Serum Long-Chain n-3 Polyunsaturated Fatty Acids and Risk of Hospital Diagnosis of Atrial Fibrillation in Men

Jyrki K. Virtanen, PhD, RD; Jaakko Mursu, PhD, RD; Sari Voutilainen, PhD, RD; Tomi-Pekka Tuomainen, MD, PhD

Background—Atrial fibrillation (AF) is a common cardiac arrhythmia. Regular fish consumption has been shown to reduce the risk of AF in some but not all studies. Long-chain n-3 polyunsaturated fatty acids (PUFAs) from fish have been suggested to account for these beneficial effects. We tested this hypothesis by studying the association between the serum long-chain n-3 PUFAs eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid and risk of AF in men.

Methods and Results—A total of 2174 men from the prospective population-based Kuopio Ischemic Heart Disease Risk Factor Study, 42 to 60 years old and free of AF at baseline in 1984 to 1989, were studied. During the average follow-up time of 17.7 years, 240 AF events occurred. In the Cox proportional hazards model, the multivariable-adjusted hazard ratio in the highest (>5.33%) versus the lowest (<3.61%) quartile of eicosapentaenoic acid plus docosapentaenoic acid plus docosahexaenoic acid was 0.65 (95% confidence interval 0.44 to 0.96, P for trend=0.07). Evaluated individually, only serum docosahexaenoic acid was associated with the risk of AF (hazard ratio in the highest versus the lowest quartile 0.62, 95% confidence interval 0.42 to 0.92, P for trend=0.02). Exclusion of subjects (n=233) with myocardial infarction or congestive heart failure either at baseline or that preceded the AF event during follow-up slightly strengthened the associations. Serum intermediate chain-length n-3 PUFA, α-linolenic acid, or hair methylmercury concentration were not associated with the risk.

Conclusions—An increased concentration of long-chain n-3 PUFAs in serum, a marker of fish or fish oil consumption, may protect against AF. Serum docosahexaenoic acid concentration had the greatest impact.

Key Words: arrhythmia • fatty acids • fibrillation • risk factors

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, especially in the elderly, increases morbidity and mortality.1,2 It is associated with fatigue, reduced tolerance for exercise, and increased risk of thromboembolic stroke.3,4

Clinical Perspective on p 2321

The evidence from prospective studies and randomized trials suggests that consumption of fish or fish oil is associated with a reduced risk of cardiovascular diseases (CVDs), especially sudden death, which is usually caused by ventricular arrhythmia.5 However, previous studies have been inconsistent with regard to the impact of fish or fish oils on cardiac arrhythmias.5 In a prospective cohort study,6 consumption of baked or broiled fish was associated with a lower incidence of AF, and in a randomized trial, fish oil supplementation prevented occurrence of AF after coronary artery bypass grafting.7 However, conflicting results were observed in 3 other prospective studies.8–10

The long-chain n-3 polyunsaturated fatty acids (PUFAs) found in fish and fish oil, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), have been suggested to have a major role in the protective effects of fish consumption against CVD.4 We tested the hypothesis that high serum concentrations of EPA, DHA, and docosapentaenoic acid (DPA [22:5n-3]), which also serve as a marker of fish or fish oil consumption are associated with risk of incident AF in middle-aged or older men. We also tested whether serum concentration of an intermediate-chain-length n-3 PUFA, α-linolenic acid (ALA, 18:3n-3), is associated with the risk of AF, especially when serum EPA+DPA+DHA concentration is low. Finally, we assessed the possible modifying effect of high methylmercury concentration in the hair on the association between serum long-chain n-3 PUFAs and risk of AF. Fish is the main source of methylmercury, and we have previously shown that a high methylmercury concentration in hair attenuated the association between serum long-chain n-3 PUFAs and risk of CVD in this study population.11

Study Population

The subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study.12 The study was designed to investigate risk factors...
for CVD, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from eastern Finland. The baseline examinations were performed between March 1984 and December 1989. The study sample was composed of 3235 men who were 42, 48, 54, or 60 years old at the baseline examination. Of these, 2682 (82.9%) participated. The baseline characteristics of the entire study population have been described previously. The Kuopio Ischemic Heart Disease Risk Factor Study protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave their written informed consent for participation.

Subjects with a history of AF at baseline (n=32) were excluded from the analyses. We also excluded men with missing data on serum PUFAs (n=200) or hair methymercury concentration (n=276), which left 2174 men. Because AF is often preceded by a myocardial infarction or congestive heart failure, in additional analyses, we also excluded men with these events at baseline (n=201) or preceding the AF event during follow-up (n=32), which left 1941 men for the additional analyses. The men who were included were younger and healthier, including having a lower prevalence of CVD, diabetes mellitus, hypertension, and current smoking, and they had a higher education and income than those who were excluded.

Measurements

The subjects came to give hair and venous blood samples between 8 and 10 AM at the baseline examinations. They were instructed to abstain from ingesting alcohol for 3 days and from smoking and eating for 12 hours before giving the sample. Detailed descriptions of the determination of serum lipids and lipoproteins, serum selenium, assessment of medical history and medications, family history of diseases, smoking, alcohol consumption, and blood pressure have been published previously. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters. Dietary intake of foods and nutrients was assessed at the time of blood sampling by use of 4-day food recording. Mercury in hair was determined by flow injection analysis—cold vapor atomic absorption spectrometry and amalgamation, as described previously.

Serum Fatty Acids

Serum esterified and nonesterified fatty acids were determined in 1 gas chromatographic run without preseparation as described previously. Fatty acids were chromatographed in an NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett-Packard 5890 series II gas chromatograph (Hewlett-Packard Company, Avondale, Pa) with a flame ionization detector. The coefficient of variation for repeated measurements of major esterified fatty acids was ~5%. Because the relative degree of saturation of fatty acids varies among esterified fatty acid types (ie, cholesterol esters, phospholipids, and triglycerides), the esterified fatty acid concentrations were adjusted for serum low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations. The coefficient of variation for major nonesterified fatty acids was ~15%. No adjustment was conducted for nonesterified fatty acids.

Ascertainment of Follow-Up Events

All AF events that occurred between study entry and December 31, 2007, were included. There was very little loss to follow-up (n=3). Data on events were obtained by record linkage from the national computerized hospitalization registry, which covers every hospitalization in Finland. Data on vital status were obtained from Statistics Finland. Cardiovascular causes of AF were coded according to International Classification of Diseases codes (8th revision code 427.4, 9th revision code 427.3, and 10th revision code I48). Subjects were hospitalized because of AF or had AF when they were hospitalized for other reasons. To verify the accuracy of the register-linked diagnoses, a random 100 records (42%) were checked manually by a physician (T.-P.T.) against the original patient records at Kuopio University Hospital. Among these 100, all but 4 could be confirmed as either AF (91 cases) or atrial flutter (5 cases). For 2 subjects, the register diagnosis of AF appeared potentially untrue, because for these subjects, despite cardiovascular examinations at the University Hospital, no evidence of AF was found. For the other 2 subjects, the only hospitalizations recorded were for other than cardiac causes, which does not exclude a true AF diagnosis at a local health center or at another hospital. Thus, a good estimate of the accuracy of AF diagnoses acquired by record linkage in the present study is 96% to 98%.

Statistical Analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs). Absolute risk reduction was calculated by multiplying the absolute risk in the reference group by the multivariable-adjusted HR reduction in the comparison group. The models were adjusted for possible confounders, selected on the basis of previously published associations with AF or associations with exposures or outcomes in the present analysis. The multivariable-adjusted models included age; examination year; history of ischemic heart disease, congestive heart failure, or stroke; diabetes mellitus; body mass index; smoking (never, former, or current); pack-years of smoking; leisure-time physical activity; serum high-density lipoprotein and low-density lipoprotein cholesterol and triglycerides; systolic and diastolic blood pressures; treated hypertension; and hair methymercury concentration. Further adjustments for income; years of education; place of residence; serum selenium; serum C-reactive protein; plasma fibrinogen and blood glucose; forced expiratory volume in 1 second; cardiomyopathy; valvular disease; pulmonary disease; family history of heart disease; use of aspirin, β-blockers, or medication for hyperlipidemia or thyroid therapy; serum ALA, linoleic acid, or arachidonic acid; and intakes of alcohol, energy, saturated fatty acids, protein, carbohydrates, fiber, milk and milk products, meat and meat products, fruits and berries, vegetables, and cereal grains did not change the associations (HR change <5%). The cohort mean was used to replace missing values (<-2.5%) of covariates. Because of the relatively modest number of cases, tertiles instead of quartiles were used in the stratified analyses. Statistical significance of the interactions on a multiplicative scale was assessed by likelihood ratio tests with a cross-product term. Tests of linear trend were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. Correlations were estimated by the Pearson correlation coefficients. All P values were 2-tailed (α=0.05). Data were analyzed with SPSS 14.0 for Windows (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

At baseline, the mean age of the cohort was 52.8 years (SD 5.3 years). Mean serum concentrations for EPA, DPA, and DHA, respectively, were 1.67% (SD 0.92%), 0.55% (SD 0.10%), and 2.46% (SD 0.74%) of all serum fatty acids. The correlation coefficient between fish intake and serum EPA+DPA+DHA was 0.47 (P<0.001). At baseline, compared with men with lower serum EPA+DPA+DHA, men with higher concentrations were more likely to have higher education and income and higher hair methymercury and serum total, high-density lipoprotein, and low-density lipoprotein cholesterol concentrations but lower serum triglyceride, linoleic acid, and ALA concentrations (Table 1). They were also less likely to be hypertensive or to use β-blockers, and they had lower energy intake but higher intake of alcohol.

Serum Long-Chain n-3 PUFAs and Risk of AF

During an average follow-up of 17.7 years (SD 5.6 years; 38 390 person-years), 240 men (11.0%) experienced an AF event. After adjustment for age and examination year (model 1; Table 2), men in the highest serum EPA+DPA+DHA concentrations were at significantly lower risk of AF compared with men in the lowest serum EPA+DPA+DHA concentrations (HR 0.47, 95% CI 0.29 to 0.75). Men in the highest serum EPA+DPA+DHA concentrations had a lower risk of AF compared with men in the lowest serum EPA+DPA+DHA concentrations after adjusting for possible confounders (HR 0.47, 95% CI 0.29 to 0.75). Men in the highest serum EPA+DPA+DHA concentrations had a lower risk of AF compared with men in the lowest serum EPA+DPA+DHA concentrations after adjusting for possible confounders (HR 0.47, 95% CI 0.29 to 0.75).
Table 1. Baseline Characteristics According to Serum EPA+DPA+DHA

<table>
<thead>
<tr>
<th>serum EPA+DPA+DHA Quartile (%)</th>
<th>1 (1.70–3.61)</th>
<th>2 (3.62–4.35)</th>
<th>3 (4.36–5.33)</th>
<th>4 (5.34–15.59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>543</td>
<td>544</td>
<td>544</td>
<td>543</td>
</tr>
<tr>
<td>Age, y</td>
<td>52.7 (5.5)</td>
<td>52.6 (5.3)</td>
<td>53.0 (5.3)</td>
<td>52.9 (5.2)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>33</td>
<td>30</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (3.6)</td>
<td>26.6 (3.3)</td>
<td>26.9 (3.5)</td>
<td>27.1 (3.5)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>135 (17)</td>
<td>134 (16)</td>
<td>134 (16)</td>
<td>134 (18)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>89 (11)</td>
<td>89 (10)</td>
<td>89 (10)</td>
<td>89 (11)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.21 (0.27)</td>
<td>1.29 (0.28)</td>
<td>1.32 (0.29)</td>
<td>1.36 (0.32)*</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.82 (0.95)</td>
<td>3.99 (1.01)</td>
<td>4.14 (1.01)</td>
<td>4.14 (0.99)*</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.66 (1.12)</td>
<td>1.34 (0.81)</td>
<td>1.19 (0.58)</td>
<td>1.08 (0.56)*</td>
</tr>
<tr>
<td>Leisure-time physical activity, kcal/d</td>
<td>137 (179)</td>
<td>136 (159)</td>
<td>136 (159)</td>
<td>156 (197)</td>
</tr>
<tr>
<td>Income, Euro</td>
<td>12 780 (7 620)</td>
<td>13 300 (8 700)</td>
<td>13 480 (9 530)</td>
<td>14 980 (9 920)*</td>
</tr>
<tr>
<td>Education, y</td>
<td>8.7 (3.3)</td>
<td>8.5 (3.2)</td>
<td>8.6 (3.4)</td>
<td>9.3 (3.9)*</td>
</tr>
<tr>
<td>Serum ALA, %</td>
<td>0.79 (0.25)</td>
<td>0.76 (0.22)</td>
<td>0.73 (0.25)</td>
<td>0.70 (0.22)</td>
</tr>
<tr>
<td>Hair mercury, μg/g</td>
<td>1.45 (1.53)</td>
<td>1.71 (1.78)</td>
<td>2.37 (2.26)</td>
<td>2.82 (2.49)*</td>
</tr>
<tr>
<td>Energy intake, kcal/d</td>
<td>2436 (589)</td>
<td>2460 (588)</td>
<td>2352 (624)</td>
<td>2313 (617)*</td>
</tr>
<tr>
<td>Alcohol intake, g/wk</td>
<td>57.4 (92.8)</td>
<td>65.4 (106.0)</td>
<td>88.8 (185.1)</td>
<td>85.0 (123.8)*</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7.4</td>
<td>2.9</td>
<td>5.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>18.6</td>
<td>12.3</td>
<td>16.7</td>
<td>14.5</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>6.8</td>
<td>5.0</td>
<td>5.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Cardiomyopathy, %</td>
<td>2.8</td>
<td>1.9</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>1.5</td>
<td>1.8</td>
<td>2.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>52.9</td>
<td>45.0</td>
<td>45.0</td>
<td>43.1*</td>
</tr>
<tr>
<td>Use of β-blockers, %</td>
<td>20.6</td>
<td>13.6</td>
<td>14.3</td>
<td>14.0*</td>
</tr>
</tbody>
</table>

Values are means (SD) or percentages. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

*P for trend across quartiles < 0.05.

quartile had a 35% (95% CI 7% to 54%; P for trend = 0.07) reduction in the HR of AF compared with the lowest quartile (absolute risk in the reference group 13.4%; absolute risk reduction 4.7%). Further adjustments for potential confounders did not appreciably change the association (model 2). When examined individually, only DHA was associated with reduced risk (Table 2; Figure); the multivariable-adjusted HR was 38% lower (95% CI 8% to 58%; P for trend = 0.02) in the highest quartile (reference group absolute risk 13.3%; absolute risk reduction 5.1%). Further adjustment for EPA and DPA did not change the association (data not shown). EPA and DPA were not associated with the risk of AF (Table 2).

The exclusion of subjects who had myocardial infarction or congestive heart failure either at baseline or that preceding the AF event during follow-up slightly strengthened the associations (Table 2; model 3). Among 1941 men, 167 AF events occurred. The multivariable-adjusted HR in the highest versus the lowest serum EPA+DPA+DHA quartile was 50% lower (95% CI 20% to 69%; P for trend = 0.02; reference group absolute risk 11.3%; absolute risk reduction 5.7%). The multivariable-adjusted HR in the highest DHA quartile was 49% lower (95% CI 18% to 68%; P for trend = 0.02) than in the lowest quartile (reference group absolute risk 10.9%; absolute risk reduction 5.3%). Similar results were observed after adjustment for intermediate events during follow-up (model 4). Again, EPA and DPA were not associated with the risk of AF (Table 2).

Serum ALA and Risk of AF

The mean serum ALA concentration was 0.74% (SD 0.24%) of all fatty acids. We did not find evidence that serum ALA was associated with the risk of AF. The multivariable-adjusted (model 2; Table 2) HRs (95% CI) in the serum ALA quartiles were 1 (referent), 1.26 (0.84 to 1.89), 0.74 (0.46 to 1.20), and 1.14 (0.72 to 1.79; P for trend = 0.98), respectively. No association was found even when the EPA+DPA+DHA concentration was low (P for interaction = 0.10). We also did not find any evidence for interaction with EPA, DPA, or DHA when they were evaluated individually (P for interactions > 0.10).

Hair Methylmercury and Risk of AF

We did not find any association between hair methylmercury concentration and risk of AF. The mean hair methylmercury concentration was 2.06 μg/g (SD 2.13 μg/g). The multivariable-adjusted (model 2; Table 2) HRs (95% CI) in hair methylmercury quartiles were 1 (referent), 1.11 (0.76 to 1.60), 1.06 (0.73 to 1.55), and 1.03 (0.70 to 1.52; P for trend = 0.96), respectively. Further adjustment for serum EPA+DPA+DHA did not change the association (P for trend = 0.80). High hair methylmercury concentration also did not modify the effects of serum EPA+DPA+DHA (P for...
interaction = 0.56). No significant interactions were found with the individual fatty acids (P for interactions > 0.10).

**Effect Modification**
We did not find any evidence that age, hypertension, systolic blood pressure, or history of ischemic heart disease modified the associations between the fatty acids and risk of AF (P for interactions > 0.20).

**Discussion**

**Principal Findings**
The results from this prospective cohort study suggest that a higher serum concentration of total long-chain n-3 PUFAs, mainly a marker of fatty fish or fish oil consumption, may be associated with a reduced risk of AF in men and that the effect may be attributable to the serum DHA concentration. The stronger association observed in subjects without myocardial infarction or congestive heart failure implies that the AF association is not mediated by the effects of long-chain n-3 PUFAs on the risk of these events. On the other hand, these intermediate events may also lead to systematic changes in favor of a healthy diet and increased fish intake, which would weaken the association between the long-chain n-3 PUFAs and risk of AF.

**Comparison With Previous Studies**

**Long-Chain n-3 PUFAs and Risk of AF**
The present results are in line with another prospective population-based study, the Cardiovascular Health Study, in which consumption of tuna or other broiled or baked fish 1 to 4 times per week was associated with a 28% lower risk of AF...
among 4815 elderly participants (mean age 72.8 years) during 12 years of follow-up. A fish consumption frequency of ≥5 times per week was associated with a 31% reduced risk in that study. Although they did not specifically examine the association between long-chain n-3 PUFAs and risk of AF, the authors suggested that these fatty acids were responsible for the beneficial effects of fish consumption. This was supported by the positive correlation between these types of fish meals and serum concentrations of EPA+DHA in a subset of participants in the Cardiovascular Health Study. Furthermore, fried fish consumption was not correlated with serum EPA+DHA concentrations, nor was it associated with lower risk of AF. In a small, open-label, randomized trial of 79 subjects and 81 controls, supplementation with 850 to 882 mg/d EPA+DHA for at least 5 days before a coronary artery bypass graft operation, which continued until the day of discharge from the hospital, reduced the incidence of AF after the surgery by 54%. In contrast, a trend toward an increased risk of AF with higher EPA+DHA intakes was observed in the prospective population-based Danish Diet, Cancer, and Health Study over 5.7 years of follow-up among 47,949 participants whose mean age was 56 years. No association with fish or EPA+DHA consumption was found during 6.4 years of follow-up in the Rotterdam Study among 5128 participants with a mean age of 67.4 years.

It has been suggested that the discrepancy between the previous 3 observational studies may be due to the heterogeneity of AF subtypes across cohorts. In older populations, AF is related to structural heart disease, systemic inflammation, atrial fibrosis, and impaired hemodynamics, whereas in younger populations, 20% to 45% of AF occurs without associated comorbidities or structural heart disease. However, the mean age in the present study cohort (52.8 years) was similar to that in the Danish cohort and much lower than in the Cardiovascular Health Study cohort, but the results were similar to those of the Cardiovascular Health Study.

Differences in other factors, such as lifestyle, socioeconomic factors, or underlying CVD, cannot be ruled out. The present finding that DHA but not EPA or DPA was associated with the risk of AF is consistent with previous studies of long-chain n-3 PUFAs and CVD risk. For example, in rats, DHA but not EPA inhibited cardiac arrhythmias. In humans, blood DHA concentration had a beneficial effect on heart rate variability, a predictor of arrhythmic events. Similar results have been observed with other CVD-related factors, such as heart rate, blood pressure, C-reactive protein, and atherosclerosis progression. Although EPA supplementation was effective in reducing the risk of nonfatal coronary events in a recent randomized trial, the preferential accumulation of DHA over EPA in myocardial cell membranes, which serve as a repository and contribute to serum/plasma levels along with dietary intake, it is possible that serum DHA might better reflect long-term fish intake patterns than the other long-chain n-3 PUFAs.

**ALA and Risk of AF**

The low palatability of fish for some people, concerns about depletion of marine fish stocks, and possible contamination of fish by environmental pollutants has made ALA a possible alternative source for n-3 PUFAs. Although ALA can be converted to EPA and DPA in the body in limited amounts, further conversion to DHA is thought to be very limited. Overall, the conversion rate of ALA to longer-chain n-3 PUFAs has been suggested to be relatively low, especially in men. ALA could also have independent cardioprotective effects, or it could be beneficial when intake of fish or fish oil is low. However, previously in the present study cohort, serum ALA concentration was not found to be associated with risk of coronary heart disease mortality. Although ALA has prevented ventricular fibrillation in dogs and dietary ALA intake has been associated with reduced coronary heart disease risk in those with low EPA+DHA intake, we did not find any evidence that high serum ALA concentrations were associated with the risk of AF, even in men with low serum long-chain n-3 PUFAs. Furthermore, no association has been found between blood ALA and heart rate variability. Overall, these findings and the results from a recent systematic review suggest that although there is relatively strong evidence for the cardioprotective effects of fish and fish oil, the role of ALA is less apparent.

**Possible Mechanisms**

Several mechanisms may explain the antiaarrhythmic effects of long-chain n-3 PUFAs. Immediate effects, such as the effects on ion channels, connexins, postischemic recovery of contractile function, vagal activity, and left ventricular filling may be more beneficial postoperatively. On the other hand, the positive long-term effects on, for example, heart rate, heart rate variability, blood pressure, and systemic vascular resistance and reactivity could better explain the effects in healthy elderly subjects. The latter is supported by the seemingly long induction...
time after which the protective effect became apparent (Figure.). However, the lack of effect during the first years of follow-up could also be explained by the relatively young age of the subjects at baseline; only 40 AF events occurred during the first 8 years. Finally, the present results do not suggest that the increased risk of CVD by mercury exposure that has been observed in the present study cohort would be explained by its effects on atrial arrhythmias.

### Study Strengths and Limitations

A strength of the present study is the use of serum long-chain n-3 PUFA measurements instead of dietary intakes for estimating the impact of these fatty acids. All of the previous prospective cohort studies used food-frequency questionnaires, which may introduce bias by misclassification. Serum long-chain n-3 PUFA concentrations correlate well with dietary intakes of fish or fish oil and reflect dietary intakes during the preceding weeks. This makes the serum long-chain n-3 PUFA concentration a good direct marker for the intake of long-chain n-3 PUFA from fish. Other strengths of the study are its population-based recruitment, prospectively collected data, and extensive examinations of potential risk factors. There was also very little loss to follow-up.

Potential limitations are also present. Because the participants in the Kuopio Ischemic Heart Disease Risk Factor Study did not visit the study site regularly, we included only AF events documented on hospital discharge records. Therefore, the findings of the present study may apply only to hospitalized AF, which may have weakened the associations. Because only hospitalized events were included, serum DHA might only be a marker of a likelihood of being hospitalized for any cause. However, this is not supported by the lack of association between serum DHA and hospitalization for any cause during the follow-up in the post hoc analysis (HR in the highest versus lowest serum DHA quartile 1.02, 95% CI 0.72 to 1.46, P for trend=0.76). Fish intake may have changed during the follow-up, so the use of a single measurement of serum long-chain n-3 PUFA concentrations at baseline would underestimate its association with risk of AF. This may also explain the null results with ALA, a large proportion of which is oxidized, such that serum levels would depend more on recent intake. The observed association may be related to other factors associated with high serum long-chain n-3 PUFA concentrations, such as a healthier lifestyle in general in those consuming fish. However, we had extensive adjustments for possible confounders, although we did not have follow-up information about obesity, which is associated with arrhythmias. Theoretically, because several associations were evaluated, it is possible that the significant association found between serum DHA and risk of AF may have been due to type I error. Finally, the present study population consisted of middle-aged and older men, so the results may not be generalizable to other age groups or to women.

### Conclusions

Our results suggest that long-chain n-3 PUFA from fish, especially DHA, may be beneficial in the prevention of AF, a common cardiac arrhythmia. Future studies are needed to explore the mechanisms and effects of individual long-chain and intermediate-chain-length n-3 PUFA on arrhythmias.

### Acknowledgments

We wish to thank our staff at the Research Institute of Public Health for helping with subject recruitment and data collection.

### Sources of Funding

The work was supported by the Academy of Finland grant 121206 to Dr Virtanen.

### Disclosures

None.

### References


45. Mozaffarian D, Gottdiener JS, Siscovick DS. Intake of tuna or other broiled or baked fish versus fried fish and cardiac structure, function, and hemodynamics. Am J Cardiol. 2006;97:216–222.


**Clinical Perspective**

Fish consumption has been associated with reduced risk of atrial fibrillation (AF) and the long-chain n-3 polyunsaturated fatty acids (PUFAs) in fish have been suggested to account for the beneficial effects. The present study assessed the relationship between serum concentrations of long-chain n-3 PUFAs eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA), which also serve as a marker of fish or fish oil consumption, and risk of AF in middle-aged or older men in Eastern Finland. During 17.7 years of follow-up, 240 men from the total cohort of 2174 men experienced an AF event that required hospitalization. Men in the highest quartile of serum EPA+DPA+DHA had a 35% lower risk of AF compared with men in the lowest quartile. Of the individual fatty acids, only serum DHA was associated with the risk, with a 38% lower risk in the highest quartile. No association with the risk was found with serum intermediate chain-length n-3 PUFA, alpha-linolenic acid, not even when the serum EPA+DPA+DHA concentration was low. Although previous studies in this study population have associated an increase in long-term low-level mercury exposure and risk of cardiovascular diseases, high mercury concentration in hair was not associated with the risk of AF in this study. In summary, long-chain n-3 PUFAs, and especially DHA, may be effective in reducing the risk of AF in men.
Serum Long-Chain n-3 Polyunsaturated Fatty Acids and Risk of Hospital Diagnosis of Atrial Fibrillation in Men
Jyrki K. Virtanen, Jaakko Mursu, Sari Voutilainen and Tomi-Pekka Tuomainen

Circulation. 2009;120:2315-2321; originally published online November 23, 2009;
doi: 10.1161/CIRCULATIONAHA.109.852657
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/23/2315

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/