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Diet and Risk of Atrial Fibrillation: Epidemiologic and Clinical Evidence

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Abstract

Dietary factors might affect the risk of atrial fibrillation (AF), but available studies have provided inconsistent results. In a review of published observational studies and randomized trials, we identified four dietary exposures that had been investigated regarding AF risk: alcohol, fish-derived n-3 polyunsaturated fatty acids, caffeine, and ascorbic acid. Though studies were highly heterogeneous in their design and results, they showed a consistently increased risk of AF in heavy alcohol drinkers, but no risk associated with moderate alcohol intake. High coffee intake was not clearly associated with an increased risk of AF, and a potential U-shaped association (lower AF risk in moderate drinkers) could exist. High intake of fish-derived n-3 polyunsaturated fatty acids from diet or supplements might prevent AF episodes following cardiovascular events, but no consistent evidence supports an effect in primary prevention. Additional large, well-conducted randomized experiments are necessary to address the role of diet in AF prevention.

Keywords

Atrial fibrillation; Diet; Alcohol drinking; Fatty acids, omega-3; Caffeine

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac dysrhythmia affecting more than 2.6 million Americans, with a lifetime risk of 1 in 4.[1] Individuals with AF have six times the risk of stroke and twice the risk of all cause mortality compared to those without AF.[2]

Though structural heart disease underlies most cases of AF,[2] its pathogenesis is not well understood. It is hypothesized that initiation of AF may be due to the effect of specific triggers (e.g. ectopic activity, generally, but not always, in one or more of the pulmonary veins) on a susceptible substrate produced by structural and electrical remodeling of the cardiac tissue that allows the arrhythmia to be maintained.[2] A number of physiopathological processes, including inflammation and fibrosis, might play a contributory role in the initiation of ectopic activity.[3]

Additionally, some evidence suggests that lifestyle, such as physical activity or diet, could affect the risk of developing AF.[4] Among dietary factors, four group foods and nutrients have been studied with respect to incident AF: alcohol; caffeine; fish/fish-derived n-3 polyunsaturated fatty acids (n-3 PUFAs); and ascorbic acid. In this article, we review the

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epidemiologic evidence linking diet with the risk of AF and summarize the potential mechanisms underlying these associations, schematically outlined in Figure 1.

LITERATURE SEARCH METHOD

We searched PubMed from 1950 to June 2010 using the following search string: (Ethanol OR Caffeine OR Fatty Acids Omega-3 OR Fish Oils OR Seafood OR Food and Beverages) AND (Atrial Fibrillation) (all MeSH terms). Only articles published in English or Spanish were considered. Overall, our search resulted in 617 articles. One additional article not captured by our search was added based on bibliographic review.

Of these articles, we eliminated articles that were not done in humans (n=267), did not have AF as an outcome (n=130), did not consider dietary exposures (n=108), were case reports/series (n=23), did not contain data (n=50), were published in a language other than English or Spanish (n=8), or were duplicates (n=2). Additionally, three articles[5–7] with results that were internally inconsistent (the odds ratios, 95% confidence intervals, and p-values contradicted) were excluded from consideration.

After exclusions, 26 articles were left for review. Those 26 covered 4 dietary exposures: alcohol (n=11), fish-derived n-3 PUFAs (n=12), caffeine (n=5), and ascorbic acid (n=1) (articles do not sum to 85 as some covered more than one exposure). Search details are presented in Figure 2.

ALCOHOL INTAKE AND AF

Alcohol is the dietary factor most frequently assessed in relation to AF. In fact, alcohol has been traditionally linked to AF through the “holiday heart” syndrome: AF episodes after periods of intense drinking on weekends or holidays.[8] Although the structural damage caused by alcohol-related cardiomyopathy could account for some AF episodes, “holiday heart” can even occur in those without preexisting structural heart damage.[8] In contrast, moderate alcohol drinking has been shown to be cardioprotective when compared to teetotalers and heavy drinkers.[9, 10] Because of these potentially opposite effects, several epidemiologic studies have investigated the association of alcohol intake with AF risk. Their characteristics and main results are summarized in Table 1.

Epidemiological evidence

Overall, results from these studies are remarkably consistent across types of AF and different study designs. Specifically, it appears that moderate drinking—compared to no drinking—does not increase risk of AF but heavy drinking/alcohol abuse does.

Studies have defined exposure to alcohol in different ways: (1) typical intake[11–17]; (2) acute intake[18–20]; and (3) alcohol abuse.[18, 19, 21] We describe each type separately.

Typical Intake of Alcohol—All studies included beer, wine, and hard liquor when assessing alcohol intake. Some studies assessed typical alcohol consumption at one time point,[5, 11–13, 17] while other studies utilized repeated measures.[14–16] Only one study considered former alcohol use as a category of alcohol intake.[15]

Most studies found a positive association between high levels of alcohol consumption and AF[11–13, 16] Of these, three studies investigated sex-specific associations[12–14] (two with sex-specific alcohol cutpoints[13, 14]) and one did not.[11]

An analysis of the US Framingham Heart Study found 33% increased odds of incident AF for those with highest consumption (>36 g/day) versus those with no consumption (95% CI: 1.01–1.78), without large differences between men and women.[12] Two prospective studies conducted in Denmark found an increased risk of AF with higher alcohol intake in men but no association in women – the first, the Danish Diet, Cancer and Health Study, found a dose-response effect (p for trend = 0.04) with a 46% increase in risk (95% CI: 1.05–2.04) in the highest quintile of alcohol intake compared to the lowest[13] and the second, the Copenhagen City Heart Study, showed a dose-response relationship (p for trend = 0.05) with a 45% increase in risk (95% CI 1.02–2.04) in men who consumed >36 drinks/week (>5 drinks/day) compared with <1 drink/week, but no increased risk with lower consumption.[14]

An additional case-control study conducted in the US found that rates of heavy drinking in cases of incident AF were significantly higher than in controls (62% vs. 33%).[11] This study defined heavy drinking as either ≥70 mL alcohol/day, documented alcohol abuse, or obvious intoxication at admission; not heavy drinkers drank <70 mL alcohol/day or were former alcohol abusers.

An analysis of the prospective Cardiovascular Health Study did not find an association between alcohol intake and AF risk, but in this older population (>65 years old at baseline) few individuals had a high alcohol intake.[15] A case-control study in the US showed an increased risk of atrial flutter (but not AF) in daily drinkers younger than 60 compared to non-drinkers (OR=17, 95% CI 1.6–192.0), and no association in older individuals.[17] A potential explanation for the lack of association in this study is the limited sample size (125 AF and 70 atrial flutter cases.

Finally, an analysis of the Women's Health Study, which included initially healthy women, found that ≥2 drinks/day (versus no alcohol) resulted in 49% increased risk for AF (HR=1.49, 95% CI: 1.05–2.11) after adjustment for multiple confounders.[16] This is the only study that found an increased risk of AF among heavy drinkers among women. Potential differences with the Danish studies that might explain the association are the larger number of women (and AF cases) who consumed ≥2 drinks/day, diversity in the patterns of alcohol consumption, and use of varied tools for assessment of alcohol intake.

Overall the studies are quite consistent, showing an elevated risk of AF among individuals with high intake of alcohol. This association appears to be stronger in men, who have higher average alcohol intake. No evidence exists that the alcohol/AF association differs by alcohol type[13–15] or that there is an age-by-alcohol interaction.[16, 17] Results were similar across differing study designs, indicating that recall bias was probably not an issue. Figure 3 shows the association of alcohol intake with AF risk in prospective studies

Acute Intake—Three studies considered acute alcohol intake in the week prior to hospitalization for AF.[18–20] A prospective Finnish study in 98 cases of AF found no association between alcohol intake and recurrence of AF. [18] In a case-control study, also in Finland, researchers found a dose-response (categorized recent alcohol intake as 0, 1–30, and >30 g/day) relationship in lone AF cases but not in cases of incident AF with known etiology.[20] Finally, a case-control study compared patients with recurrent AF to both hospital controls and population controls. There was no association in women, no association comparing men with population controls, but there was higher alcohol use in male cases when compared with hospital controls.[19]

Potential reasons for these discrepancies include differential associations by sex and recall bias. Two of the studies did not report sex-specific associations and both showed null associations when considering all cases of AF (vice idiopathic only).[18, 20] Failure to stratify by sex might

obscure a true association if the effect of acute alcohol intake differs in women and men. Also, case-control studies in subjects with incident AF may be subject to recall bias. AF patients believe alcohol is a precipitating factor of their AF[22] and differential exposure misclassification may bias associations upwards.

Alcohol Abuse—Three studies considered alcohol abuse as an exposure, defined as either alcoholism in men[21] or responses to the CAGE questionnaire[23] in both sexes.[18, 19] A prospective study in Swedish men showed increased odds of incident AF among alcoholics (OR=1.21, 95% CI: 1.02–1.42) in age-adjusted analysis.[21] This result is not likely due to recall bias as alcoholism was established via official registries. In a case-control study[19] men (but not women) with recurrent AF had higher odds of alcohol abuse (OR=3.25, $p<0.05$) compared with controls. Finally a prospective study[18] of both men and women showed null associations between alcohol abuse and recurrent AF. It should be noted, however, that the CAGE questionnaire has been shown to be less sensitive in women,[24] which might explain some of the inconsistencies.

Biological mechanisms

Several potential biological mechanisms may explain how alcohol consumption can affect risk of AF, although the actual mechanism is unknown (Figure 1). As previously stated, moderate alcohol consumption is associated with decreased risk of coronary disease.[9, 10] Because previous cardiac events can result in structural damage conducive to AF, moderate alcohol intake may be protective. However, heavy drinkers are prone to cardiomyopathy,[25] which might lead to heart failure and a consequently increased risk of AF. Additionally, a study showed that those with a previous history of alcohol-induced AF have impaired vagal heart rate and increased beta-adrenoceptor density when exposed to alcohol[26] implying that alcohol may be proarrhythmic in these individuals. Alcohol's proarrhythmic properties are further supported by evidence that alcohol increases QT interval prolongation,[27] though it is unclear how this would relate to an increased risk of AF.

FISH-DERIVED N-3 FATTY ACIDS AND AF

Ample evidence suggests that long-chain fish-derived n-3 polyunsaturated fatty acids (PUFAs) could reduce the risk of cardiovascular disease, particularly cardiac sudden death.[28] This protection could be due to an anti-arrhythmic effect of fish-derived n-3 PUFAs via stabilization of the myocyte cell membrane. Therefore, it has been hypothesized that n-3 PUFAs could also reduce the risk of AF through their anti-arrhythmic effect. Several epidemiologic studies have explored this association. Their characteristics and results are summarized in Table 2.

Epidemiologic evidence

Epidemiologic studies have focused on four exposure measures and three outcomes. Exposure measures are: (1) fish consumption measured via food-frequency questionnaires (FFQ) as a proxy for fish-derived n-3 PUFA intake; (2) fish-derived n-3 PUFA consumption estimated via FFQ; (3) fish-derived n-3 PUFAs as measured in blood plasma or cell membranes; and (4) fish-derived n-3 PUFA supplements. The three outcomes are incident/idiopathic AF, postoperative AF, and post myocardial infarction (MI) AF.

Incident/Idiopathic AF—An analysis of the US-based Cardiovascular Health Study including individuals older than 65 found that higher consumption of tuna or other non-fried fish was associated with a lower risk of AF (5+ servings/week vs. <1 serving/month, RR=0.7, 95% CI 0.53–0.93).[29] No association was found for fried fish or fish sandwiches. However, three prospective studies could not replicate this association. In an analysis of post-menopausal American women enrolled in the Women's Health Initiative, the HR (95% CI) of AF in women

who consumed 2 or more servings/week of non-fried fish compared to those with less than 0.5 servings/week was 1.02 (0.73 – 1.42). In this same analysis, intake of fish-derived n-3 PUFAs was not associated with AF risk (RR=1.02, 95% CI: 0.73 – 1.44, comparing ≥ 0.16 g/day vs. < 0.05 g/day).[30] Similar results were observed in Dutch individuals participating in the Rotterdam Study (RR=1.17, 95% CI: 0.87–1.57, comparing ≥20 grams fish/day vs. no fish intake, and RR=1.18, 95% CI 0.88–1.57, comparing ≥144 mg/d of n-3 PUFAs vs. ≤43 mg/d).[31] Finally, an analysis of the Danish Diet, Cancer and Health Study reported an increased risk of AF among those with the highest intake of fish-derived n-3 PUFAs and AF risk (RR=1.34, 95% CI 1.02–1.76, comparing extreme quintiles).[32]

Two studies have explored the associations between various fish-derived n-3 PUFAs (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA)) measured in erythrocyte membranes or blood serum, as biomarkers of fish intake, and AF risk, with mixed results. A Finnish prospective study found an inverse association between blood serum levels of total fish-derived n-3 PUFAs (RR=0.5, 95% CI 0.3–0.8, comparing extreme quartiles) and DHA (RR=0.51, 95% CI: 0.32 - 0.82, comparing extreme quartiles) with incident AF but no association was seen for other n-3 PUFAs (EPA, DPA) in this population.[33] In contrast, a recent small case-control study in Italy found that levels of n-3 PUFA in erythrocyte membranes were higher in cases of idiopathic AF than in controls (31.4% vs. 23.5%, p<0.001).[34] A major limitation of this later study is the lack of adjustment for potential confounders.

Several potential reasons might explain these discrepancies across studies. Assessment of fish intake using food frequency questionnaires may not be an accurate measure of fish-derived n-3 PUFA intake, diluting measures of association. Additionally, heterogeneity in case definition (AF hospitalization,[32] AF referred for ablation,[34] or AF detected through routine electrocardiogram (ECG) monitoring[29–31]) might lead to inconsistent results across studies if different types of AF cases have different risk profiles.

Post-operative AF—Various studies, mostly randomized trials, have explored the effect of fish-derived n-3 PUFA supplements on the risk of post-operative AF – defined as the first ECG-diagnosed episode of AF after a cardiac surgery.

A randomized trial in Icelandic subjects undergoing coronary artery bypass graft (CABG) surgery and/or valvular repair surgery administered 2.2 g of EPA+DHA or placebo pre- and post- surgery and determined the association with post-operative AF[35] - incident rates were 52.4% in the supplement group versus 52.1% in the placebo group. A similar study in the UK including patients undergoing CABG surgery administered 2 g/day fish-derived n-3 PUFAs pre-and post-surgery or placebo. No differences in post-operative AF were found between groups.[36] In contrast, a third randomized trial in Italy found that 2 g/day of fish-derived n-3 PUFAs pre-and post-surgery was associated with a reduction in the incidence of post-operative AF (15.2% in the treatment vs. 33.3% in the placebo group, p=0.01).[37]

Two observational studies have explored whether supplementation with n-3 PUFAs reduced the risk of post-operative AF. In an Italian study, the use of at least 1 g/day of fish-derived n-3 PUFA was associated with lower risk of early (e.g., before 8 weeks, 31.0% vs. 47.3%, p=0.008) post-operative AF but not late (e.g., after 8 weeks, 11.9% vs. 15.2%, p=0.43) post-operative AF.[38] A second study in the US found less post-operative AF in subjects receiving fish-derived n-3 PUFA supplementation at some point during their follow-up.[39] However, a major limitation of this last study is its potential for ‘immortal time bias’, since an individual who did not develop post-operative AF was more likely to be considered exposed to n-3 PUFAs.[40]

Notably, supplementation was not standardized across interventions and supplements differed with respect to amount and ratios of the fish-derived n-3 PUFAs. Given the differential associations by fatty acid type shown in observational studies,[33] this distinction may be important and could explain the mixed results for fish-derived n-3 PUFAs and post-operative AF. Additionally, follow-up time differed across trials, which might be relevant since some studies have found different associations for early and late post-operative AF;[38, 39] non-standard follow-up times may lead to mixed results.

Post-MI AF—One Italian study assessed the association of prescriptions for low dose n-3 fatty acids with AF following myocardial infarction in 3,242 patients.[41] The study found an 85% lower risk of AF in those who had at least one prescription for n-3 fatty acids either before or after their MI compared to those patients who had never received a prescription. A major limitation, however, is that this study results might be affected by immortal time bias.[40] The fish-derived n-3 PUFA supplement/post-MI AF relationship has not been studied in other populations.

Biological mechanisms

Fish-derived n-3 PUFAs may prevent AF through several mechanisms: (1) preventing structural heart damage; (2) inhibiting inflammation; and (3) inhibiting electrical currents via myocyte cell membrane stabilization (Figure 1). Previous research has shown that fish-derived n-3 PUFAs protect against coronary heart disease (CHD),[42, 43] particularly cardiac sudden death.[44] As such n-3 PUFAs may prevent the structural heart damage that is often a precursor to AF. Additionally, fish-derived n-3 PUFAs may inhibit the inflammatory triggers that occasionally initiate the ectopic activity in AF.[3] Even once that electrical activity has been stimulated, fish-derived n-3 PUFAs may inhibit the fast, voltage-dependent sodium current and the L-type calcium currents[45, 46] that would allow the arrhythmia to be sustained.[47]

CAFFEINE INTAKE AND AF

Caffeine is a known stimulant and can increase heart rate. Anecdotal evidence points to caffeine consumption as a trigger of AF[22, 48, 49] but observational studies have had conflicting results. Results of observational studies exploring this association are summarized in Table 3.

Epidemiological evidence

Studies have investigated the association between caffeine intake and two types of AF: (1) overall incident AF; and (2) post-MI AF. In these studies, incident AF was defined as the first diagnosed AF occurrence. Usually, but not always, these diagnoses were done in hospitalized patients. Post-MI AF was defined as the first hospital-diagnosed episode of AF after hospitalization for MI. Each of these outcomes will be addressed separately.

These studies used hospitalization or outpatient records for AF ascertainment, which lead to underascertainment of AF since an important proportion of AF patients will never experience any symptoms.[50] Thus, results from these studies might not be generalized to all AF cases.

Incident AF—Most studies conducted to date suggest that caffeine intake is not associated with incident AF. An investigation in the Danish Diet, Cancer and Health Study, a large cohort in Denmark, showed independence between caffeine intake and AF incidence (HR 0.9, 95% CI 0.7–1.2, comparing extreme intake quintiles).[51] Similar results were found in a cohort study of Swedish men.[21] Finally, an analysis of the Women's Health Study also supported lack of association, though its results supported a potential U-shaped association (lowest AF risk in the 2nd and 3rd quintiles of caffeine intake, $p<0.01$ for quadratic trend).[52] No differences were

found for different dietary sources of caffeine. Figure 4 summarizes results from prospective studies exploring the association of caffeine intake and AF incidence.

One explanation why these studies have failed to find an association is the potential for exposure misclassification, particularly in studies that used habitual coffee intake as the main exposure. [21] Using coffee as a surrogate for total caffeine intake can lead to exposure misclassification bias,[53] which would be expected to bias results towards the null (no association).

Post-MI AF—One Swedish study assessed the association of caffeine intake with AF following myocardial infarction in 1,369 patients.[54] The study found a non-significant 33% lower risk of AF with an intake of at least 7 cups/day compared to <1 cup/day (95% CI: 0.33–1.34). This cohort study used coffee as an exposure (vice caffeine) but did use standardized portion size (1 cup = 1dL) and distinguished between boiled, unfiltered, and filtered coffee.

Biological mechanisms

There are two potential mechanisms that may explain caffeine's effect on atrial fibrillation: (1) antioxidants in tea and coffee; and (2) proarrhythmic effects of caffeine (figure 1). Tea and coffee are predominant sources of caffeine,[52] and are high in antioxidants[55] which may reduce the risk of AF.[56] In contrast, caffeine has been shown to have many proarrhythmic effects including changes in the activation of cardiac channels.[57, 58] Thus, while the mechanism driving the relationship between caffeine intake and AF is unclear, it may be multifactorial, and could have competing effects.

OTHER DIETARY FACTORS AND AF

Our search revealed one other dietary exposure that is associated with AF post CABG: ascorbic acid.[59] It was hypothesized that ascorbic acid may reduce the inflammation and oxidative stress that potentially precede AF. In a trial including 100 post-CABG patients, those who received oral doses ascorbic acid (2 g before surgery, and 1g/day for 5 days after surgery) in addition to beta blockers pre- and post-surgery had 4% incidence of AF whereas those who received beta blockers only had 25% incidence (OR 0.1, 95% CI 0.02–0.4).[59] This specific hypothesis, however, has not been tested in other populations.

PUBLIC HEALTH IMPLICATIONS AND FUTURE DIRECTIONS

Existing evidence does not demonstrate a higher risk of AF in moderate alcohol drinkers. Given other potential cardiovascular benefits of moderate alcohol drinking, our review suggests that moderate alcohol should not necessarily be restricted in those at risk of AF. Heavy drinking, however, remains a consistent risk factor for AF (and other diseases) and should be considered in strategies for the prevention of AF in the general population.[4]

The relationship between fish-derived n-3 PUFAs and AF is unclear. While a few studies suggest that these fatty acids might have a protective effect for post-operative and post-MI AF, the associations between habitual intake and incident AF were generally null. More evidence is needed before recommendations can be made regarding intake of fish-derived n-3 PUFAs and primary or secondary prevention of AF. Specifically, large, placebo-controlled, blinded randomized trials are necessary before making evidence-based recommendations.

Taken together, studies of the association of caffeine with AF suggested a lack of caffeine effect. Thus, not evidence exists to support a reduction in caffeine intake in the prevention of AF.

Finally, no previous studies have explored whether dietary patterns—associated with different cardiovascular and metabolic outcomes in numerous observational studies—might be associated with the risk of AF. Future studies need to address this gap.

CONCLUSION

Our review shows that higher alcohol intake is consistently related with an increased AF risk, while moderate intake of alcohol and caffeine seem to have no effect. The association between fish-derived n-3 PUFAs and AF was inconsistent, though some evidence exists that these fatty acids might have a protective effect. Further research to clarify the role of diet in the prevention of AF is warranted.

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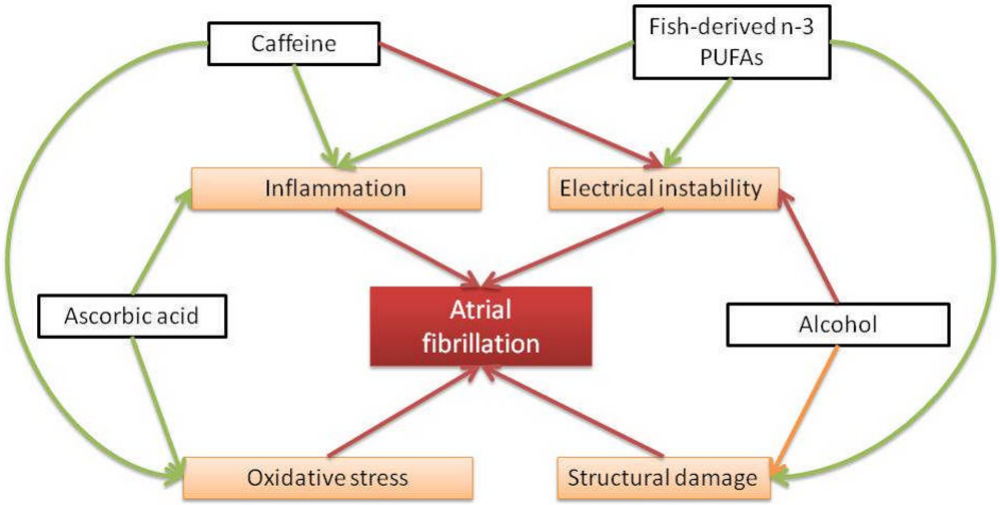

Figure 1.
Interaction of dietary exposures, pathophysiology, and atrial fibrillation. Green arrows represent protective effects (inhibition), red arrows deleterious effects (stimulation), and orange arrows, mixed effects.

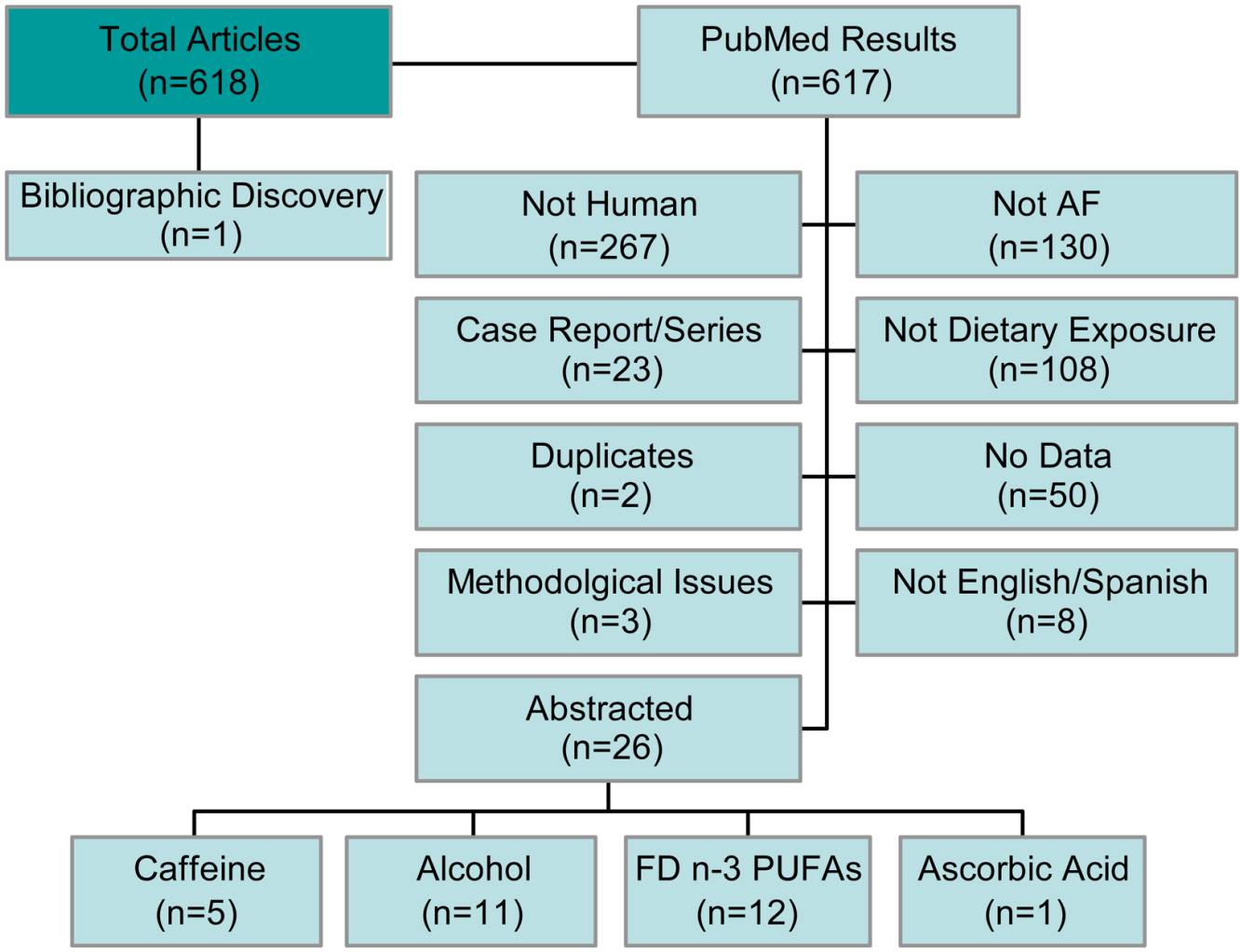

Figure 2.
Flowchart of search results. AF, atrial fibrillation; FD n-3 PUFAs, fish-derived n-3 polyunsaturated fatty acids

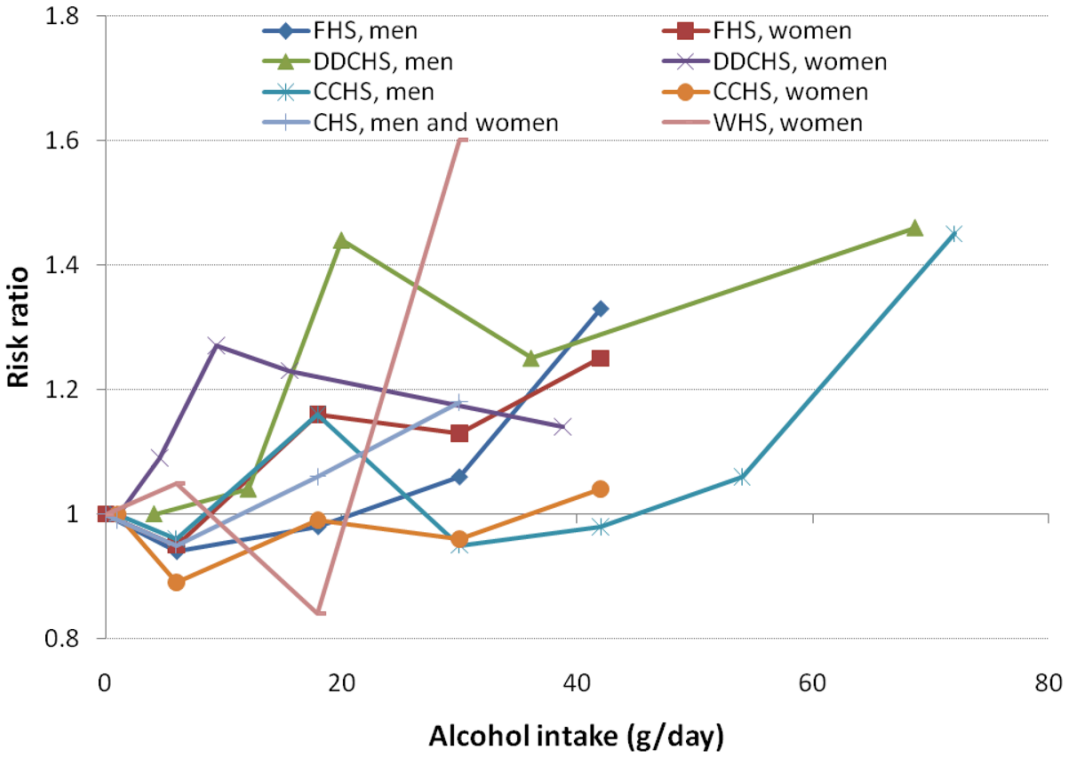

Figure 3.
Risk ratios of AF by alcohol intake (g/day) in prospective studies. FHS: Framingham Heart Study, Djousse, 2004[12]; DDCS: Danish Diet, Cancer and Health Study, Frost 2004[13]; CCHS: Copenhagen City Heart Study, Mukamal 2005[14]; CHS: Cardiovascular Health Study, Mukamal 2007[15]; WHI: Women's Health Study, Conen 2008[16].

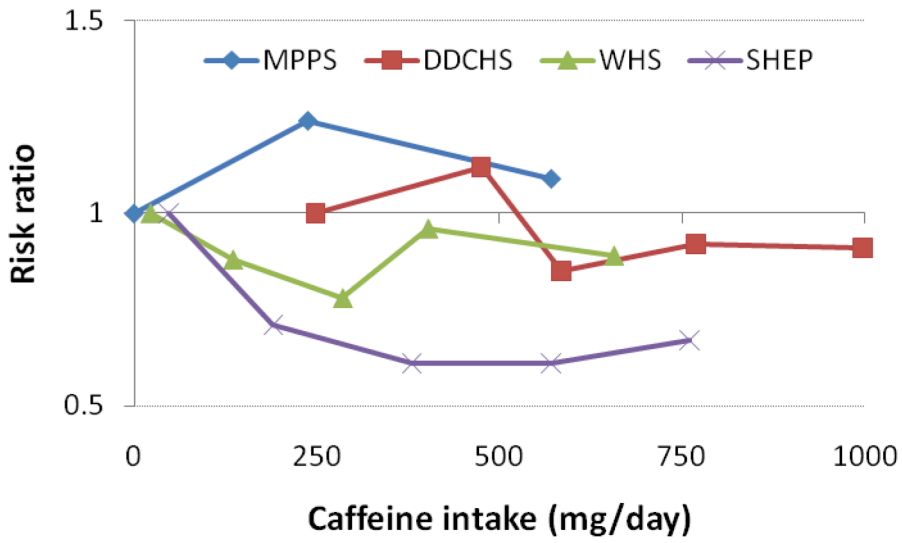

Figure 4.

Risk ratios for AF given caffeine intake (mg/day). MPPS: Multifactor Primary Prevention Study, Wilhelmsen 2001[21] (coffee only); DDCHS: Danish Diet, Cancer and Health Study, Frost 2005[51]; WHS: Women's Health Study, Conen 2010[52]; SHEP: Stockholm Heart Epidemiology Program, Mukamal 2009[54] (coffee only).

Table 1

Selected characteristics of published studies evaluating the association of alcohol intake with atrial fibrillation

Source	Study Population	Study Design	Alcohol Assessment	AF Ascertainment	Follow-up	Total N	AF Events	Main Results	Adjustment Variables
Rich 1985[11]	Both sexes; US subjects; patients hospitalized for acute idiopathic AF and 1:1 age, sex matched inpatient controls	Matched Case- control	Medical record reviews; heavy drinker was ≥70 ml alcohol/day, documented alcohol abuse, or obvious intoxication at admission; not heavy drinker was <70 mL alcohol/day or former alcohol abuser	Incident AF (acute idiopathic AF) as ascertained via discharge diagnoses - most patients had ECGs	N/A	128	64	62% of AF cases reported heavy alcohol use compared to 33% of controls	Age, sex
Koskinen 1987[20]	Both sexes; Finnish subjects; average age = 48; hospitalized cases of AF and age/sex matched acute, hospitalized controls	Matched case- control	Interview regarding amount of alcohol in prior week (grams) and if different from previous weeks; categorized into abstainers, 1–30 g/day, and >30 g/day	Incident AF (idiopathic and known etiology) diagnosed by cardiologist (85% had ECGs)	N/A	200	100	Higher alcohol intake associated with higher risk of lone AF ($p<0.05$) but not AF associated with comorbidities	Age, sex
Koskinen 1990[19]	Both sexes; Finnish subjects; average age 51.5 years; patients hospitalized with recurrent AF, age/sex matched ER controls and age/sex frequency matched community controls	Matched Case- control	Interview regarding amount of alcohol in prior week (grams) and CAGE exam; weekly alcohol categorized into 0, 1–210 grams, and >210 g	Recurrent AF as ascertained by clinical evaluation	None	246	98	No association in women; in men, multivariate analyses showed that cases had higher odds of alcohol abuse (OR=3.25, $p<0.05$) compared with all controls	Age, sex, potassium levels, heart disease, stress/lack of sleep
Koskinen 1991[18]	Both sexes; Finnish subjects; average age 48 years; patients with new onset AF	Cohort	Interview regarding amount of alcohol in prior week, if different from previous weeks, and CAGE exam	Recurrent or chronic AF	4 years	98	39 subjects with recurrences and an additional 7 transitioned to chronic.	No association	None
Wilhelmsen 2001[21]	Men only; Swedish subjects; 47–55 at baseline; population based sample	Cohort	Alcohol abuse data were obtained via registries (yes/no)	Incident AF - Outpatient and Hospitalized AF via ICD-9 codes	25.2 years	7,495	754	Alcohol abuse was associated with increased risk (RR=1.21,	Age

Source	Study Population	Study Design	Alcohol Assessment	AF Ascertainment	Follow-up	Total N	AF Events	Main Results	Adjustment Variables
								95% CI 1.02–1.42)	
Djousse 2004[12]	Both sexes; U.S. subjects; average age 42–50 at baseline; Framingham cohort cases of AF and 1: ≥5 controls matched on age, sex, age at baseline, cohort, HTN, baseline CHF, and MI	Matched case- control of cohort data	Repeated questionnaires; frequency of alcohol intake; g/day averaged from baseline until visit prior to AF onset categorized into 0, 0.1–12, 12.1–24, 24.1–36, >36	Incident AF obtained at study visit or by medical records - all confirmed with ECG	> 50 years	10,333	1,055	No effect with moderate intake. OR of AF in >36 g alcohol/day 1.33 (95% CI 1.01–1.78)	Multivariable
Frost 2004[13]	Both sexes; Danish subjects; average age 56 years; healthy population- based sample	Cohort	FFQ addressing amount (g/day), type (beer, wine, etc.), and frequency (times/ week) of alcohol consumption. Broken out into sex-specific quintiles	Incident AF as identified by hospitalization discharge ICD-8 and ICD-10 codes, outpatient discharge codes after 1/1/95	5.7 years	47,949	556	No association in women. In men, 40% higher risk among those in quintiles 3–5 compared to quintile 1 (p for trend=0.04).	Multivariable
Mukamal 2005[14]	Both sexes; Danish subjects; median age 48–56; healthy, population-based sample	Cohort	Structured questionnaire given at three different time points	Incident AF from 1 of 3 exam visits (ECG) or nationwide hospitalization registries (ICD-9 codes)	>20 years	1,645	1,071	No association in women. In men higher risk among those taking ≥5 drinks/day (HR 1.45, 95% CI 1.02–2.04)	Multivariable
Mukamal 2007[15]	Both sexes; U.S. subjects; age > 65; population-based sample	Cohort	Yearly quantity/ frequency questionnaire (until 1999) and then validated FFQ. Both had questions about frequency and amount of beer, wine, and spirits	Incident AF per annual visit or hospital discharge ICD-9 codes	9.1 years	5,609	1,232	No association	Multivariable
Conen 2008[16]	Women only; U.S. subjects; >45 years at baseline; initially healthy	Cohort	FFQ measured at two time points; questions on alcohol intake amount and type; categorized into none, <1/day, 1-<2, and ≥2	Incident AF via self-report and confirmed via ECG or medical report	12.4 years	34,715	653	Increased risk if ≥2 drinks/ day versus no alcohol (HR 1.49, 95% CI: 1.05–2.11)	Multivariable
Marcus 2008[17]	Both sexes; US subjects; AF/AFL cases; controls	Matched case- control	Structured interview asking average amount and	All AF/AFL patients reporting	None	381	125 with AF, 70 with AFL	Increased risk of AFL in younger <60	Multivariable

Source	Study Population	Study Design	Alcohol Assessment	AF Ascertainment	Follow-up	Total N	AF Events	Main Results	Adjustment Variables
	were patients with other arrhythmia and healthy controls		frequency of alcohol consumption (categorized into daily drinker vs. not daily drinker)	for ablation or cardioversion				daily drinkers vs. non-drinkers (OR 17, 95% CI 1.6–192.0)	

AF, atrial fibrillation; AFL, atrial flutter; CI: confidence interval; ECG, electrocardiogram; FFQ, food frequency questionnaire; N/A: not applicable; OR, odds ratio; RR: risk ratio

Table 2

Selected characteristics of published studies evaluating the association of fish derived n-3 fatty acids intake with atrial fibrillation

Source	Study Population	Study Design	Exposure Assessment	AF Ascertainment	Follow-up	Total N	AF Events	Main Results	Adjustment Variables
Mozaffarian 2004[29]	Both sexes; U.S. subjects; age=65+ at baseline; population based cohort	Cohort	Fish via FFQ - 2 measures (tuna, other fish, and fried fish sandwiches)	Incident AF via hospital discharge records and annual ECGs	12 years	4,815	980	No association of fried fish/ fish sandwich consumption with AF. Higher consumption of tuna or other boiled/baked fish associated with decreased risk of AF (5 + servings/wk vs. <1/month RR=0.7, 95% CI: 0.53–0.93)	Multivariable
Calo 2005[37]	Both sexes; patients undergoing CABG	Trial	Fish-derived n- 3 PUFA 2 g/ day capsule	Post Operative AF - ascertained via continuous rhythm monitoring	8 days	160	39	Fish-derived n-3 PUFAs supplementation associated with decreased risk of post-CABG AF (33.5% vs. 15.2%, p=0.01)	None
Frost 2005[32]	Both sexes; Danish subjects; 50–64 at baseline	Cohort	Fish-derived n- 3 PUFAs intake measured via FFQ	Hospitalized incident AF - identified by ICD-8 and ICD-10 discharge codes	5.7 years	47,949	556	Higher risk of AF in 5th quintile vs. 1st quintile of n-3 PUFA intake (RR=1.34, 95% CI: 1.02 – 1.76)	Multivariable
Brouwer 2006[31]	Both sexes; Dutch subjects; 55+ at baseline; population based cohort	Cohort	Fish (g/day) via FFQ; EPA and DHA via FFQ	Incident AF - defined as AF on ECG at study visits, PCPs provided medical records, hospital discharge ICD-9 codes	6.4 years	5,184	312	No association between total DHA+EPA or fish intake and AF	Multivariable
Macchia 2008[41]	Both sexes; Italian subjects; avg age=65.1; patients who had survived an MI and were free of AF during MI	Population study (all residents in the Italian civil registry)	Prescription for fish-derived n-3 PUFAs (per prescription databases - no dosage given)	Post MI AF (per hospital outcomes)	360 days	3,242	471	RR 0.15, 95% CI 0.05–0.46 comparing those with ≥1 fish-derived n-3 PUFA prescriptions vs. no prescription	Propensity score matching
Patel 2009[39]	Both sexes; U.S. subjects; avg age=59; patients undergoing PVAI	Matched nested case-control	Prescription for fish-derived n-3 PUFAs with at least 655 mg fish oil any time during the follow-up	Post Operative AF - early (0–8 weeks post ablation) and late (8+ weeks after ablation)	5 years	258	92 with early POAF and 70 with late POAF	Those treated with n-3 PUFAs had less early and late POAF than those not treated	Multivariable
Virtanen 2009[33]	Finnish men only; age 42–60 at baseline; population based cohort	Cohort	n-3 PUFAs measured in serum	Incident AF (hospitalization ICD-8 and ICD-10 discharge codes)	17.7 years	2,174	240	Total fish-derived PUFAs (Q4 vs. Q1) associated with 40% lower risk of AF (95% CI: 0.31 – 0.8). Association restricted to DHA (not to EPA or DPA)	Multivariable
Berry 2010[30]	Women only; U.S. subjects; 50–79 years at baseline; postmenopausal	Cohort	Fish (tuna, dark, and non-fried fish) via FFQ; Intake of fish-derived n-3 PUFAs via FFQ	Incident AF - defined by AF or AFL on ECG at study visits	6 years	44,720	378	No association fish intake and AF, and fish-derived n-3 PUFAs and AF	Multivariable
Heidarsdottir 2010[35]	Both sexes; Icelandic subjects; avg age = 67;	Trial	2.2 g of EPA+DHA pre- and post- surgery; fish- derived	POAF - diagnosed via continuous ECG	Until hospital discharge.	168	91	No association (52.4% vs. 52.1%)	None

Source	Study Population	Study Design	Exposure Assessment	AF Ascertainment	Follow-up	Total N	AF Events	Main Results	Adjustment Variables
	patients admitted for CABG or valvular repair surgery		n-3 fatty acids as measured in plasma	monitoring where an AF episode lasted >5 minutes					
Mariscalco 2010[38]	Both sexes; Italian subjects; avg age = 66.4; patients scheduled for initial or redo cardiac surgeries	Cohort	Pre-operative fish-derived n-3 PUFA supplements (1 g/day)	Early POAF (continuous ECG monitoring during hospitalization) and late POAF (ECGs given at least every 7 days)	Until conclusion of rehabilitation	530	early AF = 237, late AF = 78	Preop PUFA supplement associated with lower risk of early POAF (31.0% vs. 47.3%, p=0.008) but no association with late POAF 11.9% vs. 15.2%, p=0.43)	Propensity score matching
Saravanan 2010[36]	Both sexes; U.K. subjects; median age 64–68; patients undergoing CABG	Trial	2 g/day fish- derived n-3 PUFAs pre- and post-surgery	Post Operative AF (>30 seconds) measured via continuous ECG monitoring for 5 days and then daily ECGs.	Until conclusion of hospital stay	103	51	No association	None
Viviani Anselmi 2010[34]	Both sexes; Italian subjects; avg age 57–63; cases of AF/AFL and healthy controls	Case-control	Fish-derived n- 3 PUFAs as measured in erythrocytes cell membranes	Idiopathic AF (not stated if incident or not) based on referral for ablation	None	93	40	AF and AFL cases had higher erythrocyte n-3 FA compared to controls (5.3 vs. 2.8, p<0.001)	None

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery bypass graft surgery; CI, confidence interval; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; ECG, electrocardiogram; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; POAF, post-operative AF; PUFA, polyunsaturated fatty acids; PVAI, pulmonary vein antrum isolation; RR, risk ratio.

Table 3

Selected characteristics of published studies evaluating the association of caffeine intake with atrial fibrillation

Source	Study Population	Study Design	Caffeine Assessment	AF Ascertainment	Follow- up	Total N	AF Events	Main Results	Adjustment Variables
Koskiren 1987[20]	Both sexes; Finnish subjects; average age = 48; hospitalized cases of AF and age/sex matched acute, hospitalized controls	Matched case- control	Coffee only; interview regarding coffee drinking habits categorized into daily and non- daily drinkers	Incident AF (idiopathic and known etiology) diagnosed by cardiologist (85% had ECGs)	N/A	200	100	No association	Age, sex
Wilhelmsen 2001[21]	Men only; Swedish subjects; 47–55 at baseline; population based sample	Cohort	Coffee only; questionnaire regarding coffee consumption; categorized into 0, 1–5, and 5+ cups/day	Incident AF - Outpatient and Hospitalized AF via ICD-9 codes	25.2 years	7,495	754	No association	Not specified
Frost 2005[51]	Both sexes; Danish subjects; age 50–54 at baseline; population based sample	Cohort	Total caffeine; FFQ including information on consumption of coffee, tea, cola, cocoa, and chocolate categorized into quintiles of g/day	Incident AF as identified by hospitalization discharge ICD- 8 and ICD-10 codes, outpatient discharge codes after 1/1/95	5.7 years	47,949	555	No association	Multivariable
Mukamal 2009[54]	Both sexes; Swedish subjects; aged 45–70; patients hospitalized with first MI	Cohort	Coffee only; questionnaire about daily consumption of coffee categorized into 0-<1, 1-<3, 3- <5, 5-<7, 7+ cups/day	Post MI AF - Hospital discharge ICD- 9 and ICD-10 codes for AF.	6.9–9.9 years	1,369	163	No association	Multivariable
Conen 2010[52]	Women only; U.S. subjects; age >45 years at baseline	Cohort	Total caffeine; FFQ including chocolate and decaf/caffeinated versions of the following: coffee, tea, cola, low-cal cola; categorized into quintiles of caffeine intake	Incident AF via self-report and confirmed via ECG or medical report	Median 14.4 years	33,638	945	Suggest a U-shaped association between total caffeine intake and AF with lowest risk in the 2nd and 3rd quintiles ($p<0.01$ for quadratic trend)	Multivariable

AF, atrial fibrillation; ECG, electrocardiogram; FFQ, food frequency questionnaire; MI, myocardial infarction; N/A, not applicable.