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Alcohol Consumption and Risk of Incident Atrial Fibrillation in Women

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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 associated with 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 fibril-

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

Objective To prospectively assess the association between regular alcohol consumption and incident atrial fibrillation among women.

Design, Setting, and Participants Participants were 34 715 initially healthy women participating in the Women’s Health Study, a completed randomized controlled trial conducted in the United States. Participants were older than 45 years and free of atrial fibrillation at baseline and underwent prospective follow-up from 1993 to October 31, 2006. Alcohol consumption was assessed via questionnaires at baseline and at 48 months of follow-up and was grouped into 4 categories (0, >0 and <1, ≥ 1 and <2, and ≥ 2 drinks per day). Atrial fibrillation was self-reported on the yearly questionnaires and subsequently confirmed by electrocardiogram and medical record review.

Main Outcome Measure Time to first episode of atrial fibrillation.

Results Over a median follow-up of 12.4 years, 653 cases of incident atrial fibrillation were confirmed. Age-adjusted incidences among women consuming 0 (n=15 370), more than 0 and less than 1 (n=15 758), 1 or more and less than 2 (n=2228), and 2 or more (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 nondrinking women, women consuming 2 or more drinks per day had an absolute risk increase of 0.66 events/1000 person-years. The corresponding multivariate-adjusted hazard ratios (HRs) for incident atrial fibrillation were 1, 1.05 (95% CI, 0.88-1.25), 0.84 (95% CI, 0.58-1.22), and 1.60 (95% CI, 1.13-2.25), respectively. The increased hazard in the small group of women consuming 2 or more drinks per day persisted when alcohol intake was updated at 48 months (HR, 1.49; 95% CI, 1.05-2.11) or when women were censored at their first cardiovascular event (HR, 1.68; 95% CI, 1.18-2.39).

Conclusions Among healthy middle-aged women, consumption of up to 2 alcoholic beverages per day was not associated with an increased risk of incident atrial fibrillation. Heavier consumption of 2 or more drinks per day, however, was associated with a small but statistically significant increased risk of atrial fibrillation.

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lation in elderly individuals, although sex-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 nonsignificant findings may result in part from limited power to detect significant associations among women. Alternatively, sex-specific differences may exist in the

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association between alcohol consumption and risk of atrial fibrillation. 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 controlled 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, 39 876 women 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 aspirin (100 mg) every other day, vitamin E (600 IU) every other day, both agents, or placebo. The trial initially had a beta carotene group 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 that exclusion of these women did not significantly alter our results.

We also excluded 813 women with a history of atrial fibrillation at baseline, 10 with missing information on alcohol consumption, and 12 subsequently diagnosed with cardiovascular disease or cancer before randomization. The final study population for this analysis thus consisted of 34 715 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 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 6 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-oz glass, can, or bottle), red wine (per 4-oz glass), white wine (per 4-oz glass), and liquor (per shot) during the preceding 12 months as never or less than 1 drink per month, 1 to 3 drinks per month, 1 drink per week, 2 to 4 drinks per week, 5 to 6 drinks per week, 1 drink per day, 2 to 3 drinks per day, 4 to 5 drinks per day, or 6 or more 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: none, more than 0 and less than 1 drink per day, 1 or more and less than 2 drinks per day, and 2 or more drinks per day. We also performed an exploratory analysis by further separating women who consumed 2 or more but less than 3 drinks per day from those consuming 3 or more 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, more than 0 g to less than 15 g of alcohol per day, 15 g or more to less than 30 g per day, and 30 g

or more 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 (calculated as weight in kilograms divided by height in meters squared), exercise, highest education level achieved, and race/ethnicity, 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 1 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 the extended follow-up period, we contacted family members to obtain consent and additional relevant information. An end point committee of physicians used predefined criteria to review medical records for reported events. 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 this article.

Statistical Analysis

Baseline characteristics across categories of alcohol consumption were compared using Kruskal-Wallis tests for continuous variables and χ^2 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 (HRs) and 95% confidence intervals (CIs) 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 the date of the first end point, death, or 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 prespecified 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 performed a secondary analysis in which we fitted a Cox proportional hazards model that included alcohol consumption as a time-dependent covariate. Model covariates were also updated at 48 months in these analyses. Given the previously described relationship between alco-

Table 1. Baseline Characteristics According to Alcohol Consumption

Characteristic	No. (%) ^a			
	No Alcohol (n = 15 370)	<1 Drink/d (n = 15 758)	1-2 Drinks/d (n = 2 228)	≥2 Drinks/d (n = 1 359)
Age, median (IQR), y	53 (49-59)	53 (49-58)	54 (49-60)	54 (50-60)
White race	14 200 (93.2)	15 041 (96.3)	2 175 (98.2)	1 322 (97.9)
Body mass index, median (IQR) ^b	25.7 (22.9-29.8)	24.5 (22.3-27.5)	23.6 (21.6-26.1)	23.6 (21.6-26.5)
History of hypertension	4 428 (28.8)	3 464 (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	4 863 (31.7)	4 249 (27.0)	602 (27.0)	404 (29.7)
Smoking				
Current	1 837 (12.0)	1 832 (11.6)	313 (14.1)	328 (24.2)
Past	4 149 (27.0)	6 480 (41.2)	1 164 (52.2)	697 (51.3)
Never	9 371 (61.0)	7 434 (47.2)	751 (33.7)	333 (24.5)
Exercise, times per wk				
Rarely/never	6 551 (42.6)	5 254 (33.4)	740 (33.2)	548 (40.4)
<1	3 073 (20.0)	3 151 (20.0)	424 (19.1)	234 (17.2)
1-3	4 322 (28.1)	5 526 (35.1)	724 (32.5)	389 (28.7)
>3	1 418 (9.2)	1 822 (11.6)	338 (15.2)	187 (13.8)
Highest education level				
Some college	9 495 (62.9)	7 856 (50.7)	983 (44.8)	689 (51.7)
Bachelor's degree	3 180 (21.1)	4 003 (25.8)	578 (26.4)	332 (24.9)
Master's or doctorate degree	2 429 (16.1)	3 638 (23.5)	631 (28.8)	311 (23.4)

Abbreviation: IQR, interquartile range.

^aNumber of women across categories may not sum to the given number because of missing data.

^bCalculated as weight in kilograms divided by height in meters squared.

hol consumption and cardiovascular disease, it is possible that an association between alcohol intake and incident atrial fibrillation may be caused by intercurrent cardiovascular events.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 models containing a linear term for these cat-

egories using a likelihood ratio test with 2 degrees of freedom. We also compared the model fit of a threshold-effect model (alcohol consumption ≥ 2 drinks per day vs < 2 drinks per 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 related to excessive alcohol consumption was estimated using standard methods.²³ All analyses were performed using SAS version 9 (SAS Institute Inc, Cary, North Carolina). A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Baseline characteristics stratified by increasing amounts of alcohol consumption are shown in TABLE 1. Overall, 15 370 women (44.3%) were nondrinkers, 15 758 (45.4%) consumed less than 1 drink per day, 2 228 (6.4%) con-

sumed between 1 and 2 drinks per day, and 1359 (3.9%) consumed 2 or more drinks per day. While body mass index and the prevalence of diabetes decreased with increasing alcohol consumption, current smoking and the prevalence of white 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 ($P < .001$ for all comparisons).

During a median follow-up of 12.4 years, we observed 653 confirmed events of incident atrial fibrillation. Five hundred 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 experienced a transient ischemic attack

or stroke at the time of diagnosis, whereas 66 (10.1%) were asymptomatic. The majority (93%) of women 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, less than 1 drink per day, 1 to 2 drinks per day, and 2 or more 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 2 alcoholic beverages per day, compared with 1.59 events among nondrinking women. Thus, the absolute risk increase among women consuming 2 or more drinks per day was 0.66 events per 1000 person-years.

After multivariate adjustment, consuming at least 2 alcoholic beverages per day remained significantly associ-

ated with an increased risk of incident atrial fibrillation (HR, 1.60; 95% CI, 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 2 drinks per day (HR, 1.49; 95% CI, 1.05-2.11). Also, these results were not significantly altered when the 47 women who had experienced a cardiovascular event prior to the development of atrial fibrillation were censored from the analysis. Women consuming 2 or more drinks per day had an increase of 0.70 events per 1000 person-years of follow-up compared with nondrinking women, which translated into a multivariate-adjusted HR of 1.68 (95% CI, 1.18-2.39).

Further separating women who consumed 2 or more but less than 3 drinks per day (1053 [3.0%]) from those consuming 3 or more drinks per day (306 [0.9%]) provided very similar risk estimates in the 2 groups (HR, 1.57; 95% CI, 1.07-2.31 and HR, 1.68; 95% CI,

Table 2. Alcohol Consumption and Risk of Incident Atrial Fibrillation

Risk	No Alcohol (n = 15 370)	<1 Drink/d (n = 15 758)	1-2 Drinks/d (n = 2228)	≥2 Drinks/d (n = 1359)
All Atrial Fibrillation Events Included				
Events, No. (%)	294 (1.9)	284 (1.8)	35 (1.6)	40 (2.9)
Age-adjusted incidence per 1000 person-years	1.59	1.55	1.27	2.25
Relative risks, baseline examination, HR (95% CI)				
Age-adjusted (n = 34 715)	1 [Reference]	1.01 (0.86-1.19)	0.79 (0.55-1.12)	1.48 (1.06-2.06)
Multivariate-adjusted				
Model 1 (n = 33 525) ^a	1 [Reference]	1.06 (0.89-1.25)	0.87 (0.61-1.25)	1.61 (1.14-2.27)
Model 2 (n = 32 703) ^b	1 [Reference]	1.05 (0.88-1.25)	0.84 (0.58-1.22)	1.60 (1.13-2.25)
Relative risks, variables updated at 48 mo, HR (95% CI)				
Age-adjusted (n = 34 715)	1 [Reference]	0.89 (0.75-1.05)	0.84 (0.61-1.16)	1.36 (0.98-1.90)
Multivariate-adjusted				
Model 1 (n = 33 525) ^c	1 [Reference]	0.96 (0.81-1.15)	0.97 (0.70-1.36)	1.49 (1.05-2.11)
Model 2 (n = 32 703) ^b	1 [Reference]	0.95 (0.80-1.14)	0.98 (0.70-1.37)	1.49 (1.05-2.11)
Women Censored at First Cardiovascular Event^d				
Events, No. (%)	267 (1.7)	266 (1.7)	35 (1.6)	38 (2.8)
Age-adjusted incidence per 1000 person-years	1.48	1.48	1.30	2.18
Relative risks, HR (95% CI)				
Age-adjusted (n = 34 715)	1 [Reference]	1.03 (0.87-1.22)	0.86 (0.60-1.22)	1.53 (1.09-2.15)
Multivariate-adjusted				
Model 1 (n = 33 525) ^a	1 [Reference]	1.08 (0.91-1.29)	0.95 (0.66-1.37)	1.69 (1.19-2.41)
Model 2 (n = 32 703) ^b	1 [Reference]	1.07 (0.90-1.28)	0.92 (0.63-1.33)	1.68 (1.18-2.39)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age, systolic blood pressure, history of hypertension, body mass index, smoking, history of diabetes, history of hypercholesterolemia, and randomized treatment assignment.

^bAdjusted for covariates in model 1 plus exercise, race/ethnicity, and highest education level.

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

^dStroke, myocardial infarction, or coronary revascularization.

0.86-3.28, respectively). However, the small number of women who consumed more than 3 drinks per day limited our ability to determine if there is a direct linear association between alcohol consumption 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, we obtained concordant results. Compared with nondrinking women, the multivariate-adjusted HRs were 0.97 (95% CI, 0.86-1.10), 0.77 (95% CI, 0.59-1.00), and 1.36 (95% CI, 1.05-1.77) for women consuming less than

1 drink per day, 1 to 2 drinks per day, and 2 or more drinks per day, respectively.

Similar results were also obtained when average alcohol intake in grams per day was used as a measure of alcohol consumption. Across categories of increasing alcohol intake (no alcohol consumption, >0 to <15 g per day, ≥15 to <30 g per day, and ≥30 g per day), the multivariate-adjusted HRs for incident atrial fibrillation were 1 (reference), 1.05 (95% CI, 0.89-1.25), 0.85 (95% CI, 0.56-1.28) and 1.66 (95% CI, 1.10-2.50), respectively.

When examined as a continuous measure, each additional alcoholic

drink consumed per day was associated with a significantly increased risk of incident atrial fibrillation (multivariate-adjusted HR, 1.14; 95% CI, 1.02-1.27). However, a test for linear trend across categories of alcohol consumption was not statistically significant ($P=.12$). The addition of a quadratic term for alcohol consumption to this model provided a significant result ($P=.04$), 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 $\chi^2=5.28$;

Table 3. Alcohol Consumption and Risk of Incident Atrial Fibrillation, Stratified by Various Baseline Characteristics^a

Characteristic	No Alcohol	<1 Drink/d	1-2 Drinks/d	≥2 Drinks/d	Interaction P Value
Age >60 y					
Yes (n = 6939)					.39
Events/participants	131/3256	121/2819	19/532	25/332	
HR (95% CI)	1 [Reference]	1.07 (0.83-1.38)	0.89 (0.54-1.45)	1.91 (1.22-2.97)	
No (n = 25 764)					
Events/participants	151/11 171	145/12 061	14/1585	14/947	
HR (95% CI)	1 [Reference]	1.02 (0.80-1.29)	0.80 (0.46-1.39)	1.24 (0.71-2.16)	
Body mass index >30 ^b					
Yes (n = 5842)					.18
Events/participants	96/3419	71/2148	2/168	4/107	
HR (95% CI)	1 [Reference]	1.18 (0.86-1.61)	0.32 (0.08-1.30)	1.14 (0.41-3.13)	
No (n = 26 861)					
Events/participants	186/11 008	195/12 732	31/1949	35/1172	
HR (95% CI)	1 [Reference]	1.02 (0.83-1.25)	0.94 (0.64-1.38)	1.67 (1.15-2.40)	
Hypertension					
Yes (n = 8270)					.38
Events/participants	146/4151	101/3277	10/476	18/366	
HR (95% CI)	1 [Reference]	0.93 (0.71-1.21)	0.57 (0.30-1.08)	1.38 (0.83-2.29)	
No (n = 24 433)					
Events/participants	136/10 276	165/11 603	23/1641	21/913	
HR (95% CI)	1 [Reference]	1.16 (0.92-1.47)	1.08 (0.69-1.70)	1.84 (1.15-2.95)	
Hypercholesterolemia					
Yes (n = 9536)					.48
Events/participants	115/4566	84/4015	10/576	12/379	
HR (95% CI)	1 [Reference]	0.95 (0.71-1.26)	0.73 (0.38-1.41)	1.28 (0.69-2.35)	
No (n = 23 167)					
Events/participants	167/9861	182/10 865	23/1541	27/900	
HR (95% CI)	1 [Reference]	1.11 (0.89-1.38)	0.90 (0.58-1.41)	1.78 (1.17-2.72)	
Current smoking					
Yes (n = 4016)					.71
Events/participants	24/1697	20/1716	3/296	9/307	
HR (95% CI)	1 [Reference]	0.85 (0.46-1.56)	0.69 (0.21-2.33)	1.78 (0.81-3.94)	
No (n = 28 687)					
Events/participants	258/12 730	246/13 164	30/1821	30/972	
HR (95% CI)	1 [Reference]	1.10 (0.92-1.31)	0.91 (0.62-1.33)	1.60 (1.09-2.34)	

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAll HRs 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.

^bCalculated as weight in kilograms divided by height in meters squared.

$P = .07$). A threshold effect model revealed adequate model fit (likelihood ratio $\chi^2 = 2.13$; $P = .34$). Women consuming at least 2 drinks per day had an HR of 1.58 (95% CI, 1.14-2.20) compared with women consuming less than 2 drinks per day. Given that 3.9% of women in this study consumed at least 2 drinks per day, we estimated that approximately 2% 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, consuming at least 2 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; risk was also increased 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 less than 2 drinks per day. Accordingly, corresponding CIs widely overlapped, and none of the P values for interaction were statistically significant.

COMMENT

In the present study, alcohol consumption of up to 2 drinks per day was not associated with an increased risk of incident atrial fibrillation among initially healthy, middle-aged women. In contrast, the small group of women who consumed 2 or more alcoholic beverages per day had a 1.6-fold greater risk for atrial fibrillation relative to nondrinking women. While this finding needs to be interpreted with some caution because of the small number of women in some 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 2 alco-

holic beverages per day was similar to that among nondrinking women. The upper limits of the CIs 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 less than 2 drinks per day (Table 2). Thus, power seems to be an unlikely explanation for these null findings. Furthermore, models including a quadratic term suggested a nonlinear 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 2 alcoholic drinks per day does not confer an increased risk of incident atrial fibrillation.

Our findings are consistent with previous studies among men, which 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 (ie, approximately 35 drinks per week) had a 1.46-fold greater hazard of atrial fibrillation during follow-up compared with those in the lowest quintile.¹⁴ Similar findings have been reported from another Danish cohort, in which consuming at least 35 drinks per week was associated with a 1.63-fold greater hazard of incident atrial fibrillation among men.¹³ Thus, while the increase in risk was similar to that in 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 this middle-aged population. As a consequence, the absolute increase in risk associated with consuming 2 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. Because approximately 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 (approximately 8%). Taken together, our findings suggest a modest impact of increased 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 higher amounts of alcohol,^{5,13,14} several reasons may account for these differential findings. First, few women consuming higher 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, in which only 3.9% of participants consumed at least 2 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 preexisting cardiovascular disease,^{5,14,15} and since cardiovascular disease already confers a high risk of developing atrial fibrillation,²⁴⁻²⁷ it is possible that increased 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 perturbations in the autonomic nervous system,^{31,32} and 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. The study also has potential limitations. First, we included initially healthy, middle-aged female health professionals, most of them of white race. Thus, generalizability to men or to 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 these findings.

Third, screening electrocardiograms were not performed in this cohort; 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 underdetection is less likely. In support of this contention, the number of asymptomatic atrial fibrillation cases in this cohort (66 [10.1%]) was simi-

lar 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, accurately defining the initial episode of atrial fibrillation was challenging, especially when 10% of women were asymptomatic at the time of diagnosis. Misspecification of the time of incidence may have introduced some bias toward the null into the time-to-event analysis, but given the small number of events, this effect 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.

Sixth, 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.

CONCLUSIONS

In summary, these prospective data suggest that consumption of up to 2 alcoholic beverages per day is not associated with an increased risk of incident atrial fibrillation in initially healthy women. On the other hand, consuming higher amounts of alcohol was associated with an increased risk of atrial fibrillation. These findings were consistent across all subgroups considered.

Author Contributions: Dr 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.

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