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ORIGINAL CONTRIBUTION

Alcohol consumption and the risk of coronary heart disease in postmenopausal women with diabetes: Women's Health Initiative Observational Study

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Abstract
Background Although several observational studies have consistently reported an inverse association between moderate alcohol consumption and risk of coronary heart disease (CHD), it is yet not well established if this association also exists among people with type 2 diabetes. The aim of this study is to evaluate the association between the frequency and quantity of alcohol intake and the risk of developing CHD among postmenopausal women with diabetes.
Methods We conducted a prospective cohort study, which included 3,198 women with self-reported diabetes and without any history of cardiovascular disease at baseline, in the Women's Health Initiative Observational Study. Alcohol intake was assessed by a semiquantitative food frequency questionnaire. The primary outcome of this study was CHD, which was validated by medical record review. Cox proportional hazards regression was used to estimate the hazard ratio (HR) for the association of alcohol intake and risk of incident CHD while adjusting for several potential confounders.
Results During the 22,546 person-years of follow-up, there were 336 incident cases of CHD. Both frequency and quantity of alcohol intake were inversely associated with the risk of developing CHD. Compared to nondrinkers, the multivariable HRs across categories of frequency of alcohol consumption ($\leq$0.5, 0.5–2 and $\geq$2 drinks/week) were 0.89 (95% confidence intervals [CI]: 0.63, 1.26), 0.84 (95% CI: 0.56, 1.25) and 0.65 (95% CI: 0.43, 0.99), respectively (p for trend: 0.04). This association did not appear to differ based on the type of the alcoholic beverage consumed.
Conclusions Moderate alcohol consumption of postmenopausal women with type 2 diabetes may have a benefit on CHD similar to that seen in postmenopausal nondiabetic women. The potential risks of alcohol on noncardiac outcomes may need consideration when recommending alcohol to women with diabetes.

Keywords Alcohol · Cardiovascular · Women · Diabetes

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Introduction

Individuals with type 2 diabetes mellitus (DM) are at an elevated risk of coronary heart disease (CHD), which is the leading cause of death in this population. The risk of death from CHD among individuals with DM can be comparable to that in people with a previous history of myocardial infarction (MI) [1]. The presence of DM may have a greater impact on women compared to men, since the presence of DM eliminates the usual gender advantage for women with respect to CHD mortality [2].

The role of diet and lifestyle in the prevention of CHD is well established. Several prospective studies have reported an inverse association between moderate alcohol consumption and risk of developing CHD in apparently healthy men and women [3–7]. This is mainly attributed to the beneficial effect of alcohol on circulating HDL-cholesterol levels [6, 7]. Furthermore, alcohol may induce favorable effects on dyslipidemia, hyperinsulinemia and coagulation disturbances [6, 8, 9] that often co-exist in diabetic individuals. Hence, moderate alcohol consumption could potentially offer a particularly strong benefit among people with DM. However, only a few studies have prospectively evaluated the association between alcohol consumption and the risk of developing CHD among those with DM [10–14]. Although, two of these studies also included women, the number of postmenopausal diabetic women was limited [10, 13]. Therefore, we conducted a study to evaluate the association between alcohol intake and the risk of incident CHD in a large population of postmenopausal women with DM at baseline in the Women's Health Initiative Observational Study. Since metabolic derangement related to fuel homoeostasis is a predominant feature in DM, frequency was evaluated in addition to the quantity of alcohol consumption.

Methods

The Women's Health Initiative is an ongoing, ethnically and geographically diverse, multicenter clinical trial and observational study designed to address some of the major causes of morbidity and mortality in postmenopausal women. Details of the scientific rationale, eligibility requirements and other aspects of the design of the WHI have been published elsewhere [15]. Women were enrolled in the WHI Observational Study (WHI-OS) between October 1993 and December 1998 at 40 geographically dispersed clinical centers in the USA ($n = 93{,}676$). Study eligibility was limited to postmenopausal women aged 50–79 years at enrollment. At baseline, women underwent a physical examination and fasting blood specimen collection and completed screening and enrollment questionnaires. The latter elicited extensive information on several risk factors including age, education, race/ethnicity, body mass index (BMI), smoking, alcohol intake, physical activity and medical history (CHD, angina, stroke, DM, hypertension, etc.). Dietary intake data were collected using a semi-quantitative food frequency questionnaire (FFQ), the characteristics and validation of which has been previously reported [16]. The physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent of that activity (MET) and summed for all activities performed, with the result expressed as the average MET-hours per week. All participants provided a written informed consent, and the institutional review boards of each of the participating institutions (http://www.whiscience.org/collaborators/investigators.php) approved the study.

Assessment of DM at baseline

Self-reported DM at baseline was ascertained using a medical questionnaire, which enquired about diagnosis, duration of and treatment for DM. In the WHI-OS, 5,318 women reported a diagnosis of DM at baseline. In our study, we excluded women with prevalent CHD and stroke ($n = 1{,}809$) and those with missing information on alcohol consumption ($n = 183$) and follow-up data ($n = 128$). Thus, the current study was conducted among 3,198 postmenopausal women with self-reported DM at baseline.

Assessment of alcohol intake

In the WHI, women who reported to have consumed at least 12 alcoholic drinks during their entire life were asked whether they were still drinking. Nondrinkers were defined as women with <12 drinks of any kind of alcohol in their entire life. Further, among current drinkers, the frequency of alcohol consumption and the associated serving sizes were recorded in the food frequency questionnaire (FFQ) [16]. Information on intake of different alcoholic beverages including beer, wine and liquor over the past 3 months was collected separately. In addition to frequency, alcohol intake was also calculated in grams of ethanol per day. The conversion factors were 12.80, 10.97 and 13.00 g of ethanol for 12 ounces of beer, 4 ounces of wine and 1.5 ounces of liquor, respectively. Alcohol consumption was classified into groups based on frequency (nondrinkers, >0 to <0.5, 0.5 to <2 and ≥2 drinks/week) as well as quantity (nondrinkers, >0 to <1, 1 to <4 and ≥4 g/day). In a study evaluating existing studies on self-reported alcohol intake from FFQs, investigators reported that ranking of individuals according to intake was satisfactory, with weighted correlation coefficients between methods ranging from 0.63 to 0.73 [17]. A separate questionnaire was used among women who reported to be former drinkers to inquire if alcohol intake was stopped for "health problems" or "non-health problems".

Ascertainment of outcome

The primary outcome of this study was CHD, which included fatal and nonfatal MI, coronary artery bypass grafting and percutaneous transluminal coronary angioplasty. Potential outcomes were identified from self-reports

on annual medical history or third-party reports directly to clinic staff in the intervals between questionnaires. Participant deaths were identified through communication with proxy respondents and also through National Death Index searches. Medical records were obtained for all events and validated by a local physician adjudicator, who adjudicated the event using standardized criteria and coded specifics of the diagnosis. Confirmation of self-reported nonfatal MI was based on medical record review with documentation of new chest pain syndromes accompanied by characteristic evolution of electrocardiographic changes or clear evidence of myocyte damage as evidenced by elevated creatine kinase-MB or troponin values. Deaths caused by coronary disease were confirmed on the basis of death certificates, autopsy reports, circumstances of death, electrocardiogram, laboratory test results and reports from all relevant procedures. All outcomes including CHD and deaths in the WHI were then centrally adjudicated by a panel of physicians.

Statistical analysis

Person-months of follow-up for women with DM at baseline were accrued from the date of enrollment until the occurrence of a CHD event, death, dropout or August 2005. Women were divided into four categories of alcohol intake, either based on frequency (nondrinkers, >0 to <0.5, 0.5 to <2 and ≥2 drinks/week) or quantity (nondrinkers, >0 to <1, 1 to <4 and ≥4 g/day). Cox proportional hazard regression was used to calculate the hazard ratio (HR) for CHD as the ratio of the CHD incidence rate for a given category of alcohol intake compared with that for the nondrinker category. The multivariable models included several potential confounders including age (50–59, 60–69 and 70–79 years), race/ethnicity, physical activity (quintiles of METs/week), BMI (≤20, 20–24.9, 25.0–29.9 and ≥30 kg/m^2), smoking (never, past and current), family history of MI (yes/no), hypertension (yes/no), high cholesterol (yes/no), hormone use (never users, past users and current users), regular aspirin use (yes/no), duration of DM and dietary factors such as saturated and polyunsaturated lipids and fiber intakes. We evaluated the proportional hazard assumption by conducting likelihood ratio tests comparing models with and without interaction terms between exposure categories and follow-up time. None of these tests was statistically significant, i.e., there was no violation of the proportional hazards assumption. Tests of linear trend across categories of alcohol intake were conducted by assigning a score for each alcohol intake category and including this variable as a continuous variable in the model. All analyses were conducted using the Statistical Analyses Software (SAS®, Cary, NC) and p values of less than 0.05 were considered to be statistically significant.

Results

During the 22,546 person-years of follow-up among postmenopausal women who reported a diagnosis of DM at baseline, we documented 336 incident cases of CHD (fatal events = 58). In the WHI-OS, 68% of women with DM were nondrinkers and those who consumed alcohol were predominantly light-to-moderate drinkers. The median intake in the highest category was approximately 11.2 g/day. Table 1 shows the baseline characteristics among the 3,198 postmenopausal women with DM at baseline by frequency of alcohol consumption. Compared to nondrinkers, women who consumed alcohol had a lower BMI and waist circumference, less hypertension, undertook more physical activity and were more likely to use aspirin regularly.

Table 2 shows the HRs and their 95% confidence intervals (CI) for the association between frequency of alcohol consumption (drinks/week) and risk of incident CHD in diabetic women. Compared to nondrinkers, the age and race-adjusted HRs across categories of alcohol consumption (≤0.5, 0.5 to 2 and ≥2 drinks/week) were 0.90 (95% CI: 0.64, 1.26), 0.83 (95% CI: 0.56, 1.23) and 0.62 (95% CI: 0.41, 0.93), respectively (p for trend: 0.02). Further adjustment for several potential confounders including smoking, BMI, family history of MI, history of hypertension, high cholesterol, hormone and aspirin use, physical activity and DM duration did not have an impact on these HRs. Similarly, Table 3 shows the HRs for incident CHD in women with DM based on quantity (g/day) of alcohol intake. As seen for frequency of alcohol intake, diabetic women who had higher amount of alcohol intake had a reduced risk of developing CHD; the multivariate HR comparing women who consumed the highest amount of alcohol (≥4 g/day) to women who did not drink was 0.63 (95% CI: 0.42, 0.95; p for trend: 0.02). Further, the results from stratified analysis based on the number of drinks per week of specific types of alcohol (wine and non-wine beverages) suggested that the alcohol–CHD association did not vary based on the type of alcoholic beverage consumed (Table 4). However, these stratified analyses were restricted by a relatively small number of cases and should be, therefore, interpreted with caution. The results were similar when we also accounted for the type of diabetes medication; the multivariable HR comparing those with ≥2 drinks/week to those with ≤0.5 drinks/week was 0.71 (95% CI: 0.47, 1.08; p for trend: 0.037). In addition, in this study we did not observe any effect modification of the association between alcohol intake and CHD risk by age, race, smoking status, BMI, family history of MI or presence of hypercholesterolemia and hypertension, although the power for these analyses was limited.

Table 1 Baseline characteristics based on frequency of alcohol consumption among 3,198 diabetic women in the Women's Health Initiative

Characteristic	Nondrinkers ($n = 2,188$)	<0.5 drinks/week ($n = 376$)	0.5 to <2.0 drinks/week ($n = 287$)	≥2 drinks/week ($n = 347$)	p value*
Median alcohol intake (g/day)	0	0.9	2.3	11.2	
Age, mean ± SD (years)	64.3 ± 7.1	63.8 ± 7.1	63.9 ± 7.1	64.6 ± 7.1	0.33
Race/ethnicity (%)					
Caucasian	58.9	72.3	80.1	84.7	
African American	22.9	16.0	11.8	10.7	<0.0001
Others	18.2	11.7	8.0	4.6	
Body mass index, mean ± SD (kg/m^2)	31.9 ± 7.1	30.9 ± 6.9	31.0 ± 7.1	28.6 ± 6.0	<0.0001
Waist circumference, mean ± SD (cm)	97.7 ± 15.6	94.6 ± 15.2	94.7 ± 15.5	90.4 ± 14.8	<0.0001
Family history of MI (%)	40.5	48.7	42.2	44.1	0.02
Current smoking (%)	6.0	8.1	10.2	7.9	0.03
Hypertension (%)	60.0	52.9	60.3	51.0	0.002
Elevated blood cholesterol (%)	22.8	20.2	21.6	19.9	0.49
Current hormone use (%)	31.2	31.5	35.7	37.2	0.09
Regular aspirin use (%)	21.4	22.1	25.8	28.8	0.011
Physical activity, mean ± SD (METS/week)	9.8 ± 12.8	11.4 ± 13.3	11.3 ± 13.0	14.1 ± 14.9	<0.0001
Saturated lipid intake, mean ± SD (g/day)	20.4 ± 12.7	20.5 ± 11.6	22.7 ± 12.7	21.8 ± 12.6	0.01
Polyunsaturated lipid intake, mean ± SD (g/day)	13.3 ± 8.4	13.1 ± 8.1	13.9 ± 8.3	13.0 ± 7.3	0.45
Fiber intake, mean ± SD (g/day)	17.2 ± 7.4	17.4 ± 7.8	18.3 ± 6.6	17.9 ± 7.5	0.09
Median DM duration (years)	6.0	6.0	5.0	8.0	0.005

*p value is based on chi-square test, ANOVA or Kruskal–Wallis test

Table 2 Hazard ratios (HR) and 95% confidence interval (CI) for incident CHD in diabetic women based on the frequency of alcohol consumption in the Women's Health Initiative

Characteristic	Nondrinkers	<0.5 drinks/week	0.5 to <2.0 drinks/week	≥2 drinks/week	p for trend
No. of cases	241	40	28	27	
Person-years of follow-up	15,228	2,716	2,050	2,551	
Model 1	1	0.90 (0.64, 1.26)	0.83 (0.56, 1.23)	0.62 (0.41, 0.93)	0.02
Model 2	1	0.90 (0.64, 1.26)	0.85 (0.57, 1.27)	0.65 (0.43, 0.98)	0.04
Model 3	1	0.89 (0.63, 1.26)	0.84 (0.56, 1.25)	0.65 (0.43, 0.99)	0.04

Model 1 is adjusted for age (50–59, 60–69 and 70–79 years) and race/ethnicity

Model 2 = Model 1 + adjusted for body mass index (<20, 20–24.9, 25–29.9, ≥30 kg/m^2), smoking (never, past, current), family history of MI (yes/no), hypertension (yes/no), high cholesterol (yes/no), hormone use (premenopausal, postmenopausal no use, postmenopausal past use, postmenopausal current use), regular aspirin use (yes/no), quintiles of physical activity (METs/week) and duration of DM

Model 3 = Model 2 + adjusted for intake of saturated fat, PUFA, fiber (all quintiles)

We also conducted a secondary analysis to address the possibility that 'sick quitters' included in the nondrinker group may partly explain the observed inverse association of alcohol intake and CHD risk. When we excluded women who reported a reduction in alcohol intake for health reasons, multivariable HR across increasing frequency of alcohol intake were 1 (nondrinkers), 0.87 (95% CI: 0.62, 1.28), 0.80 (95% CI: 0.54, 1.20) and 0.61 (95% CI: 0.40, 0.91) for intakes of ≤0.5, 0.5–2 and >2 drinks/week, respectively. Thus, the results were similar when potential sick quitters were excluded, although the HR was statistically significant only for those consuming >2 drinks/week in comparison to abstainers.

Conclusion

In this large prospective study among postmenopausal diabetic women, both the frequency and quantity of alcohol intake were inversely associated with the risk of developing CHD. This inverse association did not appear to differ based on the type of alcoholic beverage consumed.

Table 3 Hazard ratios (HR) and 95% confidence interval (CI) for incident coronary heart disease (CHD) in diabetic women by quantity of alcohol consumption (g/day) in the Women's Health Initiative

Characteristic	Nondrinkers (n = 2,188)	<1 g/day (n = 273)	1 to <4 g/day (n = 375)	≥4 g/day (n = 362)	p for trend
Median intake (g/day)	0	0.6	1.8	10.6	
No of cases	241	32	36	27	
Person-years of follow-up	15,228	1,983	2,669	2,666	
Model 1	1	0.99 (0.68, 1.43)	0.82 (0.58, 1.17)	0.60 (0.40, 0.89)	0.01
Model 2	1	0.99 (0.68, 1.44)	0.82 (0.58, 1.17)	0.63 (0.42, 0.95)	0.02
Model 3	1	0.98 (0.67, 1.43)	0.81 (0.57, 1.16)	0.63 (0.42, 0.95)	0.02

Model 1 is adjusted for age (50–59, 60–69 and 70–79 years) and race/ethnicity

Model 2 = Model 1 + adjusted for body mass index (<20, 20–24.9, 25–29.9, ≥30 kg/m^2), smoking (never, past, current), family history of MI (yes/no), hypertension (yes/no), high cholesterol (yes/no), hormone use (premenopausal, postmenopausal no use, postmenopausal past use, postmenopausal current use), regular aspirin use (yes/no), quintiles of physical activity (METs/week) and duration of diabetes

Model 3 = Model 2 + adjusted for intake of saturated fat, PUFA, fiber (all quintiles)

Table 4 Hazard ratio (HR) and 95% confidence interval (CI) for incident CHD in diabetic women based on the type of alcoholic beverage consumed

	Nondrinkers	<0.5 drinks/week	0.5 to <2.0 drinks/week	≥2 drinks/week	p for trend
Wine					
No. of cases	241	38	15	13	
Person-years of follow-up	15,228	3,335	1,051	1,408	
Model 1	1	0.68 (0.48, 0.96)	0.84 (0.50, 1.41)	0.54 (0.31, 0.95)	0.009
Model 2	1	0.69 (0.48, 0.98)	0.91 (0.53, 1.55)	0.60 (0.34, 1.07)	0.03
Model 3	1	0.68 (0.48, 0.97)	0.91 (0.53, 1.56)	0.60 (0.34, 1.07)	0.04
Non-wine					
No. of cases	241	31	14	15	
Person-years of follow-up	15,228	2,210	915	1,380	
Model 1	1	0.85 (0.58, 1.24)	0.97 (0.56, 1.66)	0.65 (0.38, 1.09)	0.11
Model 2	1	0.85 (0.58, 1.25)	0.99 (0.56, 1.74)	0.64 (0.38, 1.09)	0.11
Model 3	1	0.84 (0.57, 1.23)	0.94 (0.53, 1.67)	0.63 (0.37, 1.08)	0.09

Model 1 is adjusted for age and race/ethnicity

Model 2 = Model 1 + adjusted for body mass index (<20, 20–24.9, 25–29.9, ≥30 kg/m^2), smoking (never, past, current), family history of MI (yes/no), hypertension (yes/no), high cholesterol (yes/no), hormone use (premenopausal, postmenopausal no use, postmenopausal past use, postmenopausal current use), regular aspirin use (yes/no), quintiles of physical activity (METs/week) and duration of DM

Model 3 = Model 2 + adjusted for intake of saturated fat, PUFA, fiber (all quintiles)

Although several studies have evaluated the association between alcohol intake and risk of CHD in apparently healthy populations [18, 19], data among people with DM are limited [10–14]. However, the number of postmenopausal diabetic women in these latter studies was limited. Our study findings among postmenopausal women are consistent with the results of these previous studies including the magnitude of the association [10–14].

The mechanisms by which moderate alcohol intake may reduce risk in CHD include its beneficial effects on known risk factors for CHD such as HDL-cholesterol [20], hypertension [21, 22], platelet aggregation [23] and fibrinolysis [24]. These alcohol effects may be more relevant in people with DM since this condition is associated with low HDL levels, increased presence of hypertension, elevated platelet aggregation and impaired fibrinolysis [25–28]. In addition to these mechanisms, alcohol may also reduce the risk of CHD due to its beneficial effect on insulin sensitivity and glycemia [8, 29–34]. Avogaro et al. [35] reported that acute alcohol consumption improves insulin sensitivity and leads to reduced lipolysis without any apparent effect on pancreatic insulin secretion. In a cross-sectional analysis among nondiabetic men and women, alcohol intake was inversely associated with levels of glycosylated hemoglobin [34]. In another cross-sectional study among 459 women aged 33–50 years, alcohol intake was inversely

associated with fasting insulin levels, but only among overweight and obese women [33]. Importantly, in a recent randomized controlled trial, 109 alcohol abstainers with DM aged 41–74 years were randomized to either receive 150 ml of wine/day (13 g of alcohol) or a nonalcohol diet beer (control group). After 3 months of intervention, the active intervention group had a significant reduction in fasting plasma glucose (-21.6 ± 41.2 vs. 1.92 ± 25.7 mg/dl) and this effect was greater in those with higher baseline glycosylated hemoglobin levels [36]. This is consistent with two other clinical trials among postmenopausal women that evaluated the effect of alcohol consumption on insulin sensitivity [37, 38]. Apart from this glycemic effect on alcohol, acetaldehyde that is formed after ethanol oxidation may reduce the formation of advanced glycation end products (AGEs) that are suggested to play a role in the accelerated atherosclerosis that occurs in DM [39–42].

Some researchers have suggested that the type of alcoholic beverage consumed may differentially affect CHD risk. For example, wine intake has been thought to provide an added benefit beyond the effect of ethanol due to the presence of certain antioxidants [43]. In this study, however, we observed that alcohol type (wine vs. non-wine) was not differentially associated with CHD risk. This is consistent with the results of a few other studies among individuals with DM that have also suggested no difference in the observed inverse association with CHD risk based on alcohol type [44]. A review of epidemiologic data linking alcohol and CHD risk has suggested that compared to other active constituents in alcoholic beverages, ethanol is more potent with respect to the effects on CHD risk factors [7]. Further, it was suggested that the observed differences for alcohol type in some studies are possibly due to differences in the patterns of drinking.

Our study has limitations that warrant consideration. Although this study was prospective, the observational nature cannot provide evidence for a causal association between alcohol intake and CHD in diabetic women. Moderate alcohol consumption can be conceived of as a marker of an overall healthy lifestyle, which may explain its inverse association with CHD risk. In our study, we adjusted for several lifestyle variables in our multivariable models to eliminate any potential bias due to a healthy lifestyle. However, residual confounding is still a potential concern. Further, our study findings are only relevant to the range of alcohol consumption observed in this cohort. This issue is more important in people with DM since very high alcohol may also have some detrimental effects on diabetic states, including worsening of microvascular complications such as neuropathy [45, 46] and retinopathy [47]. However, moderate alcohol intake is unlikely to negatively effect microvascular complications [48, 49]. Confounding due to socioeconomic status may be a limitation of our study. However, the results were similar when we adjusted the multivariable models for income. The range of alcohol consumption was low in our study population; the assessment of alcohol intake based on self-reports may have possibly resulted in underestimation of intake. Furthermore, the WHI excluded all participants with substance use problems including alcoholism at baseline and we did not use past drinkers, for whom the alcohol intake is likely to be higher than current drinkers, as a separate group in our analysis. Past drinkers form a heterogeneous group and the details concerning lifetime duration of alcohol consumption, patterns of consumption and specific reasons for quitting alcohol are not available. Although the range of alcohol intake was narrow, we observed a significant trend for alcohol intake and CHD risk suggesting that the potential benefit of alcohol also exists for the observed range of intake in this population with low alcohol consumption. In this study, the diagnosis of DM was based on self-reports. However, in sensitivity analysis when we limited our analysis to women who confirmed pharmacological treatment for DM, the results were similar.

In conclusion, we found an inverse association between the quantity and frequency of alcohol intake in relation to incident CHD among postmenopausal women with DM. Although based on observational data, our study suggests no apparent reason to have different recommendations for alcohol consumption among diabetic women. It is, however, also important to consider the potential risks of alcohol intake on cardiac and noncardiac outcomes for each specific individual with diabetes.

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