intake category was uncertain (eg, fish intake was ≥5 times per week), we assigned 1 daily serving of fish as the upper limit.

**Statistical Analysis**

Fish consumption was categorized into 5 standardized intervals: “never or less than once per month,” “1 to 3 times per month,” “once per week,” “2 to 4 times per week,” and “≥5 times per week.” We created a data set by assigning each RR extracted from each individual study into its corresponding standardized interval according to the range or median amount of fish intake in the category. If the median amount of fish consumption from more than 1 category in a single study fell into the same standardized category of fish intake in our meta-analysis, we pooled these RRs and used the combined estimate for that category. Also, if the range of fish intake in our meta-analysis, we pooled these RRs and used the corresponding SEs.

For individuals who ate fish ≥5 times per week, the risk of stroke at least per month were 0.85 (95% CI, 0.79 to 0.91) for total stroke, 0.67 (95% CI, 0.58 to 0.78) for ischemic stroke, and 1.06 (95% CI, 0.82 to 1.37) for hemorrhagic stroke.

**Discussion**

Our meta-analysis of cohort studies suggests an inverse association between fish consumption and risk of stroke, particularly ischemic stroke, although there was not a strong dose-response relationship. The findings suggest that eating fish as seldom as 1 to 3 times per month may reduce risk of ischemic stroke. The risk of ischemic stroke was reduced significantly by eating fish 1 to 3 times per month. For hemorrhagic stroke, we did not observe any significant association with fish intake (Table 2). Given the nonlinear relations between fish consumption and stroke risk, we further dichotomized fish intake as less than once per month versus at least once per month. The pooled RR for those who consumed fish at least once per month were 0.85 (95% CI, 0.79 to 0.91) for total stroke, 0.67 (95% CI, 0.58 to 0.78) for ischemic stroke, and 1.06 (95% CI, 0.82 to 1.37) for hemorrhagic stroke.

**Results**

The final data set for our meta-analysis included 9 cohorts from 8 independent studies comprising 200 575 participants (3491 stroke events) aged 34 to 103 years. Of the 9 cohorts, 6 were from the United States, 1 from Europe, 1 from China, and 1 from Japan. The sample sizes varied across studies from 552 (Zutphen Study)6 to 79 839 (Nurses’ Health Study).11 The average duration of follow-up was 12.8 years (range 4 to 30 years). Data on fish consumption were collected by in-person interviews (5 cohorts) or using self-administered FFQs (4 cohorts). Fish intake in each individual study was classified into 2 to 5 categories. All reported RRs (95% CIs) of stroke or stroke subtypes in each study were adjusted for multiple covariates (Table 1).

Compared with those who never consumed fish or ate fish less than once per month, individuals with higher fish intake had lower risk of total stroke (Table 2). The reduction in risk of total stroke was statistically significant for fish intake once per week (RR, 0.87; 95% CI, 0.77 to 0.98). Beneficial effects on stroke risk appeared to increase with greater fish intake. For individuals who ate fish ≥5 times per week, the risk of stroke was lower by 31% (RR, 0.69; 95% CI, 0.54 to 0.88).

However, the test for linear trend was statistically nonsignificant (P for trend=0.06). In addition, there was no evidence for the presence of significant heterogeneity among the 9 cohorts (χ²=12.5; P=0.13; see Figure).

In the stratified analyses, the inverse association between fish intake and risk of stroke was slightly attenuated among men. Also, this association was somewhat weaker in studies using in-person interviews (Table 2). On the basis of 3 large studies that provided data on stroke subtypes, we found an inverse threshold association between fish intake and ischemic stroke. The risk of ischemic stroke was reduced significantly by eating fish 1 to 3 times per month. For hemorrhagic stroke, we did not observe any significant association with fish intake (Table 2). Given the nonlinear relations between fish consumption and stroke risk, we further dichotomized fish intake as less than once per month versus at least once per month. The pooled RR for those who consumed fish at least once per month were 0.85 (95% CI, 0.79 to 0.91) for total stroke, 0.67 (95% CI, 0.58 to 0.78) for ischemic stroke, and 1.06 (95% CI, 0.82 to 1.37) for hemorrhagic stroke.

**Discussion**

Our meta-analysis of cohort studies suggests an inverse association between fish consumption and risk of stroke, particularly ischemic stroke, although there was not a strong dose-response relationship. The findings suggest that eating fish as seldom as 1 to 3 times per month may reduce risk of ischemic stroke.

Most studies included in our meta-analysis had a large sample size and long-term follow-up periods that increased the statistical power to examine the overall associations of fish intake and incidence of stroke. The prospective study designs also minimized selection bias and recall bias. Although randomized placebo-controlled trials are the most definitive tool for evaluation of the causality of diet–disease relations, it would be difficult to conduct a long-term, large-scale, randomized trial on fish consumption and stroke because of feasibility considerations such as long-term compliance.
TABLE 1. Characteristics of 9 Included Cohorts (From 8 Studies) of Fish Consumption and Incidence of Stroke

<table>
<thead>
<tr>
<th>Source</th>
<th>Participants</th>
<th>Age</th>
<th>Men (%)</th>
<th>Duration of Follow-Up, y</th>
<th>Exposure Assessment</th>
<th>No. of Categories</th>
<th>Outcome (No. of Events)</th>
<th>Adjusted Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keli et al 1994 Zubehor Study The Netherlands</td>
<td>552</td>
<td>50–69</td>
<td>100</td>
<td>15</td>
<td>Self-administered questionnaire</td>
<td>≤20 g/day</td>
<td>Total stroke (n = 42) ICD-8 codes 430–438</td>
<td>Age, systolic blood pressure, cigarette smoking, serum total cholesterol, energy intake, alcohol consumption, and prescribed diet</td>
</tr>
<tr>
<td>Morris et al 1995 Physicians’ Health Study USA</td>
<td>21 185</td>
<td>40–84</td>
<td>100</td>
<td>4</td>
<td>Self-administered questionnaire</td>
<td>≤20 g/day</td>
<td>Total stroke (n = 173) ICD-9 codes 430, 431, 434, 436</td>
<td>Age, aspirin, beta-carotene, cigarette smoking, personal history of diabetes, hypertension and hypercholesterolemia, parental history of myocardial infarction before age 60, alcohol use, vigorous exercise, obesity, saturated fat, vitamin supplements (E, A, C, or multiple)</td>
</tr>
<tr>
<td>Orencia et al 1996 Chicago Western Electric Study USA</td>
<td>1847</td>
<td>40–55</td>
<td>100</td>
<td>30</td>
<td>Interview based on Burke’s diet method</td>
<td>≤20 g/day</td>
<td>Total stroke (n = 76) ICD-9 or ICD-10 codes 430–434, 436–438</td>
<td>Age, systolic blood pressure, cigarette smoking, serum cholesterol, diabetes, ECG abnormalities, table salt use, alcohol intake, iron, thiamine, riboflavin, niacin, vitamin C, beta-carotene, retinol, polysaturated fatty acids, carbohydrates, total protein, and total energy</td>
</tr>
<tr>
<td>Gillum et al 1996 NURSING USA</td>
<td>2351</td>
<td>45–74</td>
<td>0</td>
<td>12</td>
<td>Interview based on questionnaire</td>
<td>Never</td>
<td>Total stroke (n = 251) ICD-9 codes 433–434, 439, 436, or 437.0–437.1</td>
<td>Age, smoking, history of diabetes, history of heart disease, education less than high school graduate, systolic blood pressure, serum albumin concentration, serum cholesterol concentration, body mass index, alcohol intake, and physical activity</td>
</tr>
<tr>
<td>Gillum et al 1996 Male participant NHANES I USA</td>
<td>2059</td>
<td>45–74</td>
<td>100</td>
<td>12</td>
<td>Interview based on questionnaire</td>
<td>Never</td>
<td>Total stroke (n = 262) ICD-9 (codes 433–434, 439, 436 or 437.0–437.1)</td>
<td>Age, smoking, history of diabetes, history of heart disease, education less than high school graduate, systolic blood pressure, serum albumin concentration, serum cholesterol concentration, body mass index, alcohol intake, and physical activity</td>
</tr>
<tr>
<td>Yuan et al 2001 Shanghai, China</td>
<td>18 244</td>
<td>45–64</td>
<td>100</td>
<td>12</td>
<td>Interview based on questionnaire</td>
<td>≤50 g/week</td>
<td>Total stroke (n = 480) ICD-9 codes 430–438</td>
<td>Age, total energy intake, level of education, body mass index, current smoker, average No. of cigarettes smoked per day, no. of alcoholic drinks consumed per week, history of diabetes, and history of hypertension</td>
</tr>
<tr>
<td>Iso et al 2001 Nurses’ Health Study USA</td>
<td>79 839</td>
<td>34–59</td>
<td>0</td>
<td>14</td>
<td>Self-administered questionnaire</td>
<td>≤100 g/week</td>
<td>Total stroke (n = 574) ICD-9 codes 430–438</td>
<td>Age, body mass index, alcohol intake, menopausal status and postmenopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, history of hypertension, and frequency of total fruit and vegetable servings, and nutrient intake of saturated fat, transunsaturated fat, linoleic acid, animal protein, and calcium</td>
</tr>
<tr>
<td>He et al 2002 Health Professional Follow-Up Study USA</td>
<td>43 671</td>
<td>40–75</td>
<td>100</td>
<td>12</td>
<td>Self-administered questionnaire</td>
<td>≤200 g/week</td>
<td>Total stroke (n = 608) ICD-9 codes 430–438</td>
<td>Age, smoking status, body mass index, physical activity, history of hypertension, aspirin, multivitamins, total energy, total fat, saturated fat, transunsaturated fat, alcohol, potassium, magnesium, fruits and vegetables, hypercholesterolemia</td>
</tr>
<tr>
<td>Sauvaget et al 2003 Hiroshima/Nagasaki, Japan Life Span Study</td>
<td>30 827</td>
<td>34–103</td>
<td>38</td>
<td>16</td>
<td>Self-administered questionnaire</td>
<td>Never</td>
<td>Total stroke (n = 1025) ICD-9 codes 430–438</td>
<td>Age, sex, birth cohort, smoking, alcohol, body mass index, education, histories of diabetes or hypertension, radiation dose, and city</td>
</tr>
</tbody>
</table>

ICD indicates International Classification of Diseases; NHANES, National Health and Nutrition Examination Survey.

*Data were summed de novo for the meta-analysis.

The study also has limitations. One concern is that most studies did not separate ischemic from hemorrhagic stroke. Therefore, our capacity to examine fish intake in relation to stroke subtypes was limited. Because of the distinct pathogeneses of these 2 types of stroke, the underlying relationship between fish intake and stroke risk may be somewhat attenuated by combining ischemic and hemorrhagic stroke in the analysis. Alternatively, our pooled results of total stroke would mostly reflect the relationship between fish consumption and risk of ischemic stroke because most studies were conducted in western countries, where ischemic stroke is the major type of stroke. Of note, 1 of the included studies was conducted in China, where one third or more cases might be hemorrhagic
stroke. In addition, 1 study in a Japanese population found that high intake of fish was inversely associated with death caused by intracerebral hemorrhage but not with death caused by cerebral infarction.

Because our analyses are based on observational studies, certain limitations of such studies may have affected our findings. For example, the individual RR estimate included in the meta-analysis was adjusted for different covariates in the different studies. Thus, the possibility of residual confounding resulting from inclusion of different factors or bias attributable to measurement errors cannot be excluded. Alternatively, a meta-analysis on the basis of individual data providing a more powerful approach. In addition, differences in follow-up period, dietary assessment method, and measurement of the stroke end point, coupled with the fact that most studies enrolled only men, might lead to difficulties in estimating true effects of fish intake on stroke risk. However, our stratified analyses did not support the presence of substantial effect modification by gender or dietary assessment method. Moreover, misclassification of fish intake was still possible when we standardized fish consumption, although most studies provided data on portion size and the range of fish intake for each exposure category.

Fish intake may also be a surrogate for some other underlying healthy lifestyle factors that protect against stroke. For example, individuals with higher fish consumption generally tended to exercise more, smoke less, and were less likely to be overweight. Although most of the included studies were well designed and adjusted for major dietary and lifestyle variables, we could not exclude completely the possibility that the inverse association between fish intake and stroke is partly explained by undefined healthy lifestyle factors.

The possibility of publication bias is always a concern in a meta-analysis. Although we do not have enough statistical power to formally test for publication bias, there was no apparent tendency for the smaller cohorts to report much larger effect estimates compared with the larger studies. More importantly, the inverse associations between fish intake and risk of stroke appeared to be consistent across most studies. Thus, the likelihood that these findings are largely a result of selective publication seems to be minimal. However, a potential bias resulting from excluding studies published in other languages (if any) is possible.

Beneficial effects of fish intake on ischemic stroke are biologically plausible. Fish is the main dietary source of long-chain omega-3 PUFAs. Such marine-derived long-chain omega-3 PUFAs have been shown to have multiple favorable effects on blood pressure, arrhythmias, lipid profile, platelet

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koll (1994)</td>
<td>0.49 (0.24-1.01)</td>
</tr>
<tr>
<td>Omevik (1996)</td>
<td>0.80 (0.57-1.14)</td>
</tr>
<tr>
<td>Gillingham W (1998)</td>
<td>1.26 (0.74-2.16)</td>
</tr>
<tr>
<td>Gillingham M (1996)</td>
<td>0.85 (0.52-1.41)</td>
</tr>
<tr>
<td>Yuen (2001)</td>
<td>1.11 (0.63-1.93)</td>
</tr>
<tr>
<td>Io (2001)</td>
<td>0.75 (0.47-1.14)</td>
</tr>
<tr>
<td>He (2002)</td>
<td>0.67 (0.46-0.96)</td>
</tr>
<tr>
<td>Savastru (2003) *</td>
<td>0.78 (0.59-1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.82 (0.72-0.94)</td>
</tr>
</tbody>
</table>

RR of stroke incidence for fish intake 2 to 4 times per week vs <1 time per month in 9 cohorts from 8 prospective cohort studies. Adjusted covariates in each study are listed in Table 1. Squares indicate the adjusted RR in each study. The size of the square is proportional to the percent weight of each study in the meta-analysis; the horizontal lines represent 95% CI. Studies are ordered by the year of publication. The random-effects pooled RRs and 95% CIs are indicated by the open diamond. *Data were analyzed de novo for the meta-analysis.
aggregation, and endothelial function\textsuperscript{22–24} that may reduce the risk of ischemic stroke. Conversely, the antiplatelet effect and the observation of high incidence of hemorrhage in Eskimos, who consume large amounts of fish, have raised concerns about possible adverse effects of high fish intake on risk of hemorrhagic stroke. In the present meta-analysis, we did not observe any significant association between fish intake and hemorrhagic stroke. One possible explanation is that the risk of hemorrhage with high fish consumption is somehow balanced by other benefits of fish intake such as lowering blood pressure. Presumably, the overall effect of fish intake on hemorrhagic stroke may be minor.

Numerous experimental studies have indicated protective effects from the use of fish oil supplements on cardiovascular diseases. However, the dose of long-chain omega-3 PUFAs used in the experimental studies is much higher than the amount typically found in the diet. It is not clear how much intake of long-chain omega-3 PUFAs may be required to significantly reduce risk of stroke. In addition, whether fish consumption provides other beneficial nutrients not present in pure fish oil remains uncertain. Because a small amount of fish intake was associated with significantly lower risk of ischemic stroke,\textsuperscript{12} the possibility of interactions between long-chain omega-3 PUFAs and some unknown constituents in fish providing synergistic effects cannot be ruled out. Accordingly, one should be cautious when advising people to use fish oil supplements instead of eating whole fish. Moreover, considering the different amounts of long-chain omega-3 PUFAs in different types of fish, one would expect to observe more benefit by eating fatty fish rich in long-chain omega-3 PUFAs if any beneficial effect of fish intake on risk of stroke is largely attributable to its content of long-chain omega-3 PUFAs. However, data are very limited regarding the effect of intake of different types of fish on stroke risk. Finally, some potentially important issues, such as how fish is cooked might modify benefits of fish consumption and what is the optimal way to cook fish, remain unanswered and call for future research.

In summary, our meta-analysis of all relevant cohort studies indicated an inverse association between fish consumption and stroke, particularly ischemic stroke. The incidence of ischemic stroke might be significantly reduced by consuming fish as seldom as 1 to 3 times per month. Because of scarce data, the effect of fish intake on the risk of hemorrhagic stroke remains equivocal. Further studies are required to better understand the potentially different effects of fish consumption on risk of stroke subtypes by gender and in different ethnic groups.

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References
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