

NIH Public Access

Author Manuscript

Am J Cardiol. Author manuscript; available in PMC 2011 March 15.

Published in final edited form as:

Am J Cardiol. 2010 March 15; 105(6): 844–848. doi:10.1016/j.amjcard.2009.11.039.

Dietary Fish Intake and Incident Atrial Fibrillation (from the Women's Health Initiative)

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Abstract

Experimental and clinical trial data suggest an association between fish oil intake and atrial fibrillation (AF). However, prior observational studies have reported conflicting results regarding this association. Thus, we sought to compare the association between dietary fish intake and incident AF in a large sample of older, postmenopausal women. We included 44,720 participants from the Women's Health Initiative clinical trials not enrolled in the dietary modification intervention arm and without AF at baseline. The dietary intake of non-fried fish and omega-3 fatty acid intake were estimated from a Food Frequency Questionnaire at study entry. Incident AF was determined by follow-up ECG at year 3 and year 6. Baseline characteristics and rates of incident AF were compared across quartiles (Q) of fish intake. Adjusted logistic regression models were used to evaluate the association between dietary non-fried fish intake and incident AF. There were 378 incident cases of AF in follow-up. In age-adjusted models, there was no association between dietary non-fried fish intake and incident AF [odds ratios (95% confidence intervals) 1.17 (0.88–1.57) for Q 4 vs. Q 1 of dietary fish intake). Similar findings were observed in multivariable models and in subgroup analyses. In a large cohort of healthy women, we found no evidence of an association between fish or omega-3 fatty acid intake and incident AF.

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Keywords

atrial fibrillation; diet; omega-3 fatty acids

Atrial fibrillation (AF) represents the most common sustained dysrhythmia in humans and is particularly prevalent in older ages, with a population prevalence of 10% in the 9th decade^{1,} ² and a lifetime risk of 25%³. Because AF is associated with higher rates of mortality^{4,5}, heart failure⁶, and stroke⁷, the high prevalence of AF in the population represents a significant public health problem⁸. Prior observational studies have shown several pharmacologic therapies and lifestyle patterns to be associated with AF in the general population. For example, observational⁹, clinical trial¹⁰, and experimental data^{11,12} suggest that omega-3 fatty acids from dietary fish and/or supplements might decrease the risk for AF. However, two additional observational studies have reported no apparent association between dietary fish intake and incident AF^{13,14}. Because of these conflicting findings and the ongoing uncertainty regarding the role of dietary fish intake and incident AF, we sought to compare the association between dietary fish intake and incident AF in a large sample of older, postmenopausal women from the Women's Health Initiative.

METHODS

Details of the eligibility criteria and recruitment methods, randomization, follow-up, data and safety monitoring, and quality assurance for the Women's Health Initiative have been published previously¹⁵. Briefly, 68,131 postmenopausal women age 50 to 79 years were recruited by population-based mailing campaigns between 1993 and 1998 to enroll in one or more clinical trials: dietary modification, calcium/vitamin D, and/or hormone replacement therapy. We excluded women in the dietary modification intervention arm (N=19,541) since the low-fat dietary change program was designed to alter usual dietary habits. We also sequentially excluded women with AF by ECG at baseline (N=135) or self-report (N=1,752), and women providing incomplete data regarding dietary fish intake (N=1,984). Therefore, we included a total of 44,720 participants for the present analysis. Baseline characteristics were measured at study entry in accordance with standard protocols as reported previously¹⁵. Participants were asked about prior history of AF or other cardiovascular disease diagnoses by standard questionnaire. In addition, participants were asked to report ethnicity using a self-report questionnaire. The protocol and consent form were approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all participants.

Dietary intake of fish was measured at study entry using the Food Frequency Questionnaire (FFQ)¹⁶. Briefly, participants are asked about frequency, amount, and preparation of 122 distinct foods or food groups. Frequencies of food portion intake ranged from "never" or "less than once per month" to "2+ servings per day" over the past three months. Portion sizes range from small, medium, and large in reference to a stated medium portion size (3 ounces of fish; ¹/₂ cup tuna). "Small" and "large" portion sizes are described as "1/2 the medium serving size" and "1 ¹/₂ times the medium serving size or more", respectively. The measurement characteristics of the WHI FFQ have been evaluated by comparison with 24-hour dietary recall and a 4-day food record¹⁶.

Non-fried fish intake was categorized as the frequency of eating three types of fish taken from the FFQ: (1) canned tuna, tuna salad, and tuna casserole, (2) white fish (broiled or baked) such as sole, snapper, cod, and (3) dark fish (broiled or baked) such as salmon, mackerel, or bluefish. Quartiles of "medium portion sizes" per week were created based on the portion size and frequency of meals. Non-fried fish intake was used as the primary exposure variable because

of previous reports demonstrating the importance of food preparation on AF and other cardiovascular endpoints^{9,17}. In subsequent analyses, fish intake was restricted to only tuna and dark fish to create quartiles of tuna/dark fish intake. In addition, secondary analyses were also performed for fried fish. Estimates of dietary omega-3 fatty acid (grams/day) were created using analysis software which incorporates 19 adjustment questions to the FFQ to estimate specific nutrient intake from food, as described previously¹⁶. Of note, there was no available data on oral omega-3 fatty acid supplements.

Standard 12-lead ECGs were recorded at baseline and the annual visit at year 3 and year 6 in the resting supine position using standardized procedures as previously described¹⁸. All ECGs received at the central ECG laboratory (EPICORE Center, University of Alberta, Alberta, Edmonton, and later by EPICARE in Wake Forest University, Winston-Salem, NC) were inspected visually to detect technical errors and those with inadequate quality were rejected from ECG data files. ECG data were stored electronically and transmitted daily to the Electrocardiographic Reading Center for analysis by using the Novacode criteria measurement and classification system¹⁹. Incident AF was defined as the presence of AF or atrial flutter on ECGs obtained at years 3 or 6 among participants free of AF at baseline.

The unadjusted incidence rate of AF by year 6 was calculated as the number of events over the number of participants in each quartile of non-fried fish intake. Logistic regression was used to compare rates of incident AF across quartiles of non-fried fish intake, with quartile 1 as the referent group. Three models are presented: Model 1 (age-adjusted); Model 2 (multivariate model adjusted for age, body mass index (BMI), ethnicity, education, diabetes history, systolic blood pressure, treated hypertension, prior CVD, and smoking); Model 3 [Model 2 covariates plus alcohol use, total energy intake (kcal/day), fruit/vegetable intake (medium servings/day), fiber intake (g/day)].

In secondary analyses, we used logistic regression to test for the association between quartiles of dark fish/tuna intake and incident AF. Similarly, we also tested for association across quartiles of omega-3 fatty acid intake with incident AF. We conducted additional analyses separately in women < 65 years and \geq 65 years and in blacks and whites separately. To test for a potential threshold effect, we conducted additional analyses among women with high levels of fish intake (\geq 5 servings/week). All statistical analyses were performed using SAS 9.1 (Cary, NC). All tests were 2-sided and p-values <0.05 were considered statistically significant.

RESULTS

Average dietary fish intake in the Women's Health Initiative was 1.5 medium servings/week which corresponded to 0.12 g of omega-3 fatty acid intake per day. As shown in table 1, women who consumed more servings of non-fried fish were slightly younger with higher educational attainment and a lower representation of ethnic minorities. In addition, these women were less likely to smoke and more likely to drink alcohol. Higher non-fried fish intake was also associated with other healthy dietary patterns, including higher dietary fiber and fruits and vegetables. As expected, the dietary omega-3 fatty acid from fish was higher among women with higher non-fried fish intake.

There were 378 cases of incident AF (including 42 cases of atrial flutter), representing 0.85% of the total sample. In age-adjusted models, there was no association between weekly non-fried fish intake and incident AF. After additional adjustment for baseline risk factors (model 2) as well as dietary factors (model 3), there was no observed association (see Table 2). Similar findings were observed for n-3 fatty acid intake (Table 3), dark fish/tuna (Table 4), and fried fish intake (data not shown).

Interaction terms for race and age were non-significant. Additional analyses stratified by age (>65 years/ \leq 65 years) and race (black/white) revealed no association between dietary fish intake and incident AF in any subgroups. Because of the overall low intake of fish and n-3 fatty acids, we performed additional analyses among women with \geq 5 non-fried fish servings per week (4.6% of 44,720 participants) which revealed no association with incident AF in age-adjusted [OR (95% confidence intervals) 1.17 (0.72–1.88)] and multivariable-adjusted models.

DISCUSSION

In the present study, we observed no apparent association between dietary fish intake and incident AF in a large-sample of postmenopausal women. These findings were consistent across age and race groups. We observed no association at very low and very high levels of fish intake even after accounting for fish type, method of preparation, and amount of fish consumption.

The present study represents the fourth observational study to report on the association between dietary fish intake and incident $AF^{9,13,14}$. There are several important differences between the negative findings in our study and the positive association observed in the Cardiovascular Health Study. First, we observed a much lower rate of incident AF (1%) compared to the 20% event rate observed in the Cardiovascular Health Study. This could reflect differences in the two cohorts as well as our definition of AF which did not capture clinical presentations of AF. However, this rate of AF is not inconsistent from the Danish Diet, Cancer, and Health Study in which there were 25,421 women with 182 cases of AF, representing 0.7% of the study sample¹⁴. Compare this with our observed AF rate of 382 cases out of 44,720 women in the Women's Health Initiative.

Second, the level of fish consumption in our study was low, with fewer than 5% of women reporting consumption 5 or more fish servings per week. In comparison, nearly 20% of participants in the Cardiovascular Health Study reported this level of fish intake⁹. Therefore, the combination of low event rates and low exposure to adequate fish intake could have obscured a potential association between fish intake and incident AF. Nevertheless, our null findings are consistent with those reported by the Rotterdam Study¹³ and the Danish Diet, Cancer and Health Study¹⁴.

In contrast to the preponderance of null findings from observational data, there is a significant body of literature to support the hypothesis that omega-3 fatty acids suppress $AF^{10,20}$. In addition, experimental data from animal studies suggests the protective effect of omega-3 fatty acids is limited to animals with structurally abnormal hearts¹². Thus, the potential association between AF and fish oil may be further complicated by the heterogeneity of AF, with distinct mechanisms promoting AF in structurally normal and abnormal hearts²⁰.

We defined incident AF using only ECGs obtained at scheduled follow-up examinations and had no available data on clinical events related to incident AF. Although measurement of AF using scheduled ECGs without clinical cases of AF might have limited our statistical power to observe a difference across dietary fish intake quartiles, prior literature suggests that AF defined using scheduled ECGs is qualitatively similar to clinical AF. For example, in the Framingham Study, Benjamin, et al² compared the association between risk factors and incident AF using two different definitions of AF: routine ECGs vs. routine ECGs + clinical AF. In almost all cases, the relative risk for each risk factor for incident AF was statistically similar regardless of the method of AF definition. Thus, we believe that our definition of AF may have reduced our statistical power without affecting qualitatively the nature of the association between dietary fish intake and AF.

Acknowledgments

Funding Sources Dr. Berry is currently funded by grant K23 HL092229 from the National Heart, Lung, and Blood Institute as well as from the Dedman Family Scholar in Clinical Care endowment at UT Southwestern. Dr Lloyd-Jones is supported in part by grants R21HL085375 and R01HL086792-02 from the NHLBI.

The Women's Health Initiative program was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, US, Department of Health and Human Services. The funding organization had representation on the Steering Committee, which governed the design and conduct of the study, the interpretation of the data, and the preparation and approval of the manuscript.

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Table 1

Baseline Characteristics by Weekly Medium Servings of Non-Fried Fish Consumption Quartiles

Or and the Structure of Weath	1	2	3	4
Quartile Servings/Week	< 1/2	¹ / ₂ – 1	1–2	≥ 2
	N = 13,002	N = 9,816	N = 11,126	N = 10,776
Age (years), mean (SD)	63.1 (7.1)	63.0 (7.1)	62.8 (6.9)	62.4 (6.9)
White	78.5%	84.4%	86.2%	85.1%
Black	12.1%	9.1%	8.1%	9.4%
Hispanic	6.9%	4.2%	3.2%	2.7%
Others/Unknown	2.5%	2.3%	2.5%	2.7%
College degree or higher	26.1%	33.0%	40.0%	45.2%
Never smoked	53.8%	51.9%	49.4%	47.2%
Current Smoker	9.7%	8.8%	7.9%	7.4%
Non-alcohol drinker	15.8%	10.2%	7.9%	6.6%
\geq 1 alcohol drinks per week	6.8%	9.6%	12.9%	15.8%
Hypertension	25.8%	25.8%	25.6%	25.4%
Diabetes mellitus	5.4%	4.5%	4.2%	4.7%
Prior Cardiovascular Disease	7.0%	6.6%	6.5%	6.5%
Systolic Blood Pressure (mmHg), mean (SD)	128.6 (17.5)	127.8 (17.5)	127.7 (17.3)	127.5 (17.2)
Body Mass Index (kg/m ²), mean (SD)	28.9 (5.9)	28.8 (5.9)	28.9 (5.9)	29.0 (6.0)
Total Cholesterol $(mg/dL)^{a}$, mean (SD)	223.3 (39.5)	223.9 (40.2)	226.5 (40.0)	224.7 (38.6)
Dietary Omega 3 from fish, EPA+DHA (g/day), mean (SD)	0.0 (0.0)	0.1 (0.0)	0.1 (0.1)	0.3 (0.2)
Dietary Fiber (g), mean (SD)	13.6 (6.2)	14.8 (6.1)	16.1 (6.2)	18.0 (6.9)
Combined Fruits / Veggies (med serv/day), mean (SD)	3.2 (1.9)	3.6 (1.8)	4.0 (1.9)	4.5 (2.1)
Atrial Fibrillation	0.75%	0.96%	0.88%	0.82%

CVD: cardiovascular disease; wk: week; EPA: Eicosapentaenoic Acid; DHA: Docosahexaenoic Acid

 $^{a}\mathrm{To}$ convert total cholesterol (mg/dL) to mmol/L, multiply by 0.259.

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Table 2

Odds Ratios (95% CI) of Atrial Fibrillation by Weekly Non-Fried Fish Consumption Quartiles

	QI	Q2	0 3	Q4	
Model	< ^{1/2} servings/wk	 $^{1/2}$ servings/wk $^{1/2}-1$ servings/wk $^{1-2}$ servings/wk $^{2/2}$ servings/wk P Trend	1–2 servings/wk	≥2 servings/wk	P Trend
1: Age-Adjusted	1.00 (REF)	1.30 (0.98, 1.73)	1.30 (0.98, 1.73) 1.23 (0.93, 1.63) 1.17 (0.88, 1.57)	1.17 (0.88, 1.57)	0.626
2: Age + Baseline Risk Factors	1.00 (REF)	1.04 (0.76, 1.42)	.04 (0.76, 1.42) 1.08 (0.79, 1.46) 1.07 (0.78, 1.46)	1.07 (0.78, 1.46)	0.735
3: Model 2 + Dietary Factors	1.00 (REF)	1.01 (0.74, 1.39)	1.01 (0.74, 1.39) 1.04 (0.76, 1.42) 1.02 (0.73, 1.42)	1.02 (0.73, 1.42)	0.916

sion, prior CVD, and smoking. 5 ņ

Model 3: Multivariate model adjusted for covariates in Model 2 and alcohol use, total energy intake, fruit/vegetables intakes, fiber intake.

CI: confidence intervals

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Table 3

Adjusted Odds Ratios (95% CI) of Atrial Fibrillation by Dietary Omega 3 from Fish Intake Quartiles

Model	QI	Q2	Q 3	Q4	
IDDOTAT	<0.049	0.049 - < 0.092	0.092 - < 0.157	0.157+	P for Trend
1: Age-Adjusted	1.00 (REF)		$1.09\ (0.82, 1.45) 1.13\ (0.85, 1.51) 1.11\ (0.83, 1.48)$	1.11 (0.83, 1.48)	0.507
2: Age + Baseline Risk Factors		1.02 (0.74, 1.39)	1.00 (REF) 1.02 (0.74, 1.39) 1.10 (0.81, 1.51) 1.08 (0.78, 1.48)	1.08 (0.78, 1.48)	0.420
3: Model 2 + Dietary Factors		1.00 (0.73, 1.37)	1.00 (REF) 1.00 (0.73, 1.37) 1.07 (0.78, 1.47) 1.02 (0.73, 1.44)	1.02 (0.73, 1.44)	0.579

ypertension, prior CVD, and smoking. Model 3: Multivariate model adjusted for covariates in Model 2 and alcohol use, total energy intake, fruit/vegetables intakes, fiber intake.

CI: confidence intervals

Table 4

Adjusted Odds Ratios of Atrial Fibrillation by Weekly Non-Fried Tuna/Dark Fish Consumption Quartiles

Modol	QI	Q2	03	Q4	
ISDATA	< ¹ /2 servings/wk	 $^{1/2}$ servings/wk $^{1/2}-1$ servings/wk $^{1/2}-2$ servings/wk P Trend	1–2 servings/wk	≥2 servings/wk	P Trend
1: Age-Adjusted	1.00 (REF)	1.17 (0.87, 1.56)	$1.17\ (0.87, 1.56) \qquad 1.04\ (0.75, 1.46) \qquad 1.02\ (0.74, 1.41)$	1.02 (0.74, 1.41)	0.544
2: Age + Baseline Risk Factors	1.00 (REF)	1.05 (0.77, 1.44)	1.05 (0.77, 1.44) 0.92 (0.64, 1.33) 0.95 (0.67, 1.35)	0.95 (0.67, 1.35)	0.627
3: Model 2 + Dietary Factors	1.00 (REF)	1.04 (0.76, 1.42)	1.04 (0.76, 1.42) 0.90 (0.62, 1.30) 0.92 (0.64, 1.32)	0.92 (0.64, 1.32)	0.569

Model 2: Multivariate model adjusted for age, BMI, ethnicity, education, treated diabetes, systolic blood pressure, treated hypertension, prior CVD, and smoking.

Model 3: Multivariate model adjusted for covariates in Model 2 and alcohol use, total energy intake, fruit/vegetables intakes, fiber intake.

CI: confidence intervals