ORIGINAL RESEARCH

Coffee Consumption and Risk of Atrial Fibrillation in the Physicians' Health Study

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***Background*—**Although coffee consumption is often reported as a trigger for atrial fibrillation (AF) among patients with paroxysmal AF, prospective studies on the relation of coffee consumption with AF risk have been inconsistent. Hence, we sought to assess the association between coffee consumption and risk of AF in men.

***Methods and Results*—**We prospectively studied men who participated in the Physicians' Health Study (N=18 960). Coffee consumption was assessed through self-reported food frequency questionnaires. The incidence of AF was assessed through annual questionnaires and validated through review of medical records in a subsample. Cox proportional hazard models were used to calculate hazard ratios and 95% CIs of AF. The average age was 66.1 years. A total of 2098 new cases of AF occurred during a mean follow-up of 9 years. Hazard ratios (95% CI) of AF were 1.0 (reference), 0.85 (0.71-1.02), 1.07 (0.88-1.30), 0.93 (0.74-1.17), 0.85 (0.74-0.98), 0.86 (0.76-0.97), and 0.96 (0.80-1.14) for coffee consumption of rarely/never, ≤1 cup/week, 2 to 4 cups/week, 5 to 6 cups/week, 1 cup/day, 2 to 3 cups/day, and 4+ cups/day, respectively; adjusting for age, smoking, alcohol intake, and exercise (*P* for nonlinear trend=0.01). In a secondary analysis the multivariable adjusted hazard ratio (95% CI) of AF per standard deviation (149-mg) change in caffeine intake was 0.97 (0.92-1.02).

***Conclusions*—**Our data suggest a lower risk of AF among men who reported coffee consumption of 1 to 3 cups/day. **(*J Am Heart Assoc*. 2019;8:e011346. DOI: 10.1161/JAHA.118.011346.)**

Key Words: atrial fibrillation • caffeine • cardiovascular disease • coffee • epidemiology and Nutrition

Atrial fibrillation (AF) is one of the most common types of serious arrhythmias, and its incidence has increased significantly during the past few years.[1] According to the Centers for Disease Control and Prevention, ≈2% of people younger than 65 years, and 9% of people older than 65 years, are living with AF in the United States, and these numbers are expected to increase in coming years.[2,3] More than 750 000 hospitalizations and 130 000 deaths are associated with AF each year in the United States, and this costs around $6 billion each year.[2,4] Mortality and morbidity related to AF remain high[5] despite advancement in AF management. Many risk factors have been identified for AF including high blood pressure,[6] diabetes mellitus,[7] heart failure,[8] obesity,[9] hyperthyroidism,[10] and ischemic heart disease.[6] However, only a few studies have examined the role of dietary habits on AF risk. Coffee is a major drink in the United States, and the trend has gone up during the past year.[11] Coffee contains caffeine, polyphenols, and diterpenes, which have been shown to influence cardiovascular disease.[12] Coffee promotes the vrelease of epinephrine, norepinephrine, and renin[13] and increases the sensitivity of myocardium to calcium,[14,15] which can affect heart rhythm. Few large studies have assessed the association of coffee consumption with the risk of AF, and results have been inconsistent. The Women's Health Study showed an increased riskof AF with 2 to 3 cups/day of caffeinated coffee.[16] On the other hand, a meta-analysis showed a nonsignificant inverse association of coffee intake with AF among women and a nonsignificant positive association among men.[17] Given the widespread use of coffee around the world and the inconsistent relation between coffee and AF, we sought to examine whether coffee intake is associated with AF risk in a cohort of men.

Methods

All data and materials have been made publicly available at the Physician Health website.

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Clinical Perspective

What Is New?

- In this prospective long-term cohort study, we found a lower risk of atrial fibrillation among men drinking 1 to 3 cups of coffee per day in the Physicians' Health Study (N=18 960, mean follow-up 9 years).
- However, we did not find any significant association between caffeine intake and atrial fibrillation risk in Physicians' Health Study participants.

What Are the Clinical Implications?

- Our findings will guide physicians making recommendations on coffee intake, one of the most consumed beverages in the world, and its long-term effect on atrial fibrillation risk, one of the most common types of arrythmia.

Study Population

We used participants from the PHS (Physicians' Health Study), which was divided into 2 phases, PHS I and PHS II. The PHS I was a randomized, double-blinded, and placebo-controlled trial of aspirin and β-carotene among 22 071 US male physicians (1982-1995). Detailed descriptions of PHS I have been published.[18,19] The PHS II evaluated the effect of different vitamin supplements on the prevention of cardiovascular disease, cancer, and age-related eye disease among 14 641 participants (1997-2007). Participants who replied to food frequency questionnaires from 1997 to 2001 were eligible for our study (N=21 082). We excluded a total of 2122 participants because of death before collection of data on coffee intake (n=7), history of AF (n=1962), and missing data on coffee consumption (n=153). The remaining 18 960 participants were used for current analyses. Each participant gave informed consent, and the study protocol was approved by the Institutional Review Board at the Brigham and Women's Hospital.

Assessment of Coffee Consumption/Caffeine Consumption

Participants provided dietary information through a food frequency questionnaire (1997-2001). Each subject was asked about average use of coffee during the past year. Possible answers were never or <1 cup/month, 1 to 3 cups/month, 1 cup/week, 2 to 4 cups/week, 5 to 6 cups/week, 1 cup/day, 2 to 3 cups/day, 4 to 5 cups/day, and 6+ cups/day. We combined adjacent categories where data were sparse for stable estimates. Nutrients including dietary caffeine were derived using Harvard University nutrient databases supplemented by manufacturers' information. The food frequency questionnaire has been validated in previous studies.[20,21]

Ascertainment of AF in the PHS

Participants reported new AF diagnoses through follow-up questionnaires. We performed a validation on 400 randomly selected AF cases. These participants were sent supplementary questionnaires to query about diagnosis and treatment of AF. In addition, we reviewed medical records for 225 new cases of AF. Self-reported AF was confirmed 99% of the time. A detailed description of the AF validation in the PHS has been published.[22]

Other Variables

Each participant provided information on age, weight, height, smoking (never, former, and current smoker), exercise (none, <1 day/week, 1-2 days/week, 3-4 days/week, and 5-7 days/week), and alcohol intake (never/rarely, monthly, weekly, daily, and >2+ cups/day), valvular heart disease, and parental history of myocardial infarction. We also obtained information on comorbidities including diabetes mellitus, blood pressure, hyperlipidemia, and heart failure at baseline and during follow-up a through self-reported questionnaire.

Statistical Analyses

We computed person-time follow-up from the food frequency questionnaire assessment until the first occurrence of atrial fibrillation, date of last follow up, death, or data-cut date (March 2012). Within each category of coffee intake we calculated the crude incidence rate of AF by dividing AF cases by person-time of follow-up. We computed hazard ratio (HR) and 95% CI through the Cox proportional model. After the crude model we controlled for age, smoking, alcohol, and exercise. We adjusted our final model for age, smoking, alcohol, exercise, body mass index, systolic blood pressure, use of blood pressure medication, diabetes mellitus, high cholesterol, heart failure, and coronary heart disease. Because we did not know the shape of the relationship between coffee and AF (linear versus nonlinear), we used a restricted cubic spline to assess the nature and shape of the relationship.

In a secondary analysis we examined the association between dietary caffeine and AF using the Cox proportional hazard model.

All data were analyzed though SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics of participants according to coffee consumption are described in Table 1. Among the 18 960

Table 1. Baseline Characteristics of 18 960 Male Physicians According to Coffee Consumption

Variables	Categories of Coffee Consumption							
	Almost Never (N=3946)	≤1 cup/wk (N=1419)	2 to 4 cups/wk (N=1036)	5 to 6 cups/wk (N=766)	1 cup/d (N=3453)	2 to 3 cups/d (N=6432)	4+ cups/d (N=1908)	*P* for Difference
Age, y*	66.6±9.5	66.9±9.0	66.9±8.8	67.7±9.1	67.9±9.4	65.3±8.8	62.7±8.2	<0.0001
Body mass index, kg/m^2*	25.5±3.3	25.6±3.4	25.7±3.5	25.9±3.3	25.5±3.2	26.0±3.3	26.3±3.5	<0.0001
Exercise, %								0.22
None	34.3	34.5	33.3	34.5	37.3	34.5	34.9	
<1 d/wk	3.2	2.5	3.2	1.9	3.0	2.8	3.4	
1 to 2 d /wk	16.1	17.0	16.7	16.8	16.4	16.8	16.5	
3 to 4 d/wk	29.2	29.7	30.6	31.8	28.9	30.6	29.1	
5 to 7 d/wk	17.2	16.3	16.3	15.1	14.6	15.3	16.1	
Alcohol use, %								<0.0001
Never	33.5	20.1	18.9	16.5	15.8	12.5	16.2	
Monthly	8.4	8.3	8.4	6.6	5.7	5.5	6.0	
Weekly	35.3	43.4	42.4	47.2	38.4	36.3	34.8	
Daily	11.2	15.5	16.3	15.8	21.2	20.3	16.8	
≥2 cups/d	11.6	12.7	14.0	14.0	19.0	25.5	26.2	
Smoking, %								<0.0001
Never	66.3	61.5	59.0	55.6	52.5	49.8	45.2	
Past	31.9	36.2	39.0	41.3	44.7	46.2	46.4	
Current	1.8	2.3	2.0	3.1	2.8	4.0	8.4	
Heart failure, %	1.8	1.7	1.2	1.2	1.6	0.8	0.6	<0.0001
Valvular heart disease, %	1.5	2.1	0.9	2.1	1.3	1.1	0.6	0.0007
Parental history of myocardial infarction, %	10.7	9.6	12.1	9.3	9.9	10.6	11.7	0.16
High cholesterol, %	42.1	45.8	44.6	47.5	44.2	41.1	38.3	<0.0001
Diabetes mellitus, %	7.3	8.6	8.7	10.1	7.9	6.5	5.7	<0.0001
Hypertension medication, %	35.9	37.5	37.5	39.8	38.2	32.8	27.7	<0.0001
Coronary heart disease, %	14.2	14.2	12.6	15.9	13.3	9.7	8.0	<0.0001
Energy intake, kcal*	1674±522	1669±532	1659±509	1541±472	1669±515	1688±510	1780±558	<0.0001
Caffeine intake, mg*	55±65	64±60	90±51	120±47	138±48	281±53	496±97	<0.0001
Systolic blood pressure, mm Hg*	129±29	129±22	129±25	131±36	131±35	129±30	127±20	0.0041

Missing numbers according to variables: body mass index (n=26), systolic blood pressure (n=1759), alcohol intake (n=44), exercise (n=340), smoking (n=12), history of hypercholesterolemia (n=464), taking hypertension medications (n=581), parenteral history of myocardial infraction (1316).
*Mean and standard deviation.

participants, the mean age was 66.1 years, and the average follow-up was 9 years. A total of 2098 new cases of AF occurred during follow-up. Crude incidence rates of AF were 13.5, 11.9, 15.0, 13.5, 12.7, 11.4, and 10.6 per 1000 person-years, from the lowest to highest category of coffee consumption, respectively.

In our primary analysis multivariable adjusted HR (95% CI) showed a lower risk of AF only among participants who reported coffee consumption of 1 to 3 cups/day (Table 2, *P* for nonlinear trend=0.01). The fitted spline curve suggested a J-shaped association between coffee consumption and AF risk with inverse association up to 3 cups/day (Figure). Inclusion of body mass index, systolic blood pressure, use of blood pressure medication, diabetes mellitus, high cholesterol, heart failure, and coronary heart disease did not alter the results (HR [95% CI] 0.84 [0.69-1.02], 1.05 [0.86-1.29], 0.88 [0.69-1.13], 0.87 [0.75-1.00], 0.85 [0.75-0.97], and 0.93 [0.77-1.12], for increasing categories of coffee intake, respectively).

In a secondary analysis we did not find any significant relationship between dietary caffeine intake and risk of AF (HR

Table 2. Incidence Rate and HR (95% CI) of AF According to Coffee Consumption Categories (N=18 960)

Coffee Consumption	Cases	Incidence Rate	Crude HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Almost never	472	13.5	1.0	1.0	1.0	1.0
≤1 cup/wk	151	11.9	0.88 (0.74-1.06)	0.86 (0.71-1.03)	0.85 (0.71-1.02)	0.84 (0.69-1.02)
2 to 4 cups/wk	137	15.0	1.11 (0.92-1.34)	1.09 (0.90-1.32)	1.07 (0.88-1.30)	1.05 (0.86-1.29)
5 to 6 cups/wk	89	13.5	1.00 (0.80-1.26)	0.95 (0.76-1.19)	0.93 (0.74-1.17)	0.88 (0.69-1.13)
1 cup/d	383	12.7	0.94 (0.82-1.08)	0.87 (0.76-0.99)	0.85 (0.74-0.98)	0.87 (0.75-1.00)
2 to 3 cups/d	675	11.4	0.84 (0.75-0.94)	0.91 (0.81-1.03)	0.86 (0.76-0.97)	0.85 (0.75-0.97)
4+ cups/d	191	10.6	0.78 (0.66-0.92)	1.02 (0.86-1.21)	0.96 (0.80-1.14)	0.93 (0.77-1.12)
P for linear trend			0.0006	0.28	0.05	0.04

Incidence rate, cases/1000 person-years. Model 1: Adjusted for age. Model 2: Adjusted for age, smoking, alcohol intake (never, rarely, monthly, weekly, daily, >2 cups/d), and exercise (none, <1 d/wk, 1-2 d/wk, 3-4 d/wk, 5-7 d/wk). Model 3: Adjusted for variables in Model 2 plus BMI, systolic blood pressure, taking blood pressure medication, diabetes mellitus, high cholesterol, heart failure, and coronary heart disease. AF indicates atrial fibrillation; BMI, body mass index; HR, hazard ratio.

[95% CI] of AF per standard deviation [149-mg] change in caffeine intake was 0.96 [0.91-1.01] in a model adjusted for age, smoking, alcohol, exercise, body mass index, systolic blood pressure, use of blood pressure medication, diabetes mellitus, high cholesterol, heart failure, and coronary heart disease).

Discussion

In this cohort of US male physicians we found a lower risk of AF only among participants drinking 1 to 3 cups of coffee per day; consumption below 1 cup/day or above 3 cups/day was not associated with AF risk.

Our findings are consistent with the NCCHC (Northern California Comprehensive Health Care Study),[23] which reported a lower risk of AF-related hospitalization among people drinking ≥4 cups of coffee per day (HR [95% CI] 0.81 [0.69-0.96]). The Northern California Comprehensive cohort assessed AF risk among hospitalized patients only, so it could have missed out-of-hospital AF cases. Furthermore, the Danish Diet Cancer and Health Study[24] also found a lower risk of AF among people consuming 6 to 7 cups of coffee per day (HR [95% CI] 0.79 [0.64-0.98]).

Contrary to our results, a study by Wilhelmsen et al[25] (N=7495, mean follow-up 25 years) reported a 24% higher risk of AF with coffee intake of 1 to 4 cups/day compared with participants who did not drink coffee (OR [95% CI] 1.24 [1.00-1.54], adjusting for age only). Of note is that Wilhelmsen et al enrolled participants at higher risk for AF than our cohort (subjects enrolled for intervention trial against smoking, blood pressure, and hypercholesterolemia). The Women's Health Study[16] also showed a 36% higher risk of AF with caffeinated coffee intake of 2 to 3 cups/day among women in a multivariable model (HR [95% CI] 1.36 [1.12-1.65]). The difference in outcomes between the Women's Health Study and our study could be due to gender difference and/or to a higher percentage of current smokers in the Women's Health Study (12.3% versus 3.5% in our study).

A study by Larsson et al did not find any significant association between coffee consumption and risk of AF among a Swedish cohort.[17] In addition, a meta-analysis by Larsson et al, including 6 studies,[17] did not find any significant association between coffee intake and AF risk,

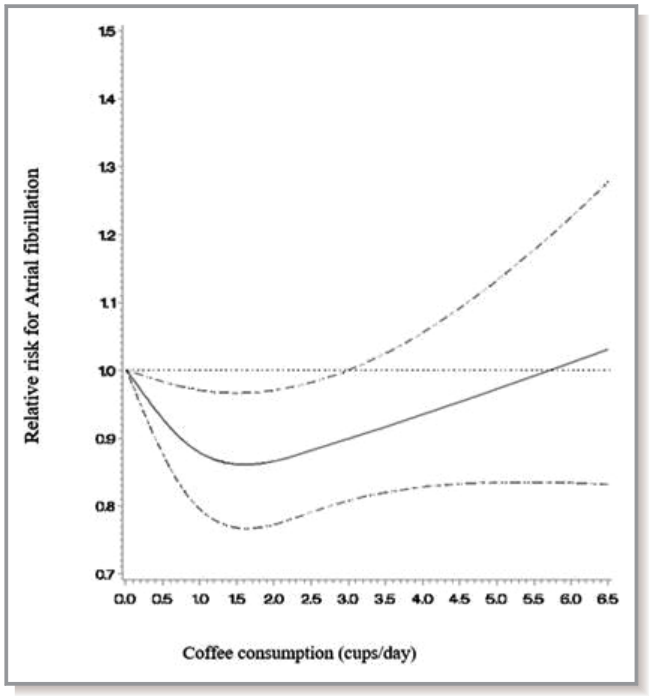

Figure. Spline curve assessing the relationship between coffee consumption and atrial fibrillation risk. (Dashed curves indicate 95% CI band.) Adjusted for age, smoking, alcohol, and exercise (*P* for nonlinear trend=0.01).

comparing the highest versus the lowest category of coffee consumption (RR [95% CI] 0.96 [0.80-1.08]).

We did not find any significant association between dietary caffeine intake and AF risk in our secondary analysis. The observed effect in the primary analysis could be due to other components of coffee. Coffee contains a high number of antioxidants including polyphenol, cafestol, polyphenol, trigonelline, chlorogenic acid, and quinine, which could reduce cardiovascular events through anti-inflammatory effect. Previous studies have reported an inverse association between polyphenols and cardiovascular disease.[26] Additionally, antioxidants have been reported to be protective against AF.[27] Furthermore, perioperative antioxidant supplementation has been reported to prevent AF after cardiac surgery in a meta-analysis.[28]

Our study has some limitations. First, our cohort consisted of male physicians, who usually are more health conscious than the general population, which could limit the generalizability of our findings. However, a significant proportion of participants used alcohol and tobacco and were not exercising. Second, we did not have data on coffee preparation methods including boiled, filtered versus unfiltered, and types of brewing; and we were unable to differentiate caffeinated versus decaffeinated coffee use in our cohort. Third, we lacked repeated measures of coffee intake over time for further analyses. However, our study has some strengths including a large sample size, long-term follow-up, prospective study design, and standard method of ascertainment of AF.

Conclusion

Our data suggest a lower risk of AF among men drinking 1 to 3 cups of coffee per day but no meaningful relationship with other frequencies of coffee intake.

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Author Contributions

Bodar and Djoussé created the study design, and Chen did the statistical analysis. Gaziano, Albert, and Djoussé were responsible for the acquisition of data. Bodar drafted this article with critical review and editing by Djoussé, Chen, Gaziano, and Albert. Gaziano and Djoussé obtained funding for this study. All authors reviewed the article and have a responsibility for its final content.

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Disclosures

None.

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