Dietary factors and incident atrial fibrillation: the Framingham Heart Study[1–3]

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ABSTRACT

Background: There have been conflicting reported associations between dietary factors and incident atrial fibrillation (AF).

Objective: We evaluated associations between consumption of alcohol, caffeine, fiber, and polyunsaturated fatty acids (PUFAs) and incident AF in the Framingham Heart Study.

Design: Participants without AF ($n = 4526$; 9640 examinations; mean age: 62 y; 56% women) from the original and offspring cohorts completed food-frequency questionnaires and were followed prospectively for 4 y. We examined the associations between dietary exposures and AF with Cox proportional hazards regression.

Results: A total of 296 individuals developed AF (177 men, 119 women). In multivariable analyses, there were no significant associations between examined dietary exposures and AF risk. Hazard ratios (HRs) for increasing quartiles of dietary factors were as follows: for alcohol, 0.73 (95% CI: 0.5, 1.05), 0.85 (95% CI: 0.61, 1.18), and 1.12 (95% CI: 0.83, 1.51) (P for trend = 0.48); for caffeine, 0.84 (95% CI: 0.62, 1.15), 0.87 (95% CI: 0.64, 1.2), and 0.98 (95% CI: 0.7, 1.39) (P for trend = 0.84); for total fiber, 0.86 (95% CI: 0.61, 1.2), 0.64 (95% CI: 0.44, 0.92), and 0.81 (95% CI: 0.54, 1.2) (P for trend = 0.16); and for n−3 (omega-3) PUFAs, 1.11 (95% CI: 0.81, 1.54), 0.92 (95% CI: 0.65, 1.29), and 1.18 (95% CI: 0.85, 1.64) (P for trend = 0.57; quartile 1 was the reference group). In exploratory analyses, consumption of >4 servings of dark fish/wk (5 cases and 21 individuals at risk) was significantly associated with AF risk compared with the consumption of <1 serving of dark fish/wk (HR: 6.53; 95% CI: 2.65, 16.06; $P < 0.0001$).

Conclusions: Consumption of alcohol, caffeine, fiber, and fish-derived PUFAs was not significantly associated with AF risk. The observed adverse association between the consumption of dark fish and AF merits further investigation. Our findings suggest that the dietary exposures examined convey limited attributable risk of AF in the general population. *Am J Clin Nutr* 2011;93:261–6.

INTRODUCTION

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice (1) and conveys increased risks of stroke, dementia, heart failure, and overall mortality (2). Its increasing prevalence poses great challenges to public health and the health care system (3). Therefore, identifying novel, modifiable risk factors for AF is a priority for preventive efforts (4). Lifestyle factors, in particular dietary intake, have been recognized as important, modifiable risk factors for cardiovascular disease (CVD). Studies have shown that dietary components, such as alcohol, caffeine, fiber, and fish-derived long-chain polyunsaturated fatty acids (PUFAs), influence CVD morbidity and mortality (5–8).

However, the effect of dietary factors on risk of AF is not well established. The associations between AF risk and alcohol and caffeine intakes have had conflicting results (9–13). Reports on the relation of fish and fish-derived fatty acid intakes on AF risk have also been inconsistent: studies have shown an alternately protective effect (14) or null to unfavorable relation (15–17). The association between dietary fiber intake and incident AF is largely unexplored. Thus, whether dietary factors predispose individuals to AF risk remains uncertain. In the setting of a community-based cohort study, we conducted longitudinal analyses of the associations of alcohol, caffeine, fiber, and fish-derived n−3 PUFA intakes with incident AF.

SUBJECTS AND METHODS

Study design

The Framingham Heart Study (FHS) is a longitudinal study that was initiated in 1948 to identify CVD risk factors. Offspring of Original cohort participants and their spouses were recruited to participate in the Framingham Offspring Study in 1971. The detailed design and methodology of the study have been pre-

viously described (18, 19). We selected participants who attended the Original Cohort 20th ($n = 1401$; 1986–1989) or 22nd ($n = 1166$; 1991–1993) examinations and the Offspring Cohort fifth ($n = 3799$, 1991–1995), sixth ($n = 3532$; 1996–1997), or seventh ($n = 3267$; 1998–2001) examinations. FHS participants who resided in institutional facilities ($n = 328$), were <45 y of age ($n = 809$), lacked clinical covariates ($n = 372$), had an invalid ($n = 599$) or incomplete food-frequency questionnaire (FFQ) ($n = 708$), or had prevalent AF at the baseline ($n = 378$) were excluded. A total of 4526 participants ($n = 9640$ examinations) were included in the final analyses. The study protocol was approved by the Boston University Medical Center Institutional Review Board. Written informed consent was obtained from participants.

Case and clinical ascertainment

AF was ascertained from interim medical evaluations at hospitals and external clinicians. The first AF event was recorded during up to two 4-y follow-up intervals. AF was validated by FHS cardiologists who reviewed and classified all available electrocardiograms from FHS clinic and outside records.

Clinical covariates

The FHS clinical examination includes an assessment for AF cardiovascular risk factors and is well described elsewhere (20). Body mass index was determined by weight (in kg) divided by height squared (in m). Seated systolic blood pressure was measured twice by the FHS physician and averaged. Hypertension treatment was determined by self-report. A heart murmur was considered significant if any diastolic murmur or ≥3 of 6 intensity systolic murmurs were auscultated by a Framingham clinic physician. Cardiovascular disease and heart failure were adjudicated by a panel of 3 investigators by using previously published criteria (20).

Dietary assessment

Dietary intakes were assessed by a validated 126-item semiquantitative FFQ (21). Participants were asked to report the frequency of consumption of listed foods during the previous year. Nutrient intakes were determined by multiplying the frequency of consumption for each food item by the nutrient content of the portion. Data from the FFQ were considered valid if <13 food items were missing and the total energy intakes reported by men and women were ≥600 and <4200 kcal/d for men or <4000 kcal/d for women. Alcohol intakes (g/d) were determined from beer, wine, and liquor consumption. Caffeine ingestion was determined from coffee, tea, and caffeinated beverage intake. Total fiber intakes were calculated from cereals, fruit, vegetables, and legumes. Salmon, swordfish, bluefish, mackerel, and sardines were classified as dark fish. Canned tuna consumption was reported separately. Eicosapentaenoic acid and docosahexaenoic acid were grouped as n−3 PUFAs. Linoleic acid and arachidonic acid were grouped as n−6 PUFAs.

Statistical analyses

Descriptive statistics were calculated for demographic characteristics, clinical risk factors, and each dietary factor for men and women. Dietary factors were organized into quartiles on the basis of the total sample. Tests for trend across categories of dietary factors were based on Cox proportional hazards regression by assigning the median intake for each quartile category to each individual in that category and then treating it as a continuous variable. The numbers of AF cases and the total number of person-years of follow-up were computed for each quartile. Cox proportional hazards regression analysis, which was shown to be robust applied to pooled data (22), was then used to generate age-, sex- and energy-adjusted and multivariable-adjusted hazards ratios of AF for each quartile of the dietary risk factors by using the lowest quartile as the reference group. The multivariable models included age, sex, energy intake, body mass index, systolic blood pressure, hypertension treatment, electrocardiographic PR interval, significant heart murmur, and history of heart failure on the basis of a previously published Framingham AF risk prediction model (20). We conducted a series of prespecified secondary analyses. We checked for interactions between sex and each dietary risk factor and showed no substantive evidence of effect modification. Considering the potential threshold effects for alcohol exposure (10, 11), we classified individuals into moderate-to-heavy alcohol drinker and nondrinker groups by using 35 g alcohol/d (equivalent to 3 drinks/d) as the cutoff for men and 25 g alcohol/d (equivalent to 2 drinks/d) as the cutoff for women. Then, we compared AF risk between the 2 groups. The proportionality of hazards assumption was not violated. All analyses were conducted with SAS for Windows, version 9 (SAS Institute, Cary, NC).

RESULTS

Of the 9640 person examinations representing 4526 individuals included in the analysis, the mean age of participants was 62 ± 10 y, and 56% of participants were women. Baseline characteristics and dietary intakes are presented in **Table 1** (*see* supplemental Table 1 under "Supplemental data" in the online issue for intakes of specific sources of fiber, alcohol, and caffeine). During the 4-y follow up, 296 cases of incident AF were identified (177 men and 119 women). In AF cases, there were potentially 28 individuals with lone AF aged <66 y and without a history of prevalent myocardial infarction, heart failure, significant heart murmur, hypertension, and electrocardiographic left ventricular hypertrophy.

Age-, sex-, and energy-adjusted and multivariable-adjusted associations between dietary factors and AF are described in **Table 2**. We did not observe significant associations between the selected dietary risk factors and incident AF (*P* for trend = 0.48 for alcohol, 0.84 for caffeine, 0.16 for fiber, and 0.57 for n−3 PUFAs, respectively). We further showed that moderate-to-heavy alcohol consumption was associated with a 1.35-fold risk or AF than nondrinkers, albeit without significance (95% CI: 0.97, 1.86; *P* = 0.07). In further analysis, the exclusion of participants who took fish-oil supplements (3.75% of participants) did not substantially alter the association between n−3 PUFAs and AF risk. There were no significant associations of other types of dietary fat including saturated fatty acids, monounsaturated fatty acids, total PUFAs, and n−6 PUFAs with AF risk (*see* supplemental Table 2 under "Supplemental data" in the online issue). The results of our primary analyses were not significantly altered after the exclusion of participants with prevalent or interim CVD ($n = 965$) (data not shown).

TABLE 1
Characteristics of participants at baseline[1]

	Men (n = 4231 examinations)	Women (n = 5409 examinations)
Clinical characteristics		
Age (y)	62.0 ± 9.8[2]	62.8 ± 10.4
BMI (kg/m^2)	28.3 ± 4.2	27.1 ± 5.5
Systolic blood pressure (mm Hg)	131 ± 18	130 ± 21
Current smoker (%)	14	15
Moderate-to-heavy alcohol drinker (%)[3]	15	9
Heart failure (%)	1	1
Significant heart murmur (%)	3	3
PR interval (ms)	170 ± 3	161 ± 2
Diabetes (%)	14	10
Hypertension treatment (%)	31	30
Dietary factors		
Total energy (kcal/d)	1951 ± 643	1724 ± 559
Total fiber (g/d)	18.5 ± 7.9	18.6 ± 8.0
Alcohol (g/d)	14.7 ± 19.3	6.6 ± 11.3
Caffeine (mg/d)	274 ± 214	232 ± 194
Saturated fatty acid (g/d)	23.0 ± 10.8	19.8 ± 9.1
Monounsaturated fatty acid (g/d)	24.9 ± 11.1	20.9 ± 9.1
PUFA (g/d)	12.4 ± 5.6	11.3 ± 5.1
n−3 PUFA, 20:5 and 22:6 (mg/d)	264 ± 244	268 ± 244
n−6 PUFA, 20:4 and 18:2 (g/d)	1.2 ± 0.5	1.3 ± 0.5
Fish intake (servings/wk)	1.9 ± 1.7	1.9 ± 1.7
Dark fish (servings/wk)	0.4 ± 0.6	0.3 ± 0.6
Canned tuna fish (servings/wk)	0.9 ± 1.1	1.0 ± 1.1
Shrimp and shellfish (servings/wk)	0.3 ± 0.4	0.3 ± 0.4

[1] PUFA, polyunsaturated fatty acid.

[2] Mean ± SD (all such values).

[3] Defined as >35 g alcohol/d for men and >25 g alcohol/d for women.

We conducted secondary analyses to test the associations between total fish and types of fish intakes and AF risk. We did not observe a significant association between total fish intake and AF risk. However, participants who consumed >4 servings of dark fish/wk were at increased risk of developing AF (hazard ratio: 6.53; 95% CI: 2.65, 16.06; $P < 0.0001$), as shown in **Table 3**. In contrast, there were no significant associations between canned tuna fish, shrimp and shellfish, or other fish and risk of AF (*see* supplemental Table 3 under "Supplemental data" in the online issue). We also examined the sources of fiber and types of grain and showed that neither fibers from cereals, vegetables, fruit, legumes, nor whole or refined grains were associated with incident AF (*see* supplemental Table 4 under "Supplemental data" in the online issue).

Because of the largely negative results, we post hoc examined the study's statistical power. We had 80% power to detect a hazard ratio ≥1.65 when the risk of AF in the first quartile of a given nutrient was compared to risk of AF in the fourth quartile of that nutrient with the assumption of an increasing association between intake and risk by using Cox proportional hazards regression analysis. For nutrients with inverse associations with AF risk, we had 80% power to detect a hazard ratio ≥0.67 when risk of AF in the first quartile of a given nutrient was compared to risk of AF in the fourth quartile of that nutrient.

DISCUSSION

In a longitudinal analysis conducted in the FHS, we observed little evidence of an association between dietary exposures from alcohol, caffeine, fiber, and fatty acids and incident AF during 4-y of follow up. In exploratory analyses, we observed that the high weekly consumption of dark fish was associated with a significantly increased risk of AF.

Acute alcohol intake and binge drinking have been related to AF (23, 24). Epidemiologic data of the long-term relation of alcohol intake have been inconsistent. Data from the early analysis of the FHS and the Cardiovascular Health Study showed no effect of alcohol intake on AF (9, 25). In recent analyses from the FHS, moderate-to-heavy alcohol consumption (≥3 drinks/d; ≈36 g alcohol) was significantly associated with increased AF risk in men (11). The association with the consumption of ≥2 drinks/d (equivalent to 25 g alcohol/d) and AF risk also has been identified in women (10). In our study, we observed only a marginal association between moderate-to-heavy drinking and increased risk of AF, possibly because of a small group of moderate-to-heavy drinkers in this population (only 9–15% of women and men in our cohort). Whereas prior evidence suggested that moderate-to-heavy drinking contributes to AF risk, the evidence from our study could neither confirm nor rule out that hypothesis. The arrhythmogenicity of chronic alcohol exposure may stem from alcoholic cardiomyopathy (26), increased oxidative stress, neurohormonal activation, and altered calcium homeostasis (27).

Caffeine is widely present in many dietary sources and may mediate AF by resulting in neurohormonal stimulation and sympathetic activation (28, 29). The clinical effect of intakes of caffeine from coffee, tea, and caffeinated soda on AF remains inconclusive. In young healthy participants in a clinical trial, acute ingestion of caffeinated instant coffee did not result in supraventricular arrhythmias (30). In contrast, an acute increase in coffee intake was associated with the recurrence or persistence of AF in patients with a first episode of AF (31). As for the habitual intake, our study and a Danish cohort showed no association of daily caffeine intake with incident AF (12). However, one study identified moderate coffee consumption (1–4 cups coffee/d) as a contributor to AF risk (32), whereas another study showed that caffeine was associated with less successful cardioversion in participants with hypertension (13). Further studies are necessary to clarify the relation of caffeine exposure to risk of incident and recurrent AF in healthy individuals and patients with a predisposition for AF.

The consumption of whole grains and dietary fiber, especially cereal fiber, reduces CVD morbidity and mortality (33, 34). The rich contents of fiber, vitamins, minerals and various phytochemicals in whole grains (35) decrease inflammation and oxidative stress (36). High intakes of whole grains also are associated with lower risk of death attributed to inflammatory diseases (37). Because emerging evidence indicates that inflammation and oxidative stress may play a role in the pathophysiology of AF (38), the high intake of whole grains and fiber may have an antiarrhythmic potential. As an important source of dietary magnesium, whole grains may provide additional protection because magnesium has been suggested to be effective in the acute management of rapid AF in clinics (39). Our data did not support the hypothesis of an antiarrhythmic relation between

TABLE 2
Risk of atrial fibrillation according to quartile (Q) of nutrient intake[1]

	Q1	Q2	Q3	Q4	P for trend
Alcohol (g/d)	0 (0–0)[2]	2 (1–3)	7 (3–13)	29 (13–161)	—
No. of cases/participants	107/2947	39/1886	56/2398	94/2409	—
Person-years of follow-up	11,154	7301	9238	9193	—
Age, sex, and energy adjusted	1 (reference)[3]	0.71 (0.49, 1.03)	0.81 (0.58, 1.12)	1.10 (0.82, 1.48)	0.59
Multivariable adjusted[4]	1 (reference)	0.73 (0.50, 1.05)	0.85 (0.61, 1.18)	1.12 (0.83, 1.51)	0.48
Caffeine (mg/d)	23 (0–82)	142 (82–186)	347 (186–366)	452 (366–1203)	—
No. of cases/participants	89/2410	77/2410	71/2410	59/2410	—
Person-years of follow-up	9153	9168	9293	9271	—
Age, sex, and energy adjusted	1 (reference)	0.86 (0.64, 1.17)	0.90 (0.65, 1.23)	0.96 (0.68, 1.35)	0.78
Multivariable adjusted[4]	1 (reference)	0.84 (0.62, 1.15)	0.87 (0.64, 1.20)	0.98 (0.70, 1.39)	0.84
Total fiber (g/d)	10 (3–13)	15 (13–17)	20 (17–23)	27 (23–95)	—
No. of cases/participants	72/2407	71/2412	62/2413	91/2408	—
Person-years of follow-up	9180	9198	9331	9176	—
Age, sex, and energy adjusted	1 (reference)	0.88 (0.63, 1.23)	0.67 (0.47, 0.97)	0.85 (0.58, 1.26)	0.28
Multivariable adjusted[4]	1 (reference)	0.86 (0.61, 1.20)	0.64 (0.44, 0.92)	0.81 (0.54, 1.20)	0.16
n−3 PUFA, 20:5 and 22:6 (mg/d)	80 (0–120)	150 (120–200)	250 (200–330)	460 (330–3800)	—
No. of cases/participants	71/2319	80/2500	66/2392	79/2429	—
Person-years of follow-up	8878	9593	9149	9266	—
Age, sex, and energy adjusted	1 (reference)	1.18 (0.86, 1.63)	0.98 (0.70, 1.38)	1.32 (0.95, 1.84)	0.23
Multivariable adjusted[4]	1 (reference)	1.11 (0.81, 1.54)	0.92 (0.65, 1.29)	1.18 (0.85, 1.64)	0.57

[1] PUFA, polyunsaturated fatty acid.
[2] Median; minimum–maximum in parentheses (all such values).
[3] Hazard ratio; 95% CI in parentheses (all such values).
[4] Cox proportional hazards regression model adjusted for age, sex, BMI, systolic blood pressure, hypertension treatment, electrocardiogram, PR interval, significant heart murmur, and heart failure.

whole grains and dietary fiber at the relatively modest amounts consumed in the FHS cohort.

Consumption of fish and fish-derived n−3 PUFAs decreases the risk of sudden cardiac death (7) mainly through preventing cardiac arrhythmia, particularly ventricular fibrillation (40). The anti-arrhythmic effects of n−3 PUFAs could be mediated through their regulation of the calcium channel, eicosanoid metabolism, inflammation, and cardiac muscle metabolism (41). In our study, dark-fish intake and n−3 PUFA intake from fish or fish-oil supplements were not associated with a lower incidence of AF. Our findings are consistent with many earlier cohort studies (15–17) but contradict a previous longitudinal cohort that reported a beneficial association between AF and n−3 PUFA from fish or

fish supplements in elderly participants of the Cardiovascular Health Study (14). The inconsistent results across observational studies may reflect differences in study populations and dietary assessment methodologies. Also, the heterogeneous nature of AF could potentially differentiate individual responses to fish-derived n−3 PUFAs (42, 43). This notion has been supported by observations that showed that the consumption of n−3 PUFAs increases parasympathetic tone (44) and may mediate lone AF risk in susceptible individuals, whereas n−3 PUFAs may have a protective role in older individuals at risk of AF secondary to structural heart disease (45). Divergent associations of fish oil with AF have also been shown in experimental studies that demonstrated that n−3 PUFAs suppress the type of AF

TABLE 3
Risk of atrial fibrillation according to total fish and dark-fish intake

	Frequency of fish intake			
	Never or <1 serving/wk	1–4 servings/wk	>4 servings/wk	P for trend
Total fish				
No. of cases/participants	107/3365	156/5460	33/815	—
Person-years of follow-up	12,872	20,919	3093	—
Age, sex, and energy adjusted	1 (reference)[1]	0.91 (0.71, 1.17)	1.33 (0.89, 1.98)	0.57
Multivariable adjusted[2]	1 (reference)	0.88 (0.69, 1.13)	1.25 (0.84, 1.86)	0.81
Dark fish				
No. of cases/participants	248/8321	43/1298	5/21	—
Person-years of follow-up	31,886	4932	67	—
Age, sex, and energy adjusted	1 (reference)	1.02 (0.74, 1.41)	8.77 (3.61, 21.27)	0.15
Multivariable adjusted[2]	1 (reference)	1.01 (0.72, 1.39)	6.53 (2.65, 16.06)	0.21

[1] Hazard ratio; 95% CI in parentheses (all such values).
[2] Cox proportional hazards regression model adjusted for age, sex, BMI, systolic blood pressure, hypertension treatment, electrocardiogram, PR interval, significant heart murmur, and heart failure.

associated with heart failure–induced atrial structural remodeling but not the type related to atrial tachycardia–induced electrical remodeling in dogs (46).

Interestingly, our data suggest that high consumption of dark fish (>4 servings/wk) paradoxically may be associated with an increased AF risk. Because of the few cohort members in this high-consumption category (21 individuals and only 5 incident cases of AF), our finding may merely represent a chance association. Because high fish intake as part of a healthier diet is often associated with other healthier behaviors, we cannot rule out the possibility of a higher rate of screening and detection of AF in participants with high fish intake, which could have introduced a bias. However, the unfavorable effect on AF risk has also been observed in a Danish population in which the mean intake of fish-derived n−3 PUFAs was higher than that in our population (17). These observations may suggest a true adverse effect of dark fish and fish oil on certain subtypes of AF. In addition, potential toxins such as dioxins and methyl mercury accumulated in certain fish may have a negative effect on cardiac arrhythmia. Nonetheless, these hypotheses require further investigation.

The current study had several limitations. First, dietary information was collected through self-reports by questionnaires. For some dietary factors, such as alcohol intake, potential underreporting may lead to underestimation of the effect of heavy drinking on risk of AF. Likewise, the associations between dietary factors and AF may be small and require larger samples with more events or longer follow-up to detect. The relatively narrow range of intake in the FHS cohort further limited our ability to detect associations between certain dietary exposures, such as fiber and fiber sources, and AF risk. In addition, there may have been threshold effects whereby higher dietary exposure amounts than were observed in our sample may be necessary to affect AF risk. Another consideration is that AF that was asymptomatic, intermittent, or did not lead to a clinical encounter may not have been captured by the FHS investigators. Our participants were middle-aged to elderly and virtually all of European ancestry. The generalizability our data to other races/ethnicities or younger individuals is unknown. Similarly, in our study, we were not able to definitively separate lone AF from AF associated with CVD, which likely involves different disease mechanisms. As a result, the heterogeneous AF in this study may have complicated our ability to detect a potential association between dietary factors and AF in specific subgroups. Finally, the dark-fish finding should be viewed as a hypothesis-generating finding because it may represent a false-positive discovery in the context of an exploratory subgroup analysis.

In conclusion, we did not observe major associations between alcohol, caffeine, fiber, fatty acids, or total fish consumption with incident AF in our community-based study. Our findings also do not support a favorable effect of fish or fish-derived n−3 PUFA on AF risk but rather may suggest an adverse effect of a high weekly consumption of dark fish. Our findings, together with previous inconsistent reports, require further investigation of dietary factors in relation to various subtypes of AF in other cohorts.

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