

**Citation:**

Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation*. 2009 Dec 8; 120 (23): 2,315-2,321. Epub 2009 Nov 23.

**PubMed ID:** [19933935](#)

**Study Design:**

Prospective Cohort Study

**Class:**

B - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

POSITIVE: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To investigate whether regular fish consumption which is the main source for long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) have beneficial effects such as reduced risk of cardiovascular diseases (CVDs), especially sudden death, which is usually caused by ventricular arrhythmia.

**Inclusion Criteria:**

Subjects who were participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHDRFS) and not fall into the met exclusion criteria category.

**Exclusion Criteria:**

Subjects with:

- History of AF at baseline (N=32)
- With missing data on serum PUFAs (N=200)
- With missing data on hair methylmercury (MeHg) concentration (N=276).

**Description of Study Protocol:****Recruitment**

- Participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHDRFS)
- Baseline examinations were performed between March 1984 and December 1989
- Study sample=3,235 men who were 42, 48, 54 or 60 years old at the baseline exam
- 2,682 (82.9%) participated
- Baseline characteristics of the entire study population described in a previous publication.

## Design

- Follow-up between study entry at baseline and December 31 2007; 18 years follow-up
- Subjects gave hair and venous blood samples between 8 and 10 a.m. at the baseline examinations
- Instructed to abstain from ingesting alcohol for three days and from smoking and eating for 12 hours prior to giving the sample
- Detailed descriptions of the determination of serum lipids and lipoproteins:
  - 13 serum selenium
  - 14 assessment of medical history and medications
  - 13 family history of diseases
  - 13 smoking
  - 13 alcohol consumption
  - 13 and blood pressure
  - 13 are published previously
- Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters
- Mercury in hair was determined by flow injection analysis-cold vapor atomic absorption spectrometry and amalgamation, as described previously
- Serum esterified and nonesterified fatty acids were determined by gas chromatography.

## Dietary Intake/Dietary Assessment methodology

Dietary intake of foods and nutrients was assessed at the time of blood sampling by use of four-day food recording.

## Blinding Used

Not applicable.

## Intervention

Not applicable.

## 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 AF1,17,18 or associations with exposures or outcomes in the present analysis
- The multivariable-adjusted models for independent variables were applied
- Further adjustments for income; years of education; place of residence; serum selenium; serum C-reactive protein (CRP); plasma fibrinogen and blood glucose; forced expiratory volume in one second; cardiomyopathy; valvular disease; pulmonary disease; family history of heart disease; use of aspirin,  $\beta$ -blockers, or medication for hyperlipidemia or thyroid therapy; serum  $\alpha$ -linolenic acid (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 less than 5%).
- The cohort mean was used to replace missing values (less than 2.5%) of covariates.<sup>19</sup>

- 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 two-tailed ( $=0.05$ ). Data were analyzed with SPSS 14.0 for Windows (SPSS Inc, Chicago, Illinois).

## Data Collection Summary:

### Timing of Measurements

- Data on events were obtained by record linkage from the national computerized hospitalization registry in Finland
- Data on vital status were obtained from Statistics Finland
- Cardiovascular causes of atrial fibrillation (AF) were coded according to International Classification of Diseases (ICD) 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. 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 as a means of verification. A good estimate of the accuracy of AF diagnoses acquired by record linkage in the present study was 96% to 98%.

### Dependent Variables

AF

### Independent Variables

- Age
- Examination year
- History of IHD
- Congestive heart failure or stroke
- Diabetes mellitus
- BMI
- Smoking (never, former or current)
- Pack-years of smoking
- Leisure-time physical activity
- Serum HDL and LDL-C and TG
- Blood pressure (SBP and DBP)
- Treated hypertension (HTN)
- Hair methylmercury concentration.

### Control Variables

None.

## Description of Actual Data Sample:

- *Initial N*: 3,235 (males)
- *Attrition (final N)*:

- 2,682 (82.9%)
- 2,174 final participants
- Loss to follow-up (N=3)
- *Age:*
  - 42-60 years old (42, 48, 54 or 60 years at baseline-1984).
  - Mean age of the cohort was 52.8 years (*SD* 5.3 years)
- *Ethnicity:* Not described
- *Other relevant demographics:*
  - Subjects were younger and healthier
  - Had a lower prevalence of CVD, diabetes mellitus, HTN, and current smoking
  - Had had a higher education and income than those who were excluded
- *Anthropometrics:* Not applicable
- *Location:* Finland.

## Summary of Results:

### Principal finding

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 the effect may be attributable to the serum DHA concentration. The stronger association observed in subjects without myocardial infarction (MI) or congestive heart failure (CHF) 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.

- 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 methylmercury and serum total cholesterol, HDL-, and LDL-cholesterol concentrations but lower serum triglyceride, linoleic acid and ALA concentrations and were also less likely to be hypertensive or to use  $\beta$ -blockers, and they had lower energy intake but higher intake of alcohol
- 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, men in the highest serum EPA+DPA+DHA 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. When examined individually, only DHA was associated with reduced risk 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
- EPA and DPA were not associated with the risk of AF. Mean serum ALA concentration was

0.74% (SD 0.24%) of all fatty acids

- There was no evidence that serum ALA was associated with the risk of AF
- The multivariable-adjusted 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), nor for interaction with EPA, DPA or DHA when they were evaluated individually (P for interactions >0.10).

#### **Author Conclusion:**

- Long-chain n-3 PUFAs 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 PUFAs on arrhythmias.

#### **Reviewer Comments:**

- *Authors recognize that potential limitations were present in the study, because the participants in the Kuopio Ischemic Heart Disease Risk Factor Study did not visit the study site regularly, and therefore, only AF events documented on hospital discharge records were included. They noted therefore that these findings may apply only to hospitalized AF, which may have weakened the associations*
- *In addition, because only hospitalized events were included, serum DHA might only be a marker of a likelihood of being hospitalized for any cause.*