Fish Consumption and Risk of Stroke
The Zutphen Study

Sirving O. Keli, MD; Edith J.M. Feskens, PhD; Daan Kromhout, PhD, MPH

Background and Purpose
A low-to-moderate average daily fish consumption has been reported to convey protection against coronary heart disease incidence and mortality. Currently there is no information about its effect on stroke risk.

Methods
In 1960, 1965, and 1970 cross-check dietary histories were obtained in 552 men aged 50 to 69 years in 1970 in the town of Zutphen, The Netherlands. The association between fish consumption and stroke incidence in the period 1970 to 1985 was assessed by Cox proportional hazards models. Adjustments were made for confounding by age, systolic blood pressure, cigarette smoking, serum total cholesterol, energy intake, alcohol consumption, and prescribed diet.

Results
The mean fish consumption in 1970 was 17.9 g/d. Men who consumed more than 20 g of fish per day in 1970 had a reduced risk of stroke compared with those who consumed less fish. The hazard ratio (HR) amounted to 0.49 (95% confidence interval [CI], 0.24 to 0.99), and did not change after adjustment for potential confounders. Fewer strokes occurred among the 301 men who always reported fish consumption between 1960 and 1970 than among the men who changed fish consumption habits between 1960 and 1970 or did not consume fish at all (HR, 0.63; 95% CI, 0.34 to 1.16).

Conclusions
These results suggest that consumption of at least one portion of fish per week may be associated with a reduced stroke incidence. (Stroke. 1994;25:328-332.)

Key Words: cerebrovascular disorders • Netherlands • risk factors • diet

Stroke incidence on a hemorrhagic basis is higher among Greenland Eskimos compared with Danes.1 A prolonged bleeding time due to a high intake of n-3 polyunsaturated fatty acids could be an explanation for this phenomenon.1,2 The effect of a small amount of these fatty acids, as may be derived from low to moderate daily fish consumption is, however, not known.

Compared with a group of subjects using no fish, the average daily intake of a small amount of fish was shown to be protective for coronary heart disease mortality in a number of prospective studies, including the Zutphen Study.3-5 It can therefore be hypothesized that a low to moderate average daily fish intake is also protective for thrombotic stroke. This hypothesis was tested in the Zutphen Study, a long-term follow-up study in which dietary data have been collected repeatedly.

Subjects and Methods
Study Population
Since 1960, a longitudinal investigation of risk factors for chronic diseases has been carried out among middle-aged men from the town of Zutphen in The Netherlands. The Zutphen Study is the Dutch contribution to the Seven Countries Study.6-9

Between 1960 and 1970, food intake data were collected by the cross-check dietary history method,9 and adapted to the Dutch situation.10 This method provides information about the usual pattern of food consumption in the 6 to 12 months before the interview. Each participant was interviewed together with his wife about his usual food consumption patterns on weekdays and weekends. The usual food consumption away from home was also recorded. The estimated average consumption of foods during a day or a week was checked against the quantity of food bought per week for the whole family. The food consumption during a typical weekday was calculated on the basis of this information. The interviews were carried out in the months May, June, and July of each year and were taken by trained dietitians, six in 1960, six in 1965, and nine in 1970. The dietitians also recorded any special diet of the participant prescribed by his general practitioner or specialist. An extended computerized version of the Netherlands food table database, containing the amounts of energy and nutrients in Dutch foods between 1960 and 1970, was used to convert the food intake data into nutrient and energy data.12

Medical Examinations
Blood pressure was measured with an ordinary mercury sphygmomanometer at the end of the physical examination at the right arm with the subject in the supine position, according to the protocol of the Seven Countries Study.7 Between 1960 and 1970 blood pressure was measured annually. For each subject, the average systolic blood pressure was calculated as
the sum of the annual systolic blood pressure readings in the period 1960 to 1970 divided by the number of measurements, provided that a total of at least four readings were taken during this period. At least one of these readings had to have been taken in the last 5 years before or in 1970.

Serum cholesterol determinations were carried out according to the method of Abell-Kendall\(^ {19} \) in the period 1960 to 1965 and the method of Zlatkis\(^ {16} \) between 1966 and 1970. The latter provides values equivalent to the Abell-Kendall method. The average serum cholesterol level over the period 1960 to 1970 was calculated in the same way as the average systolic blood pressure. Information on cigarette smoking was collected in a standardized way.\(^ {7} \) Exposure to smoke was quantified by multiplying the amount of cigarettes smoked by the duration of cigarette smoking.

During follow-up, the men were medically examined annually between 1960 and 1973, in 1977/1978, and in 1985. Questionnaires about their health status were filled in by the men in 1980 and 1982. No one was lost to follow-up. All morbidity and mortality data collected in the period 1960 to 1985 were coded by one physician in a standardized way in 1986. Stroke was defined as a sudden onset of neurological paralysis of more than 24-hour duration or leading to death. All diagnoses of stroke were confirmed in a letter from a neurologist of the hospital of Zutphen to the general practitioner. Fatal strokes were coded according to the eighth revision of the International Classification of Diseases (ICD-8 codes 430-438). Data on the incidence of stroke, being either the first nonfatal or fatal event within the study period, are presented here.

Statistical Analyses

Statistical analyses were carried out with the SAS statistical package version 6 on a DEC 5000 minicomputer.\(^ {13} \) The fish consumers were initially divided into three categories of fish intake: no fish, low fish (20 g of fish per day or less), and high fish consumption (more than 20 g of fish per day). The “no fish” and the “low fish” categories did not differ from each other in stroke survival analysis. In the final analyses these two groups were taken together. The 301 subjects who reported consuming fish at each survey were considered as subjects who always ate fish during 1960 to 1970. The 39 subjects who did not consume fish during 1960 to 1970 were grouped together with the subjects who changed their fish consumption habits to make a total of 251 subjects.

Student’s \( t \) test was used to compare levels of risk factors and nutrient intake by incidence of stroke and by fish consumption. In case of skewed variables, the Wilcoxon rank statistic was used. The relation between fish consumption and the risk of stroke was assessed by survival analysis, using the Kaplan-Meier product limit estimator and the Cox proportional hazards model.\(^ {16, 17} \) Additional adjustments for potential confounding effects of age, systolic blood pressure, serum cholesterol, cigarette smoking, intake of energy and vegetable protein, alcohol consumption, and prescribed diet were carried out. Because the average systolic blood pressure had previously been shown to be the strongest predictor of stroke,\(^ {18} \) this variable was used as covariate instead of the single observed systolic blood pressure in 1970. The same was done with the average of serum total cholesterol over the period 1960 to 1970 and lifelong smoking habits. All \( P \) values were derived from two-tailed tests of significance.

Results

During the 15-year follow-up period, 42 first strokes occurred among the 552 men, resulting in an incidence rate of 6.65/1000 person-years. The age in 1970 and the average systolic blood pressure between 1960 and 1970 were significantly higher for the men who developed stroke compared with the men who remained free of stroke (Table 1). Fish consumption in 1970 was significantly lower among the future stroke cases (Table 2). No other significant differences in macronutrient intake or in percentage on prescribed diet between incident cases of stroke and men without stroke were observed.

Comparing the 393 men who consumed fish in 1970 with non-fish-eaters, no differences in risk factors were observed (Table 3). Concerning dietary factors, fish consumption was significantly associated with the intake of energy, animal protein, polyunsaturated fatty acids, and linoleic acid. Significant inverse associations with the intake of vegetable protein and dietary cholesterol were observed. These nutrients were not associated with the incidence of stroke.

The 220 men who consumed more than 20 g of fish per day in 1970 had a significantly lower risk of stroke compared with those who ate less fish (hazard ratio: 0.49; 95% confidence interval: 0.24 to 0.99; \( P=.048 \), Table 4). Fig 1 shows the survival curves for these men.

### Table 1. Risk Factors in 552 Men Aged 50 to 69 Years in 1970 in Relation to 15-Year Incidence of Stroke: the Zutphen Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No Stroke (n=510)</th>
<th>Stroke (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.3±5.3</td>
<td>61.9±5.5*</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>142.2±14.1</td>
<td>148.9±20.11</td>
</tr>
<tr>
<td>Total cholesterol 1960-1970, mmol/L</td>
<td>6.1±0.9</td>
<td>6.1±1.0</td>
</tr>
<tr>
<td>Cigarettes per day × years to 1970</td>
<td>438±327</td>
<td>433±293</td>
</tr>
</tbody>
</table>

\*\( P<.01; \uparrow P<.05. \)

### Table 2. Fish Consumption and Other Dietary Variables in 552 Men Aged 50 to 69 Years in 1970 in Relation to 15-Year Incidence of Stroke: the Zutphen Study

<table>
<thead>
<tr>
<th>Daily Dietary Intake</th>
<th>No Stroke (n=510)</th>
<th>Stroke (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish consumption, g</td>
<td>18.3±19.8</td>
<td>12.8±12.3*</td>
</tr>
<tr>
<td>Energy intake, MJ</td>
<td>11.0±2.2</td>
<td>10.4±2.2</td>
</tr>
<tr>
<td>Total protein, % of energy</td>
<td>12.4±1.9</td>
<td>12.3±1.5</td>
</tr>
<tr>
<td>Animal protein</td>
<td>8.3±1.9</td>
<td>8.4±1.8</td>
</tr>
<tr>
<td>Vegetable protein</td>
<td>4.1±0.8</td>
<td>4.0±0.9</td>
</tr>
<tr>
<td>Total fat, % of energy</td>
<td>41.5±5.3</td>
<td>42.8±6.1</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>16.9±2.9</td>
<td>17.3±3.4</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>17.6±2.8</td>
<td>18.4±3.2</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>6.8±2.2</td>
<td>7.0±2.0</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>5.9±2.1</td>
<td>5.8±1.9</td>
</tr>
<tr>
<td>Total carbohydrates, % of energy</td>
<td>42.8±6.0</td>
<td>42.0±6.0</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>21.1±5.7</td>
<td>20.8±6.1</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>21.7±4.4</td>
<td>21.2±5.1</td>
</tr>
<tr>
<td>Alcohol consumption, % of energy</td>
<td>2.7±4.0</td>
<td>2.3±3.3</td>
</tr>
<tr>
<td>Dietary cholesterol, mg/MJ</td>
<td>38.6±15.3</td>
<td>36.2±13.2</td>
</tr>
<tr>
<td>Prescribed diet, %</td>
<td>11.0</td>
<td>7.1</td>
</tr>
</tbody>
</table>

\*\( P<.05. \)
After adjustment for confounding by age, average systolic blood pressure, average serum cholesterol, cigarette smoking, energy intake, alcohol consumption, and prescribed diet, the hazard ratio did not substantially change, although the result just failed to reach statistical significance (P = .052). Additional analysis showed that the results were also unaffected by body mass index and history of myocardial infarction and diabetes mellitus.

Spearman correlation coefficients between fish consumption in 1960, 1965, and 1970 decreased with increasing time between dietary surveys, varying from 0.41 (P < .001) for 1960 and 1965 to 0.32 (P < .001) for 1960 and 1970. As the survival curves in Fig 2 illustrate, the 301 men who always ate fish between 1960 and 1970 had a reduced risk of stroke compared with the 251 men who either changed their fish-eating habits or never ate fish between 1960 and 1970. The hazard ratio was 0.63, and increased to 0.71 after adjustment for potential confounders (Table 4).

### Discussion

In the present study, men who consumed more than 20 g of fish per day had a lower risk of stroke than men who ate less fish. This association remained essentially unchanged after adjustment for potential confounders. In addition to the data on fish consumption in 1970, information on fish consumption in 1965 and 1960 was also available. Subjects who always ate fish between 1960 and 1970 had a lower risk of stroke than subjects who either changed their fish consumption patterns or used no fish during this period, but this difference was not statistically significant using a two-sided test. Beforehand, it was hypothesized that the average fish consumption was a better predictor of stroke risk than the single-year fish consumption, due to reduction of random measurement error. This would have been comparable to what we had observed for the association between blood pressure and stroke. However, the association between fish consumption in 1970 and 15-year stroke risk was stronger. This suggests a larger effect of the more recent (1970) fish consumption than of the longer habitual (1960 to 1970) fish consumption on the incidence of stroke, which may be plausible in the light of the etiology of the disease.

To our knowledge, this is the first time that an inverse relation between fish consumption and stroke incidence has been reported. These results are, however, in accordance with those from other prospective studies reporting an inverse association between fish consumption and coronary heart disease, including our own cohort. In those studies, an inverse dose-response relationship was found between consumption of small amounts of fish and long-term mortality from coronary heart disease. In Eskimos, however, who consume large amounts of seafood, a higher incidence of hemorrhagic strokes was reported compared with Danes. It may therefore be hypothesized that small amounts of fish intake may...
reduce the incidence of coronary heart disease and the ischemic subtypes of stroke, whereas consumption of large amounts of seafood may increase hemorrhagic subtypes of stroke. Unfortunately, no information on the type of stroke is available for the Zutphen men. However, an extensive study showed that 82% of the strokes in the Netherlands are thrombotic, and it is very likely that this was also the case in the Zutphen Study.

Experimental studies in vitro and in humans showed that n-3 polyunsaturated fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid which are especially present in fish, reduce the formation of thromboxane A, This leads to a reduced aggregability of blood platelets. In addition, eicosapentaenoic acid can be transformed to thromboxane A, which does not have aggregating abilities and competes with thromboxane A in vessel walls. Besides, it also increases the synthesis of the antithrombotic agent prostaglandin E, Thromboxane A is a mediator of thrombosis and vasospasm occurring in stroke and myocardial infarction. Reduction of the thromboxane A production by small amounts of aspirin has been shown to lower the risk of stroke and myocardial infarction. Therefore, a protective effect of fish consumption on thrombotic stroke and coronary heart disease through this mechanism is conceivable. An effect of fish intake on thrombotic processes is supported by the results from a secondary intervention study among myocardial infarction patients.

Other mechanisms also may play a role. Even small amounts of fish intake increase the concentration of n-3 polyunsaturated fatty acids in phospholipids. This may lead to altered fluidity and activity of membrane-associated enzymes and receptors, resulting in protection of the vessel wall against ischemic damage. n-3 Polyunsaturated fatty acids have been shown to reduce the plasma lipids, especially triglycerides and very-low-density lipoproteins. It is, however, not very likely that this mechanism is of importance in stroke, since in general the association between serum triglycerides and stroke risk is not very strong. It has also been suggested that fish (oils) may lower blood pressure. As also shown in the present study, blood pressure is one of the most important risks for stroke. However, in intervention studies large amounts of fish oils are needed to achieve lowering of blood pressure. In the present study fish consumption was not associated with blood pressure. Thus, it is unlikely that blood pressure may play a role in explaining the protective effect of a small amount of fish on stroke incidence. Finally, it can be hypothesized that the effect may be partly caused by effects of fish intake on insulin resistance and glucose tolerance, which are also independent risk factors for stroke. The present results were, however, not affected by adjustments for presence of diabetes mellitus, and the possible intermediate pathway by carbohydrate metabolism remains to be studied.

The results of the present study suggest that an inverse relation exists between fish consumption and incidence of stroke. The possible protective effect of low to moderate fish consumption in both stroke and coronary heart disease is intriguing. More research is needed on mechanisms explaining this inverse relation. With respect to prevention of cardiovascular disease, evidence is accumulating that the consumption of at least one portion of fish per week may have a protective effect.

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