Published in final edited form as:
JAMA. 2008 December 3; 300(21): 2489–2496. doi:10.1001/jama.2008.755.

Alcohol Consumption and Risk of Incident Atrial Fibrillation in Women

David Conen, MD, MPH[1,2,4], **Usha B. Tedrow, MD, MSc**[1,2], **Nancy R. Cook, ScD**[2], **M.V. Moorthy, PhD**[1,2], **Julie E. Buring, ScD**[2], and **Christine M. Albert, MD, MPH**[1,2,3]

[1] *Center for Arrhythmia Prevention, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA* [2] *Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA* [3] *Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [4] *Cardiology Division, University Hospital, Petersgraben 4, 4031 Basel, Switzerland*

Abstract

Context—Previous studies suggest that consuming moderate-to-large amounts of alcohol on a regular basis might increase the risk of developing atrial fibrillation (AF) in men, but not in women. However, these studies were not powered to investigate the association of alcohol consumption and AF among women.

Objective—To prospectively assess the association between regular alcohol consumption and incident AF among women.

Design, Setting and Participants—34715 initially healthy women participating in the Women's Health Study who were >45 years and free of AF at baseline were prospectively followed from 1993 to October 31, 2006. Alcohol intake was assessed via questionnaires at baseline and 48 months of follow-up and grouped into the following categories: 0, >0 and <1, ≥1 and <2, and ≥2 drinks per day.

Main outcome measure—Time to a first episode of AF. AF was self-reported on the yearly questionnaires and subsequently confirmed by electrocardiogram and medical record review.

Results—Over a median follow-up of 12.4 years, 653 incident AF cases were confirmed. Age-adjusted incidences among women consuming 0 (n=15370), >0 and <1 (n=15758), ≥1 and <2 (n=2228), and ≥2 (n=1359) drinks per day were 1.59, 1.55, 1.27 and 2.25 events/1000 person-years of follow-up. Thus, compared with non-drinking women, women consuming ≥2 drinks per day had an absolute risk increase of 0.66 events/1000 person-years. The corresponding multivariable-adjusted hazard ratios (HR) (95% confidence interval (CI)) for incident AF were 1.0, 1.05 (0.88–1.25), 0.84

Correspondence and request of reprints: David Conen, Cardiology Division, University Hospital, Petersgraben 4, 4031 Basel, Switzerland, Phone: +41 61 265 25 25, Fax: +41 61 265 45 98, E-mail: conend@uhbs.ch.

Authors contributions
David Conen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Conen, Albert
Acquisition of data: Conen, Tedrow, Buring, Albert
Analysis and interpretation of data: Conen, Tedrow, Cook, Moorthy, Buring, Albert
Drafting of the manuscript: Conen
Critical revision of the manuscript for important intellectual content: Conen, Tedrow, Cook, Moorthy, Buring, Albert
Statistical analysis: Conen
Obtained funding: Conen, Buring, Albert
Administrative, technical or material support: Moorthy
Study supervision: Albert

(0.58–1.22) and 1.60 (1.13–2.25), respectively. The increased hazard in the small group of women consuming ≥2 drinks persisted when alcohol intake was updated at 48 months (HR (95% CI) (1.49 (1.05–2.11)) or when women were censored at their first cardiovascular event (HR (95% CI) 1.68 (1.18–2.39)).

Conclusion—Among healthy middle-aged women, consumption of up to two alcoholic beverages per day was not associated with an increased risk of incident AF. Heavier consumption of two or more drinks per day, however, was associated with a small but statistically significant increased AF risk.

Keywords

Atrial fibrillation; Alcohol consumption; Women; Cardiovascular diseases

Introduction

Previous studies have revealed various effects of alcohol consumption on the risk of cardiovascular disease, depending on the cardiovascular event under study and on the amount of alcohol consumed. Consuming moderate amounts of alcohol has been consistently associated with reduced risks of coronary heart disease, stroke, and congestive heart failure [1–5]. On the other hand, acutely ingesting excessive amounts of alcohol ("binge drinking") has been related to increased risks of myocardial infarction [6], stroke [7] and atrial fibrillation [8–10]. Among individuals consuming excessive amounts of alcohol on a more regular basis, an increased risk of developing alcoholic cardiomyopathy and congestive heart failure has also been described [11, 12].

In contrast to these fairly consistent associations, studies assessing the effects of regular alcohol consumption on the risk of atrial fibrillation have provided inconsistent results. Several prospective studies found significant associations between moderate to high amounts of alcohol intake and increased risks of incident atrial fibrillation among men, but not among women [5, 13, 14]. However, investigators from the Cardiovascular Health Study did not find a relationship between any level of alcohol consumption and atrial fibrillation in elderly individuals, although gender-specific information was not provided [15].

Because only a relatively small number of women consumed moderate to high amounts of alcohol in the individual studies, these non-significant results may be partly due to limited power to detect significant associations among women. Alternatively, gender-specific differences in the association between alcohol consumption and risk of atrial fibrillation may exist. To address these issues, we assessed the effects of regular alcohol consumption on the risk of incident atrial fibrillation in a large prospective cohort of 34,715 initially healthy women.

Methods

Participants

All study participants were enrolled in the Women's Health Study, a completed randomized trial evaluating the risks and benefits of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Details of the study design have been described previously [16–18].

Briefly, beginning in 1993, 39876 female health professionals in the United States who were 45 years or older and free of cardiovascular disease, cancer or other major illnesses were randomized to receive 100 mg aspirin every other day, 600 IU vitamin E every other day, both

agents or placebo. The trial initially had a beta carotene arm that was terminated early [19]. Randomized treatment ended on March 31, 2004, and women were invited to participate in continued observational follow-up, which for the current analysis was truncated on October 31, 2006. Of the original cohort, 4326 opted out of the observational follow-up. These women were excluded from this analysis because their atrial fibrillation could not be reliably confirmed. However, we performed a sensitivity analysis using self-reported atrial fibrillation events among all women as the main outcome variable to ensure exclusion of these women did not significantly alter our results.

We also excluded 813 women with a history of atrial fibrillation at baseline, 10 women because of missing information on alcohol consumption and 12 women because they were subsequently diagnosed with cardiovascular disease or cancer before randomization. The final study population for this analysis consisted of 34715 women. Written informed consent was obtained from all participants. The study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Assessment of Alcohol Intake

Information on baseline variables was collected using mailed questionnaires. Follow-up questionnaires asking participants about study outcomes and other information were sent every six months during the first year and every 12 months thereafter. Information on alcohol consumption was collected at the time of randomization and at 48 months of follow-up. Participants were asked to indicate the average frequency of consumption of beer (per 12-ounce glass or can), red wine (per 4-ounce glass), white wine (per 4-ounce glass) and liquor (per shot) during the preceding 12 months as never or <1 drink per month, 1–3 drinks per month, 1 drink per week, 2–4 drinks per week, 5–6 drinks per week, 1 drink per day, 2–3 drinks per day, 4–5 drinks per day or ≥6 drinks per day.

Given the reported associations between higher levels of alcohol intake and atrial fibrillation among men, we categorized women into one of the following categories of alcohol intake: 0, >0 and <1 drink per day, ≥1 and <2 drinks per day, and ≥2 drinks per day. We also performed an exploratory analysis by further separating women who consumed ≥2 but <3 drinks per day from those consuming ≥3 drinks per day. Finally, we also assessed the relationship between total amount of alcohol consumed per day and atrial fibrillation. We determined alcohol intake by multiplying the consumption of each beverage by its ethanol content (13.2 g for beer, 10.8 g for wine, and 15.1 g for liquor) and summing all beverages [20]. We then categorized women into one of the following groups: No alcohol consumption, >0 and <15 grams of alcohol per day, ≥15 and <30 grams per day, and ≥30 grams per day. A validation study among a subset of participants in the Nurses' Health Study indicated a high correlation (r=0.84) between alcohol intake measured by the 1984 food frequency questionnaire (similar to that used for the Women's Health Study) and four 1-week dietary records in 1980 [21]. In addition, alcohol consumption assessed by the 1984 food frequency questionnaire was correlated with plasma concentrations of high density lipoprotein cholesterol (r=0.40), which is known to be sensitive to alcohol [21].

Covariates of interest were self-reported at study entry and included age, smoking, blood pressure, history of hypertension, diabetes, history of hypercholesterolemia, body mass index (weight in kilograms divided by the square of height in meters), exercise, highest education level achieved and race/ethnicity, which was self-reported by the participants as white, black, Hispanic American, Asian American, or other.

Ascertainment of incident atrial fibrillation

Women were asked to report diagnoses of incident atrial fibrillation at baseline, 48 months, and then annually thereafter. Beginning on September 19, 2006, women enrolled in the continued observational follow-up who reported an incident atrial fibrillation event on at least one yearly questionnaire were sent an additional questionnaire to confirm the episode and collect additional information. They were also asked for permission to review their medical records, particularly available electrocardiograms, rhythm strips, 24-hour electrocardiograms and information on cardiac structure and function. For all deceased participants who reported atrial fibrillation during the trial and extended follow-up period, we contacted family members to obtain consent and additional relevant information. An endpoint committee of physicians reviewed medical records for reported events according to predefined criteria. An incident atrial fibrillation event was confirmed if there was electrocardiographic evidence of atrial fibrillation or if a medical report clearly indicated a personal history of atrial fibrillation. The earliest date in the medical records when documentation was believed to have occurred was set as the date of onset of atrial fibrillation. Only confirmed events are included in the present report.

Statistical analysis

Baseline characteristics across categories of alcohol consumption were compared using Kruskal-Wallis tests for continuous variables and chi square tests for categorical variables. The primary analysis assessed the association between baseline alcohol intake and atrial fibrillation. Cox proportional-hazards models were constructed to calculate hazard ratios and 95% confidence intervals for alcohol consumption as a continuous measure and across categories of alcohol consumption. For each woman, person-years of follow-up were calculated from the date of return of the baseline questionnaire to date of first endpoint, death or to October 31, 2006, whichever came first. Women who indicated no alcohol consumption were chosen as the reference group for all analyses. Age-adjusted models were further adjusted for a broad range of potential confounders that were pre-specified based on previous association studies of incident atrial fibrillation and cardiovascular disease, including systolic blood pressure, history of hypertension, body mass index, smoking, history of hypercholesterolemia, history of diabetes and randomized treatment assignment. In a third step, we additionally adjusted for race/ethnicity, exercise and education level.

To take into account potential changes in alcohol consumption over time, we fitted a Cox proportional-hazards model that included alcohol consumption as a time dependent covariate in a secondary analysis. Model covariates were also updated at 48 months in these analyses. An association between alcohol intake and incident atrial fibrillation may be caused by intercurrent cardiovascular events, given the previously described relationship between alcohol consumption and cardiovascular disease [1–3]. We therefore refitted the Cox proportional-hazards models after censoring all women with an intercurrent cardiovascular event at the date of the event. An intercurrent cardiovascular event was defined as confirmed myocardial infarction, stroke or coronary revascularization.

Multiplicative interaction terms between alcohol consumption and various baseline characteristics were evaluated in the fully adjusted models using likelihood ratio tests. Tests for linear trend were performed by assigning all women the median value of drinks per day for the respective category. We tested for deviation from linearity by including a quadratic term in the trend model and by comparing a model containing indicator variables for all categories of alcohol intake with those containing a linear term for these categories using a likelihood ratio test with two degrees of freedom (df). We also compared the model fit of a threshold effect model (alcohol consumption ≥2 drinks/day versus <2 drinks/day) to the indicator variable model. The proportional hazards assumption was examined for all models by including

categories of alcohol intake by logarithm of time interaction terms into the model [22]. The assumption was found to be met for all models. The population-attributable risk (PAR) related to excessive alcohol consumption was estimated using standard methods [23]. All analyzes were carried out using SAS version 9 (SAS Institute Inc, Cary, NC). A two-tailed p value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics stratified by increasing amounts of alcohol consumption are displayed in Table 1. Overall, 15370 (44.3%) women were non-drinkers, 15758 (45.4%) consumed <1 drink per day, 2228 (6.4%) consumed between 1 and 2 drinks per day and 1359 (3.9%) consumed ≥2 drinks per day. While body mass index and the prevalence of diabetes decreased with increasing alcohol consumption, current smoking and the prevalence of Caucasian women increased. We observed a U-shaped relationship between alcohol consumption and age, hypertension, hypercholesterolemia, exercise and highest education level achieved. All differences in baseline characteristics across categories of alcohol consumption were statistically significant (p <0.0001 for all comparisons).

During a median follow-up of 12.4 years, we observed 653 confirmed events of incident atrial fibrillation. Five hundred and four (77.2%) of the episodes were confirmed by electrocardiogram and 149 (22.8%) by a physician's report in the medical record that clearly indicated a personal history of atrial fibrillation. Among these, 15 (2.3%) had a transient ischemic attack or stroke at the time of diagnosis, whereas 66 (10.1%) were asymptomatic. The majority of women (93%) who had an assessment of cardiac function at the time of diagnosis had a left ventricular ejection fraction of 50% or greater.

There were 294 (1.9%), 284 (1.8%), 35 (1.6%) and 40 (2.9%) atrial fibrillation events among women who consumed no alcohol, <1 drink per day, 1–2 drinks per day and ≥2 drinks per day, respectively. As shown in Table 2, 2.25 events of incident atrial fibrillation per 1000 person-years of follow-up occurred in the small group of women consuming at least two alcoholic beverages per day, compared with 1.59 events among non-drinking women. Thus, the absolute risk increase among women consuming ≥2 drinks per day was 0.66 events per 1000 person-years.

After multivariable adjustment, consuming at least two alcoholic beverages per day remained significantly associated with an increased risk of incident atrial fibrillation (hazard ratio (95% confidence interval) 1.60 (1.13–2.25)) (Table 2). Updating the daily amount of alcohol consumption at 48 months of follow-up did not change our findings for women consuming at least two drinks per day (hazard ratio (95% confidence interval) 1.49 (1.05–2.11)). Also, these results were not significantly altered when the 47 women who had a cardiovascular event prior to the development of atrial fibrillation were censored from the analysis. Women consuming ≥2 drinks per day had an increase of 0.70 events per 1000 person-years of follow-up compared with non-drinking women, which translated into a multivariable adjusted hazard ratio (95% confidence interval) of 1.68 (1.18–2.39).

Further separating women who consumed ≥2 but <3 drinks per day (n=1053, 3.0%) from those consuming ≥3 drinks per day (n=306, 0.9%) provided very similar risk estimates in the two groups (hazard ratio (95% confidence interval) 1.57 (1.07–2.31) and 1.68 (0.86–3.28), respectively. However, the extremely small number of women who consumed over three drinks per day limited our ability to determine if there is a direct linear association between alcohol and atrial fibrillation at higher levels of intake.

When we repeated our analyses using all 1250 self-reported atrial fibrillation events among 38934 women apparently free of atrial fibrillation at baseline, concordant results were obtained.

Compared with non-drinking women, the multivariable adjusted hazard ratios (95% confidence intervals) were 0.97 (0.86–1.10), 0.77 (0.59–1.00) and 1.36 (1.05–1.77) for women consuming <1 drink per day, 1–<2 drinks per day and ≥2 drinks per day, respectively.

Similar results were also obtained when the average alcohol intake in grams per day was used as a measure of alcohol consumption. Across categories of increasing alcohol intake, the multivariable hazard ratios (95% confidence intervals) for incident atrial fibrillation were 1.0 (referent), 1.05 (0.89–1.25), 0.85 (0.56–1.28) and 1.66 (1.10–2.50).

When examined as a continuous measure, each additional drink consumed per day was associated with a significantly elevated risk of atrial fibrillation (adjusted hazard ratio 1.14 (1.02–1.27)). However, a test for linear trend across categories of alcohol consumption was not statistically significant (p=0.12). The addition of a quadratic term for alcohol consumption to this model provided a significant result (p=0.04), confirming the visual impression of a nonlinear relationship between alcohol consumption and risk of incident atrial fibrillation. The likelihood ratio test for deviation from linearity was of borderline statistical significance (likelihood ratio chi square 5.28, 2 df, p=0.071). A threshold effect model revealed adequate model fit (likelihood ratio chi square 2.13, 2 df, p=0.34). Women consuming at least two drinks per day had a hazard ratio (95% confidence interval) of 1.58 (1.14–2.20) compared with women drinking less than two drinks per day. Given that 3.9% of women in this study consumed at least two alcoholic drinks per day, we estimated that about two percent of atrial fibrillation cases were attributable to this level of alcohol intake.

As shown in Table 3, our findings appeared to be consistent across all major subgroups evaluated, although power to detect subgroup effects was limited. Although most individual risk estimates were not statistically significant, drinking at least two alcoholic beverages per day was consistently associated with an increased risk of incident atrial fibrillation across different categories of age, body mass index or smoking, and for women with or without hypertension, diabetes or hypercholesterolemia. As in the main analyses, none of the subgroups revealed an increased risk of atrial fibrillation in women consuming <2 drinks per day. Accordingly, corresponding confidence intervals widely overlapped and none of the p values for interaction was statistically significant.

Comment

In the present study, alcohol consumption of up to two drinks per day was not associated with an increased risk of incident atrial fibrillation among initially healthy, middle-aged women. In contrast, in the small group of women who consumed two or more alcoholic beverages per day, there was a 1.6 greater risk for atrial fibrillation relative to non-drinking women. While this finding needs to be interpreted with some caution due to the small number of women in these subgroups, it supports a possible threshold effect in the relationship between alcohol consumption and risk of atrial fibrillation among women.

The risk of atrial fibrillation among women consuming less than two alcoholic beverages per day was similar to that of non-drinking women. The upper limits of the confidence intervals in our main analysis suggest that our study can exclude an increased risk of incident atrial fibrillation in excess of 22 to 25% in women consuming <2 alcoholic drinks per day (Table 2). Thus, power seems to be an unlikely explanation for these null findings. Furthermore, models including a quadratic term also suggested a non-linear relationship. A nonlinear relationship was further supported by the fact that a threshold effect model provided adequate model fit compared with the indicator variable model. If confirmed, these results imply that in women, consuming less than two alcoholic drinks per day does not confer an increased risk of incident atrial fibrillation.

Our findings are consistent with previous studies among men, who have also shown that the consumption of moderate-to-large amounts of alcohol on a regular basis is associated with incident atrial fibrillation [5, 13, 14]. For example, Frost et al demonstrated that men in the highest quintile of alcohol consumption (i.e. approximately 35 drinks per week) had a 1.46 greater hazard of atrial fibrillation during follow-up compared to those in the lowest quintile [14]. Similar findings have been reported from another Danish cohort, where consuming at least 35 drinks per week was associated with a 1.63 greater hazard of incident atrial fibrillation among men [13]. Thus, while the increase in risk was similar to the present study, the risk threshold may be substantially lower among women. Our findings among women suggest an increased risk of atrial fibrillation starting at 14 drinks per week.

In the present study, the risk of developing incident atrial fibrillation was small, as would be expected for an initially healthy, middle-aged population. As a consequence, the absolute increase in risk associated with drinking two or more drinks per day was small, 0.66 events per 1000 person-years of follow-up. These findings are similar to those reported among initially healthy Danish men who consumed approximately 5 drinks per day[14]. This amount of alcohol consumption was associated with an increase of 1.09 events per 1000 person-years of follow-up. As about 20% of participants in the Danish study were exposed to this amount of alcohol, the percentage of atrial fibrillation attributable to excessive alcohol intake was higher than in the present study (≈8%). Taken together, our findings suggest a modest impact of elevated alcohol consumption on the overall atrial fibrillation burden in initially healthy, middle-aged women. However, the impact of alcohol consumption may be higher in other population groups consuming higher amounts of alcohol or having a higher underlying risk of developing atrial fibrillation, and should not be underestimated.

Although previous studies suggested no increase in risk of incident atrial fibrillation in women consuming elevated amounts of alcohol [5, 13, 14], several reasons may account for these differential findings. First, few women consuming elevated amounts of alcohol on a regular basis were included in previous studies, and power to detect a significant association may have been limited. This hypothesis is supported by findings from the present study, where only 3.9% of participants consumed at least two alcoholic beverages per day. Given the large sample size, we nevertheless observed enough events to detect a significant relationship between alcohol consumption and incident atrial fibrillation. However, even within this large study population, we had limited ability to reliably assess the shape of the relationship among women consuming high levels of alcohol. Second, some of the previous studies included a considerable number of participants with pre-existing cardiovascular disease [5, 14, 15], and since cardiovascular disease already confers a high risk of developing atrial fibrillation [24–27], it is possible that elevated alcohol consumption may not be associated with substantially further increased risks among affected individuals.

Factors mediating the association between alcohol consumption and risk of atrial fibrillation are unclear. In the present study, the interim development of cardiovascular disease did not appear to mediate the relationship between increased alcohol consumption and risk of atrial fibrillation. Although excessive amounts of alcohol ingestion may precipitate alcoholic cardiomyopathy and congestive heart failure [11, 12], more moderate levels have been associated with reduced risks of congestive heart failure in several populations [4, 28]. Other possible mechanisms include direct effects on right atrial structure and electrophysiology [29], alterations in oxidative stress [30], perturbances in the autonomic nervous system [31, 32], and/or electrolyte imbalances [32].

Strengths and limitations

Strengths of the present study include its prospective design, sample size, and long-term follow-up with a large number of confirmed events. Potential study limitations also require discussion.

First, we included initially healthy, middle-aged female health professionals, most of them being of Caucasian origin. Thus, generalizability to men or other female populations may be limited. Second, alcohol intake was self-reported and only assessed twice during follow-up and we may have missed subtle changes of alcohol consumption over time. However, health professionals have been found to reliably report alcohol use [21]. Given the stability of our findings, it is unlikely that more precise assessment of alcohol consumption would have substantially altered our findings.

Third, screening electrocardiograms were not performed in this cohort; and therefore, it is possible that asymptomatic cases of atrial fibrillation may have gone undetected. However, in this cohort of health professionals, who are medically sophisticated and have access to health care, significant under-detection is less likely. In support of this contention, the number of asymptomatic atrial fibrillation cases in this cohort (n=66, 10.1%) was similar to the number of cases detected by screening electrocardiograms in other cohorts [13, 26]. For example, in a general population cohort from Denmark only 68 of 1071 cases (6.3%) were detected by screening only [13]. Furthermore, any misclassification or underdetection of incident atrial fibrillation is expected to occur at random and independent of alcohol intake. If anything, our results would therefore underestimate the true risk associated with alcohol consumption.

Fourth, defining the initial episode of atrial fibrillation accurately is challenging, especially when 10% of women were asymptomatic at the time of diagnosis. Misspecification of the time of incidence may have introduced some bias towards the null into the time-to-event analysis, but given the small number of events, this would be expected to be small. Fifth, standardized data on left ventricular function and congestive heart failure, potential mediators in the association between excessive alcohol consumption and atrial fibrillation, were not available. Finally, as with any observational study, the association between alcohol consumption and atrial fibrillation could, at least in part, be due to residual confounding by other lifestyle factors, although controlling for those available had little impact on risk estimates.

Conclusion

In summary, these prospective data suggest that consumption of up to two alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation in initially healthy women. On the other hand, consuming heavier amounts of alcohol was associated with an increased risk of atrial fibrillation. These findings were consistent across all subgroups considered.

Acknowledgements

Financial Disclosures

David Conen was supported by the grant PASMA 118586/1 from the Swiss National Science Foundation. The Women's Health Study was supported by grants HL-043851, HL-080467 from the National Heart, Lung and Blood Institute and CA-047988 from the National Cancer Institute.

The funding organization had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

References

1. Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med 1988;319 (5):267–73. [PubMed: 3393181]

2. Tolstrup J, Jensen MK, Tjonneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. Bmj 2006;332(7552):1244–8. [PubMed: 16672312]
3. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. Jama 2003;289(5):579–88. [PubMed: 12578491]
4. Walsh CR, Larson MG, Evans JC, et al. Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med 2002;136(3):181–91. [PubMed: 11827493]
5. Djousse L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. Am J Cardiol 2004;93(6):710–3. [PubMed: 15019874]
6. McElduff P, Dobson AJ. How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event. Bmj 1997;314(7088):1159–64. [PubMed: 9146388]
7. Hansagi H, Romelsjo A, Gerhardsson de Verdier M, Andreasson S, Leifman A. Alcohol consumption and stroke mortality. 20-year follow-up of 15,077 men and women. Stroke 1995;26(10):1768–73. [PubMed: 7570723]
8. Ettinger PO, Wu CF, De La Cruz C Jr, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "Holiday Heart": alcohol-associated cardiac rhythm disorders. Am Heart J 1978;95(5):555–62. [PubMed: 636996]
9. Thornton JR. Atrial fibrillation in healthy non-alcoholic people after an alcoholic binge. Lancet 1984;2(8410):1013–5. [PubMed: 6149396]
10. Koskinen P, Kupari M, Leinonen H, Luomanmaki K. Alcohol and new onset atrial fibrillation: a case-control study of a current series. Br Heart J 1987;57(5):468–73. [PubMed: 3593617]
11. Lazarevic AM, Nakatani S, Neskovic AN, et al. Early changes in left ventricular function in chronic asymptomatic alcoholics: relation to the duration of heavy drinking. J Am Coll Cardiol 2000;35(6):1599–606. [PubMed: 10807466]
12. Gavazzi A, De Maria R, Parolini M, Porcu M. Alcohol abuse and dilated cardiomyopathy in men. Am J Cardiol 2000;85(9):1114–8. [PubMed: 10781762]
13. Mukamal KJ, Tolstrup JS, Friberg J, Jensen G, Gronbaek M. Alcohol consumption and risk of atrial fibrillation in men and women: the Copenhagen City Heart Study. Circulation 2005;112(12):1736–42. [PubMed: 16157768]
14. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. Arch Intern Med 2004;164(18):1993–8. [PubMed: 15477433]
15. Mukamal KJ, Psaty BM, Rautaharju PM, et al. Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study. Am Heart J 2007;153(2):260–6. [PubMed: 17239687]
16. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. JAMA 2005;294(1):56–65. [PubMed: 15998891]
17. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. J Womens Health Gend Based Med 2000;9(1):19–27. [PubMed: 10718501]
18. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352(13):1293–304. [PubMed: 15753114]
19. Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. J Natl Cancer Inst 1999;91(24):2102–6. [PubMed: 10601381]
20. Zhang SM, Lee IM, Manson JE, Cook NR, Willett WC, Buring JE. Alcohol consumption and breast cancer risk in the Women's Health Study. Am J Epidemiol 2007;165(6):667–76. [PubMed: 17204515]
21. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133(8):810–7. [PubMed: 2021148]
22. Cox DR. Regression models and life tables. J Roy Stat Soc B 1972;34:187–220.
23. Wacholder S, Benichou J, Heinemann EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 1994;140(4):303–09. [PubMed: 8059765]

24. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. Jama 1994;271 (11):840–4. [PubMed: 8114238]
25. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982;306(17):1018–22. [PubMed: 7062992]
26. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96(7):2455–61. [PubMed: 9337224]
27. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98(5):476–84. [PubMed: 7733127]
28. Djousse L, Gaziano JM. Alcohol consumption and risk of heart failure in the Physicians' Health Study I. Circulation 2007;115(1):34–9. [PubMed: 17130341]
29. Marcus GM, Smith LM, Whiteman D, et al. Alcohol intake is significantly associated with atrial flutter in patients under 60 years of age and a shorter right atrial effective refractory period. Pacing Clin Electrophysiol 2008;31(3):266–72. [PubMed: 18307620]
30. Meagher EA, Barry OP, Burke A, et al. Alcohol-induced generation of lipid peroxidation products in humans. J Clin Invest 1999;104(6):805–13. [PubMed: 10491416]
31. Maki T, Toivonen L, Koskinen P, Naveri H, Harkonen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. Am J Cardiol 1998;82(3):317–22. [PubMed: 9708660]
32. Denison H, Jern S, Jagenburg R, Wendestam C, Wallerstedt S. Influence of increased adrenergic activity and magnesium depletion on cardiac rhythm in alcohol withdrawal. Br Heart J 1994;72(6): 554–60. [PubMed: 7857739]

Table 1

Baseline characteristics according to alcohol consumption

Characteristic	No alcohol (n=15370)	<1 drink/day (n=15758)	1–<2 drinks/day (n=2228)	≥2 drinks/day (n=1359)
Age, years	53 (49–59)	53 (49–58)	54 (49–60)	54 (50–60)
Body mass index, kg/m^2	25.7 (22.9–29.8)	24.5 (22.3–27.5)	23.6 (21.6–26.1)	23.6 (21.6–26.5)
White race (%)	14200 (93.2)	15041 (96.3)	2175 (98.2)	1322 (97.9)
History of hypertension (%)	4428 (28.8)	3464 (22.0)	497 (22.3)	385 (28.3)
Diabetes mellitus (%)	591 (3.9)	221 (1.4)	22 (1.0)	10 (0.7)
History of hypercholesterolemia (%)	4863 (31.7)	4249 (27.0)	602 (27.0)	404 (29.7)
Smoking (%)				
Current	1837 (12.0)	1832 (11.6)	313 (14.1)	328 (24.2)
Past	4149 (27.0)	6480 (41.2)	1164 (52.2)	697 (51.3)
Never	9371 (61.0)	7434 (47.2)	751 (33.7)	333 (24.5)
Exercise, times/week (%)				
Rarely/never	6551 (42.6)	5254 (33.4)	740 (33.2)	548 (40.4)
<1	3073 (20.0)	3151 (20.0)	424 (19.1)	234 (17.2)
1–3	4322 (28.1)	5526 (35.1)	724 (32.5)	389 (28.7)
>3	1418 (9.2)	1822 (11.6)	338 (15.2)	187 (13.8)
Highest education level (%)				
Less than a bachelor’s degree	9495 (62.9)	7856 (50.7)	983 (44.8)	689 (51.7)
Bachelor’s degree	3180 (21.1)	4003 (25.8)	578 (26.4)	332 (24.9)
Master’s degree or doctorate	2429 (16.1)	3638 (23.5)	631 (28.8)	311 (23.4)

Data are medians (interquartile ranges) or counts (percentages). Number of women across categories may not sum to the given number because of missing data.

Table 2

Alcohol consumption and risk of incident atrial fibrillation

	No alcohol (n=15370)	<1 drink/day (n=15758)	1–<2 drinks/day (n=2228)	≥2 drinks/day (n=1359)
ALL ATRIAL FIBRILLATION EVENTS INCLUDED				
Number of events (%)	294 (1.9)	284 (1.8)	35 (1.6)	40 (2.9)
Age-adjusted incidence/1000 py	1.59	1.55	1.27	2.25
Relative risks (Baseline examination)				
Age-adjusted (n=34715)	Referent	1.01 (0.86–1.19)	0.79 (0.55–1.12)	1.48 (1.06–2.06)
Multivariable adjusted I (n=33525)*	Referent	1.06 (0.89–1.25)	0.87 (0.61–1.25)	1.61 (1.14–2.27)
Multivariable adjusted II (n=32703)†	Referent	1.05 (0.88–1.25)	0.84 (0.58–1.22)	1.60 (1.13–2.25)
Relative risks (Variables updated at 48 months)				
Age-adjusted (n=34715)	Referent	0.89 (0.75–1.05)	0.84 (0.61–1.16)	1.36 (0.98–1.90)
Multivariable adjusted I (n=33525)‡	Referent	0.96 (0.81–1.15)	0.97 (0.70–1.36)	1.49 (1.05–2.11)
Multivariable adjusted II (n=32703)†	Referent	0.95 (0.80–1.14)	0.98 (0.70–1.37)	1.49 (1.05–2.11)
WOMEN CENSORED AT THE FIRST CARDIOVASCULAR EVENT§				
Number of events (%)	267 (1.7)	266 (1.7)	35 (1.6)	38 (2.8)
Age-adjusted incidence/1000 py	1.48	1.48	1.30	2.18
Relative risks				
Age-adjusted (n=34715)	Referent	1.03 (0.87–1.22)	0.86 (0.60–1.22)	1.53 (1.09–2.15)
Multivariable adjusted I (n=33525)*	Referent	1.08 (0.91–1.29)	0.95 (0.66–1.37)	1.69 (1.19–2.41)
Multivariable adjusted II (n=32703)†	Referent	1.07 (0.90–1.28)	0.92 (0.63–1.33)	1.68 (1.18–2.39)

Data are incidence rates or hazard ratios (95% confidence interval)

*Adjusted for age, systolic blood pressure, history of hypertension, body mass index, smoking, history of diabetes, history of hypertercholesterolemia and randomized treatment assignment

†Additionally adjusted for exercise, race/ethnicity and highest education level

‡Adjusted for age, systolic blood pressure, history of hypertension, body mass index, smoking, history of diabetes, history of hypertercholesterolemia and randomized treatment assignment; all variables were updated at 48 months.

§A cardiovascular event was defined as stroke, myocardial infarction or coronary revascularisation.

Table 3

Alcohol consumption and risk of incident atrial fibrillation, stratified by various baseline characteristics

	No alcohol	<1 drink/day	1–<2 drinks/day	≥2 drinks/day	$P_{interaction}$
Age >60 years					0.39
Yes (n=6939)					
Events/participants	131/3256	121/2819	19/532	25/332	
Hazard ratio (95% CI)	Referent	1.07 (0.83–1.38)	0.89 (0.54–1.45)	1.91 (1.22–2.97)	
No (n=25764)					
Events/participants	151/11171	145/12061	14/1585	14/947	
Hazard ratio (95% CI)	Referent	1.02 (0.80–1.29)	0.80 (0.46–1.39)	1.24 (0.71–2.16)	
Body mass index >30 kg/m^2					0.18
Yes (n=5842)					
Events/participants	96/3419	71/2148	2/168	4/107	
Hazard ratio (95% CI)	Referent	1.18 (0.86–1.61)	0.32 (0.08–1.30)	1.14 (0.41–3.13)	
No (n=26861)					
Events/participants	186/11008	195/12732	31/1949	35/1172	
Hazard ratio (95% CI)	Referent	1.02 (0.83–1.25)	0.94 (0.64–1.38)	1.67 (1.15–2.40)	
Hypertension					0.38
Yes (n=8270)					
Events/participants	146/4151	101/3277	10/476	18/366	
Hazard ratio (95% CI)	Referent	0.93 (0.71–1.21)	0.57 (0.30–1.08)	1.38 (0.83–2.29)	
No (n=24433)					
Events/participants	136/10276	165/11603	23/1641	21/913	
Hazard ratio (95% CI)	Referent	1.16 (0.92–1.47)	1.08 (0.69–1.70)	1.84 (1.15–2.95)	
Hypercholesterolemia					0.48
Yes (n=9536)					
Events/participant	115/4566	84/4015	10/576	12/379	
Hazard ratio (95% CI)	Referent	0.95 (0.71–1.26)	0.73 (0.38–1.41)	1.28 (0.69–2.35)	
No (n=23167)					
Events/participants	167/9861	182/10865	23/1541	27/900	
Hazard ratio (95% CI)	Referent	1.11 (0.89–1.38)	0.90 (0.58–1.41)	1.78 (1.17–2.72)	
Current smoking					0.71
Yes (n=4016)					
Events/participants	24/1697	20/1716	3/296	9/307	
Hazard ratio (95% CI)	Referent	0.85 (0.46–1.56)	0.69 (0.21–2.33)	1.78 (0.81–3.94)	
No (n=28687)					
Events/participants	258/12730	246/13164	30/1821	30/972	
Hazard ratio (95% CI)	Referent	1.10 (0.92–1.31)	0.91 (0.62–1.33)	1.60 (1.09–2.34)	

CI Confidence interval

All hazard ratios are adjusted for age, systolic blood pressure, history of hypertension, body mass index, race/ethnicity, smoking, history of diabetes, history of hypercholesterolemia, exercise, education and randomized treatment assignment

JAMA. Author manuscript; available in PMC 2009 December 3.