Fish Consumption and the Risk of Stroke
A Dose–Response Meta-Analysis
Susanna C. Larsson, PhD; Nicola Orsini, PhD

Background and Purpose—Fish consumption has been postulated to reduce the risk of stroke. We conducted a dose–response meta-analysis to summarize the evidence from prospective studies regarding the association between fish consumption and stroke risk.

Methods—Pertinent studies were identified by searching Embase and PubMed through May 2011 and by reviewing the references of retrieved articles. We included prospective studies that reported relative risks with 95% CIs of stroke for ≥3 categories of fish consumption. Results were combined using a random-effects model.

Results—Fifteen prospective studies, with 9360 stroke events among 383,838 participants, were included. An increment of 3 servings/week in fish consumption was associated with a 6% reduction in risk of total stroke (relative risk, 0.94; 95% CI, 0.89–0.99) without heterogeneity among studies (P = 0.15, I² = 25.7%). Among 9 studies with results for stroke subtypes, the relative risks were 0.90 (95% CI, 0.84–0.97) for ischemic stroke and 0.90 (95% CI, 0.76–1.06) for hemorrhagic stroke.

Conclusions—These findings indicate that fish consumption is weakly inversely associated with the risk of stroke.

Key Words: diet ■ fish ■ meta-analysis ■ prospective studies ■ stroke

It has been postulated that fish consumption may reduce the risk of stroke. Fish contains long-chain omega-3 polyunsaturated fatty acids, which have been demonstrated to have antiatherosclerotic and antithrombotic effects. We conducted a systematic review and a dose–response meta-analysis of prospective studies to assess the relation between fish consumption and the risk of total stroke and stroke subtypes.

Methods
We performed a literature search of the Embase and PubMed databases from January 1966 through May 2011 using the key words fish and stroke without restrictions. Furthermore, we reviewed the reference lists of retrieved articles. Prospective studies were included if they reported relative risks (RRs) with 95% CIs of stroke incidence or mortality for ≥3 quantitative categories of fish consumption.

We estimated for each study a RR with 95% CI for a 3-servings/week increase of fish consumption. For 1 study that reported results for fish intake in grams only,1 we derived servings by assuming that 1 serving equals 100 g. For each study, the median or mean fish intake for each category was assigned to each corresponding RR. To examine a potential nonlinear relationship between fish consumption and stroke, we first created restricted cubic splines (3 knots at fixed percentiles) and then for each study we assessed potential departure from a simpler linear trend by testing the coefficient of the second spline equal to zero. Study-specific results were combined using a random-effects model. All statistical analyses were conducted using Stata (StataCorp, College Station, TX). Probability values < 0.05 were considered to be statistically significant.

Results
Our literature search identified 15 independent prospective studies of fish consumption and stroke risk (Figure 1).1–15 Combined, these studies included 9360 stroke events and 383,838 participants (Supplemental Table I; http://stroke.ahajournals.org). Seven studies...
were conducted in the United States, 4 in Europe, 3 in Japan, and 1 in China. All studies provided risk estimates that were adjusted for age, smoking, and history of hypertension or measured blood pressure. Most studies also controlled for alcohol consumption (13 studies), body mass index or obesity (14 studies), history of diabetes (13 studies), physical activity (9 studies), and other dietary factors (8 studies).

There was evidence of a nonlinear association between fish consumption and stroke risk in only 1 study. The pooled RR of total stroke for a 3-servings/week increment in fish consumption was 0.94 (95% CI, 0.89–0.99) without heterogeneity among studies (P = 0.15, I² = 25.7%; Figure 2). In a sensitivity analysis in which 1 study at a time was removed and the rest analyzed, the pooled RRs ranged from 0.93 to 0.95, indicating that the pooled estimate was robust and not influenced by a single study. When the RR for each study for the highest versus lowest category of fish consumption was combined, the RR was 0.88 (95% CI, 0.81–0.96). There was no evidence of publication bias (Egger regression test, P = 0.87).

Nine studies provided results for stroke subtypes. Among these studies, the RRs for a 3-servings/week increase in fish consumption were 0.90 (95% CI, 0.84–0.97) for ischemic stroke (heterogeneity: P = 0.51, I² = 0%) and 0.90 (95% CI, 0.76–1.06) for hemorrhagic stroke (heterogeneity: P = 0.32, I² = 12.8%).

Discussion
This meta-analysis of 15 prospective studies found that fish consumption is weakly inversely associated with stroke risk. For each 3-servings/week increase of fish consumption, the risk of stroke decreased by 6%. Potential mechanisms by which long-chain omega-3 polyunsaturated fatty acids in fish may reduce the risk of stroke include reduced triglyceride concentrations, decreased blood pressure, and improved endothelial function.

The possibility of confounding as a potential explanation for the observed association cannot be excluded. Although the majority of studies adjusted for known risk factors for stroke, there remains the possibility for residual confounding. Another limitation is measurement error in the assessment of fish consumption. However, because of the prospective design, any misclassification of fish consumption is most likely random and leads to underestimation of the true relation between fish consumption and stroke. Because only 2 studies assessed lean and fatty fish consumption separately, we could not analyze lean and fatty fish separately.

In summary, results from this meta-analysis suggest that fish consumption may be weakly inversely associated with the risk of stroke.

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Disclosures
None.

References
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### Supplemental Table 1. Prospective studies of fish consumption and risk of stroke

<table>
<thead>
<tr>
<th>Source, cohort study, country</th>
<th>No. of participants and age (follow-up)</th>
<th>No. of cases</th>
<th>RR (95% CI) for highest vs. lowest category of fish intake</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al., 1995;¹ Physicians’ Health Study, USA</td>
<td>21,185 men, 40-84 y (4 y)</td>
<td>Total stroke (n = 173)</td>
<td>≥5 servings/wk vs. &lt;1 serving/wk: RR = 0.6 (0.3-1.6)</td>
<td>Age, smoking, aspirin, beta-carotene, history of diabetes, hypertension and hypercholesterolemia, family history of MI before age 60 y, obesity, vigorous exercise, intake of alcohol, saturated fat, and vitamin supplements (A, C, E, or multiple)</td>
</tr>
<tr>
<td>Gillum et al., 1996;² NHANES I, USA</td>
<td>4410 men and women, 45-74 y (12 y)</td>
<td>Total stroke (n = 513)</td>
<td>&gt;1/wk vs. never: RR = 0.85 (0.49-1.46) in men and RR = 0.55 (0.32-0.93) in women</td>
<td>Adjusted for age, smoking, history of BMI, physical activity, diabetes, history of heart disease, education, systolic blood pressure, serum albumin, serum cholesterol, and alcohol intake</td>
</tr>
<tr>
<td>Orencia et al., 1996;³ Chicago Western Electric Study, USA</td>
<td>1847 men, 40-55 y (30 y)</td>
<td>Total stroke (n = 222)</td>
<td>&gt;2 servings/wk vs. none: RR = 1.26 (0.74-2.16)</td>
<td>Adjusted for age, smoking, systolic blood pressure, serum cholesterol, diabetes, ECG abnormalities, table salt use, and intakes of alcohol, total energy, carbohydrates, total protein, polyunsaturated fatty acids, iron, thiamine, riboflavin, niacin, vitamin C, beta-carotene, and retinol</td>
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<tr>
<td>Yuan et al., 2001;⁴ Shanghai, China</td>
<td>18,244 men, 45-64 y (12 y)</td>
<td>Total stroke death (n = 480)</td>
<td>≥4 servings/wk vs. &lt;1 serving/wk: RR = 1.05 (0.77-1.43) for fish</td>
<td>Age, education, smoking, BMI, history of diabetes and hypertension, intakes of alcohol and total energy</td>
</tr>
<tr>
<td>Iso et al., 2001;⁵ Nurses' Health Study, USA</td>
<td>79,839 women, 34-59 y (14 y)</td>
<td>Total stroke (n = 574); ischemic stroke (n = 303); hemorrhagic stroke (n = 181)</td>
<td>≥5 servings/wk vs. &lt;1 serving/month: RR = 0.48 (0.21-1.06)</td>
<td>Age, smoking, menopausal status, history of hypertension, postmenopausal hormone use, BMI, vigorous exercise, aspirin use, multivitamin use, intakes of alcohol, total</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Outcome Measures</td>
<td>RR (95% CI)</td>
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<tr>
<td>He et al., 2002; Health Professional Follow-Up Study, USA</td>
<td>43,671 men, 40-75 y (12 y)</td>
<td>Total stroke (n = 608); ischemic stroke (n = 377); hemorrhagic stroke (n = 106)</td>
<td>≥5 servings/wk vs. &lt;1 serving/month: RR = 0.83 (0.53-1.29)</td>
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<tr>
<td>Sauvag et al., 2003; Hiroshima/Nagasaki Life Span Study, Japan</td>
<td>37,130 men and women, 34-103 y (16 y)</td>
<td>Total stroke (n = 1462); ischemic stroke (n = 655); hemorrhagic stroke (n = 354)</td>
<td>Almost daily vs. never: RR = 0.71 (0.48-1.05) for fish (except broiled) and RR = 0.60 (0.37-0.98) for broiled fish*</td>
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<tr>
<td>Folsom et al., 2004; Iowa Women's Health Study, USA</td>
<td>41,836 women, 55-69 y (14 y)</td>
<td>Total stroke death (n = 313)</td>
<td>≥2.5 servings/wk vs. &lt;0.5 serving/wk: RR = 1.06 (0.67-1.67)</td>
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<td>Mozaffarian et al., 2005; Cardiovascular Health Study, USA</td>
<td>4778 men and women, 65-98 y (12 y)</td>
<td>Total stroke (n = 626); ischemic stroke (n = 537); hemorrhagic stroke (n = 73)</td>
<td>≥5 times/wk vs. &lt;1 time/month: RR = 0.77 (0.56-1.07) for tuna/other fish and RR = 1.33 (1.05-1.68) for fried fish/fish sandwich†</td>
<td></td>
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<tr>
<td>Nakamura et al., 2005; NIPPON, Japan</td>
<td>8879 men and women, ≥30 y (19 y)</td>
<td>Total stroke death (n = 288)</td>
<td>≥14/wk vs. 1-2/wk: RR = 0.79 (0.44-1.43)</td>
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<tr>
<td>Myint et al., 2006; EPIC-Norfolk, UK</td>
<td>24,312 men and women, 40-79 y (8.5 y)</td>
<td>Total stroke (n = 421)</td>
<td>&gt;2 portions/wk vs. &lt;1 portion/ wk: RR = 1.34 (0.93-2.93) in men and RR = 0.86 (0.60–1.24) in women</td>
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</tbody>
</table>

Age, smoking, BMI, physical activity, history of hypertension, hypercholesterolemia, use of aspirin, fish oil, and multivitamins, intake of alcohol, total energy, total fat, saturated fat, trans-unsaturated fat, linoleic acid, animal protein, and calcium

Age, smoking, BMI, physical activity, history of hypertension, hypercholesterolemia, use of aspirin, fish oil, and multivitamins, intake of alcohol, total energy, total fat, saturated fat, trans-unsaturated fat, potassium, magnesium, total fruits and vegetables

Stratified by sex and birth cohort, and adjusted for city, radiation dose, education, smoking, BMI, history of diabetes or hypertension, alcohol habits

Age, education, smoking, age at first live birth, estrogen use, vitamin use, BMI, waist/hip ratio, diabetes, hypertension, intakes of alcohol, total energy, whole grains, fruit and vegetables, red meat, cholesterol, and saturated fat

Age, sex, education, smoking, diabetes, prevalent coronary heart disease, aspirin use, BMI, leisure-time physical activity, systolic blood pressure, LDL and HDL cholesterol, triglyceride, C-reactive protein, alcohol use, and total energy

Age, sex, smoking, hypertension, BMI, diabetes, alcohol, and total cholesterol

Age, smoking, systolic blood pressure, BMI, physical activity, cholesterol, diabetes, fish oil supplement use, intakes of alcohol and total energy
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
<th>Risk Factor Adjusted</th>
<th>Additional Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wennberg et al., 2007;12 NA, Sweden‡</td>
<td>1107 men and women, NA (15.5 y)</td>
<td>Total stroke (n = 369)</td>
<td>1 serving/week increase: RR = 1.24 (1.01-1.51) in men and RR = 0.90 (0.73-1.12) in women</td>
<td>Age, residential area, diabetes, hypertension, BMI and smoking</td>
</tr>
<tr>
<td>Yamagishi et al., 2008;13 JACC Study, Japan</td>
<td>57,972 men and women, 40-79 y (12.7 y)</td>
<td>Total stroke death (n = 972); ischemic stroke (n = 319); intraparenchymal hemorrhage (n = 223); subarachnoid hemorrhage (n = 153)</td>
<td>Almost every day vs. rarely: RR = 0.91 (0.74-1.13)</td>
<td>Age, sex, education, smoking, history of hypertension and diabetes, BMI, walking, sports, mental stress, intakes of alcohol, total energy, saturated and omega-6 polyunsaturated fatty acids, cholesterol, vegetables, and fruits</td>
</tr>
<tr>
<td>Montonen et al., 2009;14 Finnish Mobile Clinic Health Examination Survey, Finland</td>
<td>3958 men and women, 40-79 y (28 y)</td>
<td>Total stroke (n = 659); thrombosis or embolia (n = 364); intracerebral hemorrhage (n = 80)</td>
<td>504 g/wk vs. 42 g/wk: RR = 1.01 (0.81-1.27)</td>
<td>Age, sex, geographic area, smoking, occupation, BMI, physical activity, diabetes, use of post-menopausal hormones, hypertension, serum cholesterol, and intakes of total energy, butter, vegetables, fruits, and berries</td>
</tr>
<tr>
<td>Larsson et al., 2011;15 Swedish Mammography Cohort, Sweden</td>
<td>34,670 women, 49-83 y (10.4 y)</td>
<td>Total stroke (n = 1680); ischemic stroke (n = 1310); hemorrhagic stroke (n = 233)</td>
<td>&gt;3 servings/wk vs. &lt;1 serving/wk: RR = 0.84 (0.71-0.98)</td>
<td>Age, education, smoking, BMI, total physical activity, history of diabetes, history of hypertension, aspirin use, family history of MI before 60 y, intakes of alcohol, total energy, processed meat, unprocessed red meat, fruit, and vegetables</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer; HDL, high-density lipoprotein; JACC, Japan Collaborative Cohort Study for Evaluation of Cancer Risk; LDL, low-density lipoprotein; MI, myocardial infarction; NA, not available; NHANES, National Health and Nutrition Examination Survey.
*Results for fish (except broiled) were used in the analysis.
†Results for tuna/other fish were used in the analysis.
‡Prospective nested case–control study.
References