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,1 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 RR s and 95% CIs of total stroke and stroke subtypes in the corresponding categories. RR s 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 covariates.

In the stratified analyses, the inverse association between fish intake and risk of stroke appeared to increase with greater fish intake. The findings suggest that eating fish as seldom as 1 to 3 times per month may reduce risk of 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.
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.
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 with subsequent adjustment for identified covariates may provide 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 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 2: Pooled RR and 95% CI of Stroke According to Fish Consumption

<table>
<thead>
<tr>
<th>Subtype of stroke</th>
<th>No. of participants (events)</th>
<th>Less than once per month</th>
<th>1 to 3 times per month</th>
<th>Once per week</th>
<th>2 to 4 times per week</th>
<th>≥5 times per week</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>154 337 (1138)</td>
<td>1.0</td>
<td>0.69 (0.48–0.99)</td>
<td>0.68 (0.52–0.88)</td>
<td>0.66 (0.51–0.87)</td>
<td>0.80 (0.56–1.40)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>154 337 (548)</td>
<td>1.0</td>
<td>1.47 (0.81–2.69)</td>
<td>1.21 (0.78–1.85)</td>
<td>0.89 (0.56–1.40)</td>
<td>—</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Two studies (100%) and one study (62%) involved female participants.
†Three studies used self-administered FFQ.
‡Three studies with relevant data for both ischemic and hemorrhagic stroke.

Table 1: Efficacy of Fish Consumption on Stroke Incidence

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of participants (events)</th>
<th>Less than once per month</th>
<th>1 to 3 times per month</th>
<th>Once per week</th>
<th>2 to 4 times per week</th>
<th>≥5 times per week</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>87 558 (1641)</td>
<td>1.0</td>
<td>0.95 (0.78–1.15)</td>
<td>0.90 (0.78–1.04)</td>
<td>0.88 (0.75–1.06)</td>
<td>0.77 (0.52–1.14)</td>
<td>0.38</td>
</tr>
<tr>
<td>Women</td>
<td>113 017 (1850)</td>
<td>1.0</td>
<td>0.85 (0.66–1.10)</td>
<td>0.82 (0.67–1.00)</td>
<td>0.72 (0.58–0.90)</td>
<td>0.64 (0.46–0.88)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 2: Efficacy of Fish Consumption on Stroke Incidence

<table>
<thead>
<tr>
<th>Dietary assessment</th>
<th>No. of participants (events)</th>
<th>Less than once per month</th>
<th>1 to 3 times per month</th>
<th>Once per week</th>
<th>2 to 4 times per week</th>
<th>≥5 times per week</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-administered FFQ</td>
<td>175 522 (2380)</td>
<td>1.0</td>
<td>0.84 (0.64–1.10)</td>
<td>0.83 (0.70–0.98)</td>
<td>0.75 (0.62–0.90)</td>
<td>0.69 (0.54–0.88)</td>
<td>0.19</td>
</tr>
<tr>
<td>Interview</td>
<td>25 053 (1111)</td>
<td>1.0</td>
<td>0.95 (0.79–1.13)</td>
<td>0.91 (0.78–1.07)</td>
<td>0.84 (0.60–1.19)</td>
<td>—</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Table 3: Efficacy of Fish Consumption on Stroke Incidence

<table>
<thead>
<tr>
<th>Subtype of stroke</th>
<th>No. of participants (events)</th>
<th>Less than once per month</th>
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<td>0.31</td>
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aggregation, and endothelial function\(^2\)\(^3\)-\(^4\) 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
intake of long-chain omega-3 PUFAs may be required to
diseases. However, the dose of long-chain omega-3 PUFAs
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stroke. Conversely, the antiplatelet effect and stroke incidence. The NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey).

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