HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2016 August 15.

Published in final edited form as:

Am J Cardiol. 2015 August 15; 116(4): 563–566. doi:10.1016/j.amjcard.2015.05.009.

Chocolate Consumption and Risk of Atrial Fibrillation (From the Physicians' Health Study)

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Abstract

Chocolate consumption has been shown to protect against various cardiovascular endpoints, however little is known about the association between chocolate consumption and incident atrial fibrillation (AF). Therefore, we prospectively examined the association between chocolate consumption and incident AF in a cohort of 18,819 US male physicians. Chocolate consumption was ascertained between 1999 and 2002 via a self-administered food frequency questionnaire. Incident AF was ascertained through yearly follow-up questionnaires. Cox regression was used to estimate relative risks of AF. The average age at baseline was 66 (±9.1) years. During a mean follow up of 9.0 (±3.0) years, 2,092 cases of AF occurred. Using <1/month of chocolate consumption as the reference group, multivariable adjusted hazard ratios (95% confidence interval) for AF were 1.04 (0.93-1.18), 1.10 (0.96-1.25), 1.14 (0.99-1.31), and 1.05 (0.89-1.25) for chocolate intake of 1-3/month, 1/week, 2-4/week, and ≥5/week (p for trend 0.25), respectively. In a secondary analysis, there was no evidence of effect modification by adiposity (p interaction = 0.71) or age (p interaction = 0.26). In conclusion, our data did not support an association between chocolate consumption and risk of AF among US male physicians.

Keywords

Chocolate consumption; Atrial Fibrillation; Risk factors; Epidemiology

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Atrial fibrillation (AF) is an extremely common cardiac arrhythmia in clinical practice. Approximately 2.2 million people in the United States (US) and 4.5 million people across Europe are diagnosed with AF [1]. The annual incidence of AF increases from <0.1% among those under 40 to 1.5% in women and 2% in men older than 80 years of age [2,3]. The prevalence of AF increases with advancing age (approaching 8% among those >80 years [4-6]). While AF can be associated with structural heart disease, a large proportion of AF occurs in the absence of known cardiac disease. Data from prior studies have demonstrated beneficial effects of light-to-moderate physical activity on AF risk [7]. In contrast, there is a positive relation between obesity [8], inflammation [9], heavy alcohol consumption [10], hypertension [10], type 2 diabetes mellitus (T2DM) [11], and dyslipidemia [12] with AF. There is evidence for a beneficial effect of certain foods such as olive oil, nuts, fish, fruits, vegetables, fiber, whole grains on cardiovascular health [13,14]. Recent studies have shown beneficial effects of chocolate consumption on several risk factors for AF including hypertension [15,16], T2DM [17,18], CHD [19,20], and heart failure (HF) [21]. However, the association between chocolate consumption and incident AF has not been investigated in a prospective cohort study. Therefore, the current study sought to prospectively assess the association of chocolate consumption with incident AF among US male physicians.

METHODS

The Physicians' Health Study (PHS) I is a completed randomized, double-blind, placebo-controlled trial, designed to study the effects of low-dose aspirin and beta-carotene on cardiovascular disease and cancer among US male physicians. In 1997, PHS II trial enrolled 7,641 physicians from PHS I along with 7,000 newly recruited physicians to study the effects of vitamins on cardiovascular disease and cancer. A detailed description of the PHS I and II has been published [22,23]. Of the 29,071 total participants in the PHS, 21, 075 completed a food frequency questionnaire (FFQ) between 1999 and 2002. We excluded people with prevalent AF (n=1,962) and missing data on chocolate consumption (n=294). Thus, a final sample of 18,819 participants was used for current analyses. Each participant gave written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

Information on chocolate consumption was obtained by using a FFQ. Participants were asked to report average consumption of 1 oz (approx. 28.4 g) of chocolate during the past year. Possible responses were: never or less than once per month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, and 6+/day. The validity and reproducibility of FFQs have been previously published [24,25].

Incident AF was ascertained through follow-up questionnaires. In PHS, self-reported AF has been previously validated in a random sample of 400 PHS participants, using a more detailed questionnaire on the diagnosis of AF and the review of medical records by cardiologists [26].

Data on demographics, anthropometrics, smoking, alcohol, exercise frequency, energy intake, along with history of hypertension, T2DM and CHD were obtained at baseline. For alcohol consumption, subjects were asked the following question: "How often do you

usually consume alcoholic beverages?" Possible responses were: rarely/never, 1–3 times/month, 1 time/week, 2–4 times/week, 5–6 times/week, daily, and ≥ 2 times/day. Hypertension was defined as anyone who self- reported a diagnosis of hypertension, blood pressure >140/90 mmHg, or use of antihypertensive drugs. CHD diagnosis (angina, myocardial infarction, and coronary artery bypass grafting) was validated by the PHS Endpoint Committee [23]. T2DM diagnosis was self-reported and validated by detailed review of the medical records in a subsample [27].

We classified each subject into one of the following categories of chocolate consumption: <1/month, 1-3/month, 1/week, 2-4/week, and ≥5/week. We computed person-time of follow up from the time when chocolate consumption was assessed until the first occurrence of a) AF, b) death, or c) the date of last available follow up. Baseline demographic variables were recorded and compared across the categories of chocolate consumption.

We used Cox proportional hazard models to compute multivariable adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) using participants reporting <1/month chocolate consumption as the reference group. Potential confounding was assessed for established risk factors of AF. First, we adjusted for age (≤55, >55-≤65, >65-≤75, >75 years) in model 1. Second, we additionally controlled for body mass index (continuous), smoking status (never, past, and current smokers), alcohol consumption (never, monthly, weekly, and daily), exercise frequency (rarely/never, 1-2 days/week, 3-4 days/week, and 5-7 days/week), and energy intake (quintiles) in model 2. Finally, in model 3, we adjusted for factors included in model 2 as well as potential mediators such as history of hypertension, T2DM, and CHD.

In secondary analysis, we evaluated whether there were statistically significant interactions between chocolate consumption and body mass index or age by using a product term of both variables in a hierarchical model. Assumptions for proportional hazard models were tested (by including main effects and product terms of chocolate consumption and logarithmic-transformed person-time of follow up) and were met (all p values >0.05). All analyses were conducted using SAS, version 9.3 (SAS Institute, NC). Significance level was set at 0.05.

RESULTS

Table 1 shows baseline characteristics according to chocolate consumption. Mean age of the study participants at baseline was 66.0 ±9.1 years. Compared with chocolate consumption of <1/month, higher chocolate consumption was associated with a higher energy intake, higher proportion of being white or never smoker and a lower proportion of daily alcohol consumption, exercising frequency <1/week, T2DM, hypertension, CHD, and higher energy intake.

During a mean follow up of 9.0 (±3.0) years, 2,092 cases of AF occurred. Using <1/month chocolate consumption as the reference group, multivariable adjusted hazard ratios (95% CI) for AF were 1.04 (0.93-1.18), 1.10 (0.96-1.25), 1.14 (0.99-1.31), and 1.05 (0.89-1.25) for people reporting an average chocolate consumption of 1-3/month, 1/week, 2-4/week, and ≥5/week (p for trend 0.25), respectively (Table 2).

In a secondary analysis, there was no effect modification seen for chocolate consumption-AF association by adiposity (p interaction = 0.71) or age (p interaction = 0.26).

DISCUSSION

Our data showed no significant association between chocolate consumption and incident AF. In a secondary analysis, neither adiposity nor age modified the relationship between chocolate consumption and incident AF. To the best of our knowledge, this is the first large prospective study to assess the association between chocolate consumption and incident AF.

Despite a lack of association seen in our study, chocolate consumption has been associated with favorable effects on important risk factors for AF. Ried et al [15] in a meta-analysis of randomized controlled trials demonstrated a beneficial effect of dark chocolate consumption on blood pressure. The effect seen was only significant among prehypertensive and hypertensive subgroups. Our results are consistent with the aforementioned study demonstrating no beneficial effects of chocolate on risk factor for AF among healthy participants. Of note is that the mean duration of follow up in our study (9.0 y) which was much longer than that reported in above study (longest duration 18 wks).

Djousse et al [19] in a cross-sectional design study on National Heart, Lung, and Blood Institute Family Heart Study participants demonstrated an inverse relationship between chocolate consumption and prevalent CHD. Lewis et al [20] in a prospective cohort study of elderly women followed for >9.5 yrs demonstrated a lower risk of hospitalization or death from CHD. Matsumoto et al [18] in a prospective cohort study, conducted on cohort similar to ours, demonstrated a beneficial effect of moderate chocolate consumption on the risk of T2DM. Although the study designs, participants, and duration of follow up for these studies were very comparable to our study, we failed to demonstrate any mediator effects of T2DM or CHD.

Chocolate is derived from the plant theobroma cacao, components of which include methylxanthine alkaloids, theobromine, and caffeine. In a meta-analysis of 6 prospective cohort studies an inverse association was seen between habitual caffeine intake and AF risk (overall trend p=0.015;) in a dose-response meta-analysis [28]. However, we did not have information on caffeine content of chocolate used in our study to explain the observed difference in results.

Several additional factors could have lead to this null association. Information on chocolate consumption was self-reported. Inaccurate recall, exposure misclassification, and inability to completely capture all episodes of chocolate consumption could have biased our results. A single assessment of chocolate consumption might have been inadequate to evaluate the role of chocolate consumption on incident AF. We did not have data on the amount or type of chocolate consumed. Our inability to capture asymptomatic (subclinical) AF could have led to underestimation of incident AF in our study. Furthermore, participants in this study were male and mostly Caucasian physicians, thereby limiting the generalizability of our findings to other ethnic groups or general population. In the absence of randomization, we cannot exclude chance, confounding by unmeasured factors, or residual confounding as possible

explanation for our findings. Nevertheless, the large sample size, more than 5 years of follow up, a standardized and systematic collection of covariates, availability of a large number of covariates, and a validation of AF and comorbidities in the PHS are strengths of this study.

ACKNOWLEDGEMENTS/FUNDING

We are indebted to the participants in the PHS for their outstanding commitment and cooperation and to the entire PHS staff for their expert and unfailing assistance.

This work was supported by the National Heart, Lung, and Blood Institute (R21 HL088081 to L.D.). The Physicians' Health Study is supported by grants CA-34944, CA-40360 and CA-097193 from the National Cancer Institute and grants HL-26490, and HL-34595, from the National Heart, Lung and Blood Institute of Health, Bethesda, MD. Funding agencies play no role in the data collection, analysis and manuscript preparation.

Acknowledgement to all contributors who do not meet the criteria for authorship: N/A

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Table 1

Baseline characteristics of 18,819 US male physicians according to chocolate consumption

Variables	Chocolate Consumption				
	<1/month (n=4930)	1-3/month (n=5513)	1/week (n=3655)	2-4/week (n=2993)	≥5/week (n=1728)
Age (years)	67 ± 9	66 ± 9	66 ± 9	66 ± 10	66 ± 10
Body mass index (kg/m^2)	26 ± 3	26 ± 3	26 ± 3	26 ± 3	26 ± 3
White	85 %	91 %	94 %	95 %	96 %
Smoker					
Never	51 %	54 %	57 %	58 %	57 %
Past	45 %	42 %	40 %	38 %	39 %
Current	4 %	3 %	3 %	3 %	4 %
Exercise (days a week)					
<1	38 %	38 %	36 %)	37 %	37 %
1-2	15 %	17 %	17 %	16 %	15 %
3-4	28 %	29 %	30 %	31 %	30 %
5-7	17 %	15 %	15 %	14 %	16 %
Alcohol Consumption					
Never	17 %	15 %	17 %	19 %	20 %
Monthly	7 %	7 %	8 %	9 %	9 %
Weekly	36 %	39 %	40 %	40 %	39 %
Daily	39 %	37 %	35 %	32 %	32 %
Prevalent hypertension	49 %	45 %	44 %	41 %	43 %
Prevalent diabetes mellitus	12 %	7 %	5 %	5 %	5 %
Prevalent coronary heart disease	14 %	12 %	10 %	10 %	11 %
Prevalent heart failure	1 %	1 %	1 %	1 %	2 %
Calories (kcal)	1534 ± 484	1622 ± 481	1703 ± 497	1792 ± 512	2040 ± 588

Data are presented as means ±SD or percentages. Few participants had missing data: Race (n=67), smoking (n=12), alcohol (n=106), exercise (n=335), diabetes (n=8), hypertension (n=39), calories (n=846), and body mass index (n=2).

Table 2

Hazard ratios (95% CI) for atrial fibrillation according to chocolate consumption in Physicians' Health Study

Chocolate Consumption	Cases/n	Crude Incidence Rate (per 1000 person-years)	Hazards Ratio (95% Confidence Interval)			
			Unadjusted	Model 1	Model 2	Model 3
<1/month	522/4930	11.92	1.0	1.0	1.0	1.0
1-3/month	613/5513	12.22	1.02 (0.91-1.15)	1.06 (0.95-1.20)	1.04 (0.92-1.17)	1.04 (0.93-1.18)
1/week	417/3655	12.54	1.05 (0.92-1.20)	1.09 (0.96-1.24)	1.07 (0.94-1.22)	1.10 (0.96-1.25)
2-4/week	352/2993	12.85	1.08 (0.94-1.23)	1.12 (0.98-1.28)	1.10 (0.96-1.26)	1.14 (0.99-1.31)
≥5/week	188/1728	12.23	1.02 (0.87-1.21)	1.03 (0.88-1.22)	1.03 (0.87-1.22)	1.05 (0.89-1.25)
p for linear trend			0.45	0.33	0.38	0.25

Model 1: Age adjusted.

Model 2: Age, body mass index, smoking, alcohol, exercise, and calories.

Model 3: Age, body mass index, smoking, alcohol, exercise, and calories, history of hypertension, diabetes mellitus, and coronary heart disease.