A U-shaped association between consumption of marine n-3 fatty acids and development of atrial fibrillation/atrial flutter—a Danish cohort study

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Aims
Previous studies have suggested a lower risk of atrial fibrillation (AF) with higher intakes of fish and marine n-3 polyunsaturated fatty acids (PUFAs), but the results have been inconsistent. The aim was to investigate the association between consumption of marine n-3 PUFA and risk of incident AF.

Methods and results
A total of 57,053 Danish participants 50–64 years of age were enrolled in the Diet, Cancer, and Health Cohort Study between 1993 and 1997. Dietary intake of fish and marine n-3 PUFA was assessed by a semi-quantitative food frequency questionnaire. In total, 3345 incident cases of AF occurred over 13.6 years. Multivariate Cox regression analyses (3284 cases and 55,246 participants) using cubic splines showed a U-shaped association between consumption of marine n-3 PUFA and risk of incident AF, with the lowest risk of AF at a moderate intake of 0.63 g/day. For quintiles of marine n-3 PUFA intake, a 13% statistically significant lower risk of AF was seen in the middle vs. lowest quintile: Q1 reference, Q2 HR 0.92 (95% CI 0.82–1.03), Q3 HR 0.87 (95% CI 0.78–0.98), Q4 HR 0.96 (95% CI 0.86–1.08), and Q5 HR 1.05 (95% CI 0.93–1.18). Intake of total fish, fatty fish, and the individual n-3 PUFA eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid also showed U-shaped associations with incident AF.

Conclusion
We found a U-shaped association between consumption of marine n-3 PUFA and risk of incident AF, with the lowest risk close to the median intake of total marine n-3 PUFA (0.63 g/day).

Keywords
Atrial fibrillation  •  n-3 Polysaturated fatty acids  •  Fish  •  Diet

Introduction
Atrial fibrillation (AF) is a common arrhythmia with an increasing prevalence of 5–15% at Age ≥ 80,¹ and is associated with considerable morbidity, mortality, and economic costs.² Prevention of AF therefore would be of major public interest, and interestingly, fish consumption has been associated with a lower risk of incident AF, although data are inconsistent.³ A reduction in experimentally induced AF has been shown in animals treated with marine n-3 polyunsaturated fatty acids (PUFAs).³ Initially, a 28% lower risk of AF was found in the Cardiovascular Health Study in persons consuming fish one to four times per week compared with an intake of less than once per month⁴—findings that were later supported by results from measurements of n-3 PUFA in plasma.⁵ A similar association was found in a Finnish cohort study showing a 35% lower risk of AF in the highest vs. lowest quartile of n-3 PUFA in serum,⁶ while other studies have been unable to confirm this.⁷–¹¹ A beneficial effect of fish consumption has been attributed to the content of marine n-3 (omega-3) PUFA in fish, in particular eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and perhaps also docosapentaenoic acid (DPA). The aim of the present study was to examine the hypothesis of a negative association between consumption of fish and marine n-3 PUFA and development of AF.

Materials and methods
Study population
Diet, Cancer, and Health is a cohort study initiated with the primary objective of analysing the role of diet in the development of cancer and has
Present study, participants registered at baseline with AF or atrial fibrillation, e.g. in case of delay in registration at the Cancer Registry. For the criteria if a prior diagnosis of cancer at the time of invitation was later discovered, the Danish Data Protection Agency. The cohort study has been approved by the relevant Ethics Committees and the Danish Data Protection Agency.

Participants were excluded according to the intention-to-include criteria if a prior diagnosis of cancer at the time of invitation was later discovered, e.g. in case of delay in registration at the Cancer Registry. For the present study, participants registered at baseline with AF or atrial fibrillation (AFL) were also excluded.

Dietary assessment and baseline information

At baseline, participants filled in a detailed, previously validated semi-quantitative food frequency questionnaire with 192 items including 24 questions regarding intake of fish and food products containing fish. Participants were asked to report the average intake for the last year from a list of fishes divided into types of hot fish meals or fish on bread. The categories were never, <1, 1, 2–3 per month, 1, 2–4, 5–6 per week, 1, 2–3, 4–5, 6–7, or ≥8 times daily. The primary exposure was the dietary consumption of total marine n-3 PUFA (EPA + DHA + DPA) calculated from Danish food composition tables using the software FoodCalc (Center for Applied Computer Science, University of Copenhagen, Denmark; www.ibtku.dk/jesper/foodcalc). Consumption of total fish, lean fish (<1 g n-3 PUFA/100 g), and fatty fish (>1 g n-3 PUFA/100 g) was also explored. Participants reported their intake of fish oil supplements, but there was not sufficient information on the content of marine n-3 PUFA in the supplements to add this to the dietary intake of EPA, DHA, and DPA. Additionally, the participants answered questions about health, lifestyle, and medications. In order to minimize errors, an interviewer reviewed the questionnaires together with the participant at the baseline visit. Finally, blood pressure and anthropometric variables were obtained, and biological material was collected.

Follow-up and outcome

In Denmark, every citizen is identified by a personal identification number for use in all national registries, and updated day-to-day information is available on the vital status including emigration and death. Hospital contacts and discharge diagnoses from all hospitals are recorded by date in the Danish National Patient Registry. In this registry, discharge diagnoses from in-hospital patients have been registered since 1977, and since 1995 diagnoses from emergency rooms and outpatient visits have been recorded as well.

The outcome in this study was defined as incident AF and/or AFL during the study period. The diagnoses were recorded using the Eighth International Classification of Diseases (ICD-8) until the end of 1993 (AF (427.93) and AFL (427.94) in the Danish version which is equivalent to AF or AFL (427.4) in the international version). From January 1994, the ICD-10 classification was used with the diagnosis of AF and/or AFL (I.48). The validity of the combined diagnosis of AF and/or AFL is high, with a positive predictive value of 92.6% in this cohort. If a patient had both an emergency room visit and a hospital admission on the same date, only the in-hospital diagnosis was considered in order to avoid possible misclassification. In line with previous observational studies, we refer to the combined diagnosis of ‘AF and/or AFL’ as AF. The last date for follow-up was end of 2009.

Statistical analysis

In a cohort study design, time-to-event data were analysed using a Cox proportional hazards regression model with delayed entry and age as the time axis. Participants were treated as at-risk from baseline until the first registration of AF, death, emigration, or end of follow-up. Data analyses were planned a priori, including a predefined list of potential confounders with the added post hoc adjustment for total energy intake. Exposures of interest were included as continuous variables and modelled using restricted cubic splines with five knots. The risk of AF was modelled with a Cox regression model. Initially, data for men and women were analysed separately, and no effect modification from sex was found. Subsequently, data from both sexes were pooled and analysed in a sex-stratified Cox regression model assuming equal effects of the exposure for the two sexes but allowing for different baseline hazards.

The multivariate model was adjusted for baseline information on the following potential confounders: hypertension (yes/no), systolic blood pressure, body-mass index, waist circumference, smoking (never, former, <15, 15–25, or >25 cigarettes), alcohol intake, years in school (≤7 years, 8–10 years, >10 years), hypercholesterolaemia and/or cholesterol treatment (yes/no), non-fasting total cholesterol, angina pectoris (yes/no), diabetes mellitus (yes/no), and total energy intake. Also, using data from the National Patient Registry, adjustment was made for inpatient diagnoses of myocardial infarction or heart failure at baseline. Continuous covariates were included using restricted cubic splines with five knots. Age was used as the time axis in the models in order to provide optimal adjustment for age. In post hoc sensitivity analyses, the model was further adjusted for consumption of fruits (tartlets), vegetables (tartlets), red meat (g/day), poultry (g/day), and fatty dairy products (g/day).

Convention by, the reported plots represent the hazard ratios modelled as a cubic spline function for the 2.5–97.5 percentile range of the exposure variable in order not to interpret extreme values for which there were only limited data. This model explores non-linear associations. The median value of the exposure was chosen as reference in the spline plots, and the 95% confidence bands refer to this reference. For comparison with previous studies, supplementary analyses based on exposure quintiles in the cohort were performed using the lowest quintile as reference in a corresponding sex-stratified adjusted Cox regression model. Data were analysed using the Stata statistical software (version 11, Stata-Corp LP, College Station, USA), and a 95% confidence level was considered statistically significant.

What’s new?

- Largest study to date to examine the association between consumption of marine n-3 polyunsaturated fatty acids and incident atrial fibrillation (AF).
- First study to document a U-shaped association between consumption of marine n-3 fatty acids and AF.
- With the greater statistical power from 3284 incident cases of AF, this study offers more insights than an earlier study from the same cohort published in 2004.
Persons with missing data in one or more covariates in the multivariate model were excluded. The proportional hazards assumption in the Cox regression analyses was not found to be violated when evaluated graphically by cumulative hazard plots and log-minus-log plots for quintiles of n-3 PUFA, as well as plots of scaled Schoenfeld residuals vs. age.

Differences in dietary patterns for persons with levels of marine n-3 PUFA intake were assessed graphically in radar plots, in which the mean values for a number of selected food products were visualized for the highest and lowest quintiles of n-3 PUFA consumption compared with the overall mean consumption.

Results

In total, 3345 incident cases of AF occurred during a median of 13.6 years of follow-up (Figure 1). Baseline characteristics of the participants are listed in Table 1. Incident AF was more common in men (incidence rate 6.5 per 1000 person-years) than in women (incidence rate 3.2 per 1000 person-years). Complete data were available for multivariate analysis of 55 246 participants including 3284 cases of AF (Figure 1).

The median consumption of total marine n-3 PUFA was 0.70 (5/95 percentiles 0.24/1.66) g/day in men and 0.57 (0.19/1.40) g/day in women. Overall, the median consumption of marine n-3 PUFA was 0.63 g/day. In separate analyses for men and women, U-shaped associations between the intake of marine n-3 PUFA and the risk of incident AF were found in both sexes (Supplementary material online, Figure S2), and no effect modification from sex was found (Wald test $P = 0.62$). Thus, data for men and women were pooled.

Combined, sex-stratified Cox regression analyses showed a U-shaped association with the lowest risk close to the median intake in this population and a higher risk at both lower and higher than median intake (Figure 2). No major differences between crude and adjusted analyses were observed (data not shown). A Cox regression model based on quintiles of consumption of marine n-3 PUFA was also explored and this showed a similar U-shaped association with a 13% lower hazard of AF (HR 0.87 (95% CI 0.78–0.98)) in the third quintile compared with the lowest quintile of n-3 PUFA consumption (Table 2). Sensitivity analyses with additional adjustment for intake of selected food groups had no effect on the associations reported (Table 2).

In secondary analyses, the model was also fitted for intake of total fish, lean fish, fatty fish, and separately for the individual fatty acids EPA, DHA, and DPA (Supplementary material online, Figures S4 and S5). For all exposures, the association was U-shaped, although less so for lean fish. Intake of fatty fish and lean fish was low to moderately correlated ($r = 0.46$). Intakes of EPA, DHA, and DPA were highly correlated (EPA and DHA, $r = 0.97$) and the statistical analyses exploring individual n-3 PUFA provided similar results to the analyses on total n-3 PUFA.

Further analyses were undertaken to assess the robustness of the models. The main results were robust for restricted cubic splines with three to seven knots. Similar results were seen when grouping participants into birth-year groups. Also, analyses without adjustment for the presence of angina pectoris, myocardial infarction, and heart failure as potential intermediate factors provided similar results. Overall, 83% reported no intake of fish oil supplements. Among non-users, the results corresponded to the primary analysis (Supplementary material online, Figure S6). Among those who reported the use of fish oil supplements, a U-shaped association was also found with the minimal risk at a slightly lower intake of around 0.5 g n-3 PUFA/day.

A radar plot of selected food groups showed that persons in the highest quintile of marine n-3 PUFA had a higher intake of poultry, vegetables, and vegetable oil, and a lower intake of butter, fatty dairy products, cereals, and sugar compared with the lowest quintile (Supplementary material online, Figure S7).

Discussion

This study of 3284 incident cases of AF showed a U-shaped association between dietary consumption of marine n-3 PUFA and risk of AF. Likewise, U-shaped associations were also found for the intake of total fish, fatty fish, and the individual n-3 fatty acids EPA, DHA, and DPA. Separate analyses for men and women showed no evidence of effect modification from sex.

Strengths and limitations

The present study has a number of strengths. The large number of cases provides good statistical power, and the study was designed to obtain information also on non-linear associations with the use of cubic spline models. All statistical analyses were planned a priori with the exception of the reference value for the spline plots. We chose to report the median value as reference to address the finding of a U-shaped association, but importantly this does not affect the pattern of the estimated curves. Furthermore, the study...
provides detailed baseline information, accurate information on the
vital status, and prospective follow-up from any hospital in the

country.

Our study also has limitations. It is an observational study and can
by design only report on associations (and not causation) between
the diet and the risk of AF. The study only included middle-aged
persons who had survived without a diagnosis of AF until inclusion
into the study, and concerns only the first registration of AF or AFL
from a hospital visit. Therefore, the study does not include
undiagnosed persons with asymptomatic AF or patients only
treated by their general practitioner; however, most patients with
diagnosed AF are likely to have been referred for a subsequent hos-
pital contact such as for echocardiography or cardioversion. Overall,
no selection bias in terms of a systematic error related to both the
exposure and the outcome seems likely.

The food frequency questionnaire used had been carefully devel-

<table>
<thead>
<tr>
<th>Quintiles of consumption of marine n-3 PUFA</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of AF</td>
<td>597</td>
<td>587</td>
<td>591</td>
<td>682</td>
<td>827</td>
</tr>
<tr>
<td>Men (%)</td>
<td>36.2</td>
<td>42.1</td>
<td>47.6</td>
<td>51.9</td>
<td>60.0</td>
</tr>
<tr>
<td>Age at entry (years)</td>
<td>55 (51; 62)</td>
<td>55 (51; 62)</td>
<td>56 (51; 63)</td>
<td>56 (51; 63)</td>
<td>57 (51; 63)</td>
</tr>
<tr>
<td>Hypertension (self-reported, %)</td>
<td>15.6</td>
<td>15.1</td>
<td>16.2</td>
<td>16.2</td>
<td>17.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136 (112; 164)</td>
<td>137 (115; 166)</td>
<td>138 (115; 167)</td>
<td>138 (116; 167)</td>
<td>140 (117; 167)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25.3 (21.2; 31.2)</td>
<td>25.4 (21.3; 31.05)</td>
<td>25.6 (21.5; 31.2)</td>
<td>25.6 (21.6; 31.0)</td>
<td>25.8 (21.7; 31.2)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>86 (71; 104)</td>
<td>87 (72; 105)</td>
<td>89 (72; 105)</td>
<td>89 (73; 105)</td>
<td>91 (74; 106)</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>9.7 (0.8; 40.7)</td>
<td>12.1 (1.6; 44.9)</td>
<td>13.3 (1.8; 47.9)</td>
<td>15.0 (2.1; 49.0)</td>
<td>16.1 (2.3; 54.7)</td>
</tr>
<tr>
<td>Hypercholesterolaemia (self-reported, %)</td>
<td>6.7</td>
<td>6.2</td>
<td>6.6</td>
<td>7.7</td>
<td>9.5</td>
</tr>
<tr>
<td>Serum cholesterol (total non-fasting, mmol/L)</td>
<td>6.0 (4.7; 7.6)</td>
<td>6.0 (4.8; 7.6)</td>
<td>6.0 (4.7; 7.6)</td>
<td>6.1 (4.8; 7.6)</td>
<td>6.0 (4.7; 7.6)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never (%)</td>
<td>37.5</td>
<td>36.3</td>
<td>36.3</td>
<td>34.8</td>
<td>30.9</td>
</tr>
<tr>
<td>Former (%)</td>
<td>26.0</td>
<td>28.5</td>
<td>28.6</td>
<td>29.1</td>
<td>30.7</td>
</tr>
<tr>
<td>Current &lt;15 (%)</td>
<td>13.2</td>
<td>12.9</td>
<td>13.0</td>
<td>13.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Current 15–25 (%)</td>
<td>16.4</td>
<td>16.0</td>
<td>15.5</td>
<td>16.1</td>
<td>17.0</td>
</tr>
<tr>
<td>Current &gt;25 (%)</td>
<td>6.4</td>
<td>6.4</td>
<td>6.6</td>
<td>7.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Years in school &gt;10 years (%)</td>
<td>19.7</td>
<td>20.4</td>
<td>21.4</td>
<td>21.6</td>
<td>21.8</td>
</tr>
<tr>
<td>Angina pectoris (self-reported, %)</td>
<td>2.7</td>
<td>2.1</td>
<td>2.4</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Diabetes mellitus (self-reported, %)</td>
<td>1.9</td>
<td>2.0</td>
<td>1.7</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>1.8</td>
<td>1.5</td>
<td>1.5</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Fish oil supplements (self-reported, %)</td>
<td>15.1</td>
<td>15.5</td>
<td>16.9</td>
<td>17.4</td>
<td>17.8</td>
</tr>
<tr>
<td>Energy intake (kJ/day)</td>
<td>8043 (3520; 11 304)</td>
<td>8836 (6339; 12 097)</td>
<td>9431 (6858; 12 754)</td>
<td>10 059 (7346; 13 610)</td>
<td>112 85 (8228; 15 528)</td>
</tr>
<tr>
<td>Vegetables (g/day)</td>
<td>131 (46; 282)</td>
<td>148 (60; 286)</td>
<td>158 (69; 302)</td>
<td>174 (80; 318)</td>
<td>196 (89; 357)</td>
</tr>
<tr>
<td>Fruit (g/day)</td>
<td>147 (30; 398)</td>
<td>159 (39; 398)</td>
<td>165 (44; 414)</td>
<td>176 (49; 425)</td>
<td>198 (57; 472)</td>
</tr>
<tr>
<td>Dietary intake of marine n-3 PUFA (g/day)</td>
<td>0.27 (0.14; 0.36)</td>
<td>0.46 (0.39; 0.53)</td>
<td>0.62 (0.56; 0.70)</td>
<td>0.84 (0.74; 0.96)</td>
<td>1.25 (1.04; 1.84)</td>
</tr>
<tr>
<td>Dietary intake of DHA (g/day)</td>
<td>0.17 (0.08; 0.22)</td>
<td>0.29 (0.24; 0.33)</td>
<td>0.39 (0.35; 0.46)</td>
<td>0.53 (0.47; 0.61)</td>
<td>0.79 (0.65; 1.18)</td>
</tr>
<tr>
<td>Dietary intake of EPA (g/day)</td>
<td>0.06 (0.03; 0.09)</td>
<td>0.12 (0.09; 0.14)</td>
<td>0.16 (0.13; 0.20)</td>
<td>0.22 (0.19; 0.27)</td>
<td>0.36 (0.28; 0.54)</td>
</tr>
<tr>
<td>Dietary intake of DPA (g/day)</td>
<td>0.04 (0.02; 0.06)</td>
<td>0.06 (0.04; 0.08)</td>
<td>0.07 (0.05; 0.10)</td>
<td>0.09 (0.06; 0.11)</td>
<td>0.12 (0.09; 0.17)</td>
</tr>
<tr>
<td>Total fish consumption (g/day)</td>
<td>16.9 (6.1; 27.6)</td>
<td>28.5 (19.7; 40.6)</td>
<td>37.7 (27.6; 52.0)</td>
<td>49.3 (36.8; 66.7)</td>
<td>73.3 (52.8; 113.1)</td>
</tr>
<tr>
<td>Lean fish (g/day)</td>
<td>11.8 (3.8; 22.2)</td>
<td>18.7 (10.4; 31.6)</td>
<td>23.1 (13.4; 38.6)</td>
<td>28.1 (15.9; 47.2)</td>
<td>37.8 (19.7; 68.5)</td>
</tr>
<tr>
<td>Fatty fish (g/day)</td>
<td>4.3 (0.6; 7.9)</td>
<td>9.3 (5.5; 13.3)</td>
<td>13.6 (9.1; 19.9)</td>
<td>19.8 (13.6; 28.3)</td>
<td>34.5 (22.3; 54.5)</td>
</tr>
</tbody>
</table>

Baseline characteristics of participants with complete data in the Diet, Cancer and Health Cohort Study. Median (10th, 90th percentile) or %.
PUFA, polyunsaturated fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid.
of fatty acids. The large size of the cohort also helps make up for imprecision in the individual measures. Importantly, the participants answered the questionnaire at baseline without specific focus on fish intake or knowledge of later development of AF, and therefore any imprecision in exposure information is likely to be unbiased. Overall, this would lead to regression towards no association. Another concern is that a person may change dietary habits during follow-up. The participants were between 50 and 64 years of age when entering the study, and people this age and older may be more stable in their dietary habits than younger persons. Also, in the general Danish population the consumption of fish has been unchanged in the period from 1995 to 2004. It seems unlikely that systematic changes in the diet should occur that would affect the rank order of participants in regard to the intake of n-3 PUFA and, at the same time, be related to incident AF. The outcome of this study was incident diagnosis of AF and/or AFL. The validity of this diagnosis is high, with a positive predictive value >92% in the present study. Misclassified cases are not likely to be associated with the exposure and would therefore lead to regression towards no association and thereby underestimate associations.

No major differences in the results of adjusted and unadjusted models were observed. However, we cannot exclude the presence of residual confounding. Since a potential mechanism of action of marine n-3 PUFA may be through an intermediate beneficial effect on ischaemic heart disease, the model was also fitted without adjustment for angina pectoris, myocardial infarction, and heart failure, but the results were not substantially affected. The intake of selected food groups varied between persons with the highest and lowest intake of marine n-3 PUFA (Supplementary material online, Figure S7). The diet in the high-intake group was slightly more heart healthy. We decided not to control for potential confounding from diet in the primary model as control would make the interpretation of the fatty acid results more difficult. The intake of marine n-3 fatty acids may also be a marker of a healthy diet; however, sensitivity analyses adjusting for intake of selected food groups did not affect the associations found. We also have explored a model of the absolute intake of marine n-3 fatty acids (not adjusted for energy intake) which could be biologically relevant as n-3 fatty acids could have a rhythm stabilizing effect independent of the energy intake. However, there was no difference in the results of the two strategies (data not shown).

In theory, reverse causation in terms of a bias towards a harmful effect of a high consumption of n-3 PUFA could be induced if, for some reason (disease or fear of disease), some persons with a higher risk of AF had chosen to eat more fish to improve their health status. However, the association was similar in separate analyses for the first 2 years compared with the rest of the follow-up time (data not shown). Also, such persons would possibly be more likely to consume fish oil supplements as well, and sensitivity analyses excluding persons using supplementary fish oil showed similar results with a U-shaped association.

The intake of n-3 PUFA in the present study was relatively high compared with previously reported cohort studies (Table 3), but direct comparison between studies of the amounts of fish and marine n-3 PUFA consumed is difficult. Food habits vary between populations in terms of types, amounts, and preparation of seafood. Also, the methods for assessing dietary intakes may not be directly comparable. From the present cohort, a smaller and

![Figure 2](https://academic.oup.com/europace/article-abstract/16/11/1554/603562) Dietary consumption of total marine n-3 polyunsaturated fatty acids (PUFAs) and risk of incident AF. Median intake as reference (red vertical line). The 20, 40, 60, and 80 percentiles of intake are marked by dashed lines. Shaded green area shows the 95% CI for the hazard ratio for AF (black curve). Only the 2.5–97.5 percentile of exposure is shown.

<table>
<thead>
<tr>
<th>Intake of marine n-3 PUFA g/day</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.39 g/day</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>0.39–0.53 g/day</td>
<td>0.92</td>
<td>0.82–1.03</td>
</tr>
<tr>
<td>0.54–0.73 g/day</td>
<td>0.87</td>
<td>0.77–0.97</td>
</tr>
<tr>
<td>0.74–0.99 g/day</td>
<td>0.95</td>
<td>0.85–1.07</td>
</tr>
<tr>
<td>&gt;0.99 g/day</td>
<td>1.06</td>
<td>0.95–1.18</td>
</tr>
</tbody>
</table>

Table 2 Quintiles of dietary intake of marine n-3 PUFA and risk of incident AF

1. PUFA: polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval; Q, quintile.
2. Adjusted for age, sex, hypertension, systolic blood pressure, body-mass index, waist circumference, smoking, alcohol intake, years in school, hypercholesterolaemia and/or cholesterol treatment, total serum cholesterol, angina pectoris, diabetes mellitus, myocardial infarction, heart failure, and total energy intake.
3. Sensitivity analysis further adjusted for consumption of fruits, vegetables, red meat, poultry, and fatty dairy products.
underpowered substudy of participants (including 179 cases of AF) was suggestive of a negative dose–response association between the content in adipose tissue of marine n-3 PUFA and AF, however not statistically significant, and larger studies are needed.\textsuperscript{19} Studies using biomarkers could be also helpful when comparing studies in different populations.

### Marine n-3 polyunsaturated fatty acids and atrial fibrillation

Observations of a higher risk of AF with high intakes of marine n-3 PUFA have previously been reported. Thus, in an exploratory analysis, Shen et al. noted a significantly higher risk of AF (HR 6.53, 95\% CI 2.65–16.06) among rather few participants (n = 26) consuming more than four servings of dark fish per week.\textsuperscript{10} Also, in a Japanese case–control study\textsuperscript{20} with a very high intake of n-3 PUFA, patients with lone AF (n = 74) had significantly higher serum levels of EPA compared with controls (n = 36) and with patients with both AF and ischaemic heart disease (n = 36). Furthermore, in an Icelandic trial there was a trend towards a U-shaped association between the plasma phospholipid content of n-3 PUFA and the risk of post-operative AF, with a lower risk in the second quartile and a higher risk in the highest quartile which was statistically significant for DHA.\textsuperscript{21} Recently, Gronroos et al. reported data from a large

### Table 3  Studies on dietary consumption of fish and marine n-3 PUFA and risk of incident AF

<table>
<thead>
<tr>
<th>References</th>
<th>Study population (mean age at entry)</th>
<th>Incident cases of AF</th>
<th>Mean intake</th>
<th>Follow-up</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozaffarian et al.\textsuperscript{4} USA</td>
<td>Cardiovascular Health Study (73 years)</td>
<td>980 4815</td>
<td>2.2 fish servings/week</td>
<td>12 years</td>
<td>28% lower risk of AF with fish intake one to four times per week (HR 0.72, 95% CI 0.58–0.91, P = 0.005), and 31% lower risk with fish intake five or more times per week (HR 0.69, 95% CI 0.52–0.91, P = 0.008) compared with less than one per month</td>
</tr>
<tr>
<td>Brouwer et al.\textsuperscript{7} Holland</td>
<td>Rotterdam Study (67 years)</td>
<td>312 5184</td>
<td>0.15 g n-3 PUFA/day (1 fish serving/week)</td>
<td>6.4 years</td>
<td>No association. A non-significant higher risk of AF comparing highest with lowest tertile of n-3 PUFA intake (HR 1.18, 95% CI 0.88–1.57)</td>
</tr>
<tr>
<td>Virtanen et al.\textsuperscript{6} Finland</td>
<td>Kuopio IHD Risk Factor Study (53 years)</td>
<td>240 2174</td>
<td>Not stated (serum n-3 PUFA)</td>
<td>17.7 years</td>
<td>35% lower risk of AF comparing highest with lowest quartile of n-3 PUFA in serum (HR 0.65, 95% CI 0.44–0.96). DHA was associated with a lower risk of AF (HR 0.62, 95% CI 0.42–0.92)</td>
</tr>
<tr>
<td>Berry et al.\textsuperscript{9} USA</td>
<td>Women’s Health Initiative (63 years)</td>
<td>378 44 720</td>
<td>0.12 g n-3 PUFA/day (1.5 fish servings/week)</td>
<td>6 years</td>
<td>No association. A non-significant higher risk of AF for the highest vs. lowest quartile of fish intake (OR 1.17, 95% CI 0.88–1.57)</td>
</tr>
<tr>
<td>Shen et al.\textsuperscript{10} USA</td>
<td>Framingham Heart Study (62 years)</td>
<td>296 4526</td>
<td>0.27 g n-3 PUFA/day (1.9 fish servings/week)</td>
<td>4 years</td>
<td>No association. In exploratory subgroup analyses, more than four servings of fish/week was associated with significantly higher risk of AF compared with less than one per week (HR 6.53, 95% CI 2.65–16.06, P &lt; 0.001)</td>
</tr>
<tr>
<td>Gronroos et al.\textsuperscript{11} USA</td>
<td>ARIC cohort study (54 years)</td>
<td>1604 14 222 (3743 in subgroup)</td>
<td>0.19 g n-3 PUFA/day</td>
<td>17.6 years</td>
<td>No association based on dietary data. In a subgroup with plasma phospholipid n-3 PUFA measured, a lower risk was seen in the second quartile of DHA in plasma (Q1 HR 1.0 (reference), Q2 HR 0.71 (95% CI 0.54–0.95), Q3 0.82 (95% CI 0.63–1.08), Q4 0.84 (0.63–1.11)), and the authors noted a marginal U-shaped association</td>
</tr>
<tr>
<td>Rix et al.\textsuperscript{19} Denmark (present study)</td>
<td>Diet, Cancer, and Health Study (57 years)</td>
<td>3345 55 996</td>
<td>0.72 g n-3 PUFA/day</td>
<td>13.6 years</td>
<td>U-shaped association with lower risk of AF close to the median consumption, and higher risk at lower and higher levels (HR 1.13 (95% CI 1.02–1.25) at the 10th percentile and HR 1.18 (95% CI 1.06–1.32) at the 90th percentile).</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; n-3 PUFA, marine n-3 polyunsaturated fatty acids; EPA, eicosapentanoic acid; DHA, docosahexanoic acid; HR, hazard ratio; CI, confidence interval.
marinone n-3 PUFA: on the contrary, both high and low levels of intake were associated with a higher risk of AF in this large study. These findings may be important when interpreting contradictory results from studies on consumption of marine n-3 PUFA and AF, suggesting that a moderate consumption of marine n-3 PUFA may be preferable for primary prevention of AF.

Supplementary material

Supplementary material is available at Europace online.

Conflict of interest: none declared.

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References


Conclusion

We found a U-shaped association between consumption of marine n-3 PUFA and risk of AF, with the lowest risk close to the median intake of total marine n-3 PUFA (0.63 g/day). Similar associations were found for intake of fish. We were unable to find evidence of a beneficial dose–response effect at higher levels of consumption of marine n-3 PUFA.


