Alcohol Consumption and Risk of Coronary Heart Disease by Diabetes Status

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Background—An inverse association between moderate alcohol consumption and coronary heart disease (CHD) has been observed in several epidemiological studies. To assess whether a similar association exists among diabetics, we examined the relation between light to moderate alcohol consumption and CHD in men with and without diabetes mellitus in a prospective cohort study.

Methods and Results—A total of 87,938 US physicians (2790 with diagnosed diabetes mellitus) who were invited to participate in the Physicians’ Health Study and were free of myocardial infarction, stroke, cancer, or liver disease at baseline were followed for an average of 5.5 years for death with CHD as the underlying cause. During 480,876 person-years of follow-up, 850 deaths caused by CHD were documented: 717 deaths among nondiabetic men and 133 deaths among diabetic men. Among men without diabetes at baseline, the relative risk estimates for those reporting rarely/never, monthly, weekly, and daily alcohol consumption were 1.00 (referent), 1.02, 0.82, and 0.61 (95% CI 0.49 to 0.78; \( P \) for trend < 0.0001) after adjustment for age, aspirin use, smoking, physical activity, body mass index, and history of angina, hypertension, and high cholesterol. Among men with diabetes at baseline, the relative risk estimates were 1.00 (referent), 1.11, 0.67, and 0.42 (95% CI 0.23 to 0.77; \( P \) for trend = 0.0019).

Conclusions—These results suggest that light to moderate alcohol consumption is associated with similar risk reductions in CHD among diabetic and nondiabetic men. (Circulation. 2000;102:500-505.)

Key Words: alcohol ■ coronary disease ■ diabetes mellitus ■ risk factors

For the millions of people with diabetes mellitus, coronary heart disease (CHD) is a major cause of morbidity and mortality. A recent survey of a representative cohort of 14,734 US adults with diabetes, for example, found that CHD was listed on 69% of death certificates.1 Age-adjusted rates for CHD are substantially higher among diabetic men and women than among those without diabetes, and clinically apparent CHD appears at an earlier age among people with diabetes than it does in the general population.2–4

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In general populations, epidemiological studies have consistently demonstrated an inverse association between moderate alcohol consumption and CHD incidence and mortality.5–9 The reduced risk of CHD associated with alcohol is believed to be due, at least in part, to the effect of alcohol on the lipid profile, including favorable increases in HDL cholesterol and its subfractions.10 Whether or not alcohol consumption has a similar association with CHD among individuals with diabetes, however, is a largely unexamined question. It has been suggested that alcohol increases sensitivity to insulin and has favorable effects on glucose metabolism.11–14 Yet, moderate alcohol consumption has been associated with decreased risk of type 2 diabetes mellitus in some15,16 but not all17 studies. Given this uncertainty, many patients with diabetes are advised to avoid alcohol.

To address this question, we examined the relation between alcohol intake and CHD mortality according to diabetes status in prospective data from the Physicians’ Health Study (PHS) enrollment cohort.

Methods

Study Population

The PHS was a randomized, double-blind, placebo-controlled trial of low-dose aspirin (325 mg every other day) and \( \beta \)-carotene (50 mg every other day) in the primary prevention of cardiovascular disease and cancer. Potentially eligible participants were male physicians

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living in the United States. In 1982 to 1983, letters of invitation, informed consent forms, and baseline questionnaires were mailed to 261,248 physicians listed on the American Medical Association’s mailing tape. By the end of December 1983, 104,353 completed questionnaires had been returned. After further evaluation, 16,415 men were excluded because of missing diabetes status (n = 5,290), missing alcohol data (n = 3,775), and history of myocardial infarction, stroke, cancer, or liver disease (n = 11,959) at baseline, leaving a total of 87,938. This study includes these 87,938 respondents, of whom 21,852 were subsequently randomized in the trial.

Baseline Data
Information about alcohol consumption and several other risk factors was collected at baseline. The physicians were asked how often they usually consumed alcoholic beverages (beer, wine, liquor) and offered 7 possible responses: rarely/never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, and ≥2 per day. We interpreted their responses to be the number of drinks consumed in the specified time period. Information was also collected about other CHD risk factors, including age, cigarette smoking (never, past, or current, including number of cigarettes smoked per day for current smokers), use of antihypertensive medications, systolic and diastolic blood pressure, cholesterol level, use of cholesterol-lowering medications, frequency of vigorous exercise, and history of angina pectoris and diabetes mellitus. Body mass index (kg/m²) was calculated by means of self-reported weight and height. Participants were considered diabetic if they reported a history of diabetes mellitus or use of insulin or other antidiabetic medication.

End Points
Death was the primary end point that we determined for the entire enrollment cohort. Deaths were identified through systematic searches of the National Death Index for the entire enrollment cohort, and death certificates were obtained for all cases to determine cause of death. All deaths occurring before February 1, 1988, were recorded. Trained nosologists who had no knowledge of cohort members’ alcohol consumption status classified deaths by using the first revision of the Ninth International Classification of Diseases (ICD) in conjunction with the Automated Classification of Medical Entities Decision Tables. Men for whom cause of death was classified as ischemic heart disease and myocardial infarction (ICD codes 410-414) were classified as CHD deaths for this analysis.

Because the enrollment cohort was followed for mortality only, we could not identify incident cases of CHD. However, incidence information was available for the subset of respondents who were randomized into the PHS. These participants reported new diagnosis of CHD on annual questionnaires, which were then confirmed by medical record review. For this subgroup, the morbidity and mortality follow-up was >99% complete for >12 years (through December 31, 1995). In our secondary analyses, we evaluated incident CHD cases among the randomized subgroup.

Statistical Analysis
We used 4 categories of alcohol intake at baseline: rarely/never, monthly (≥1 drink per month but <1 drink per week), weekly (≥1 drink per week but <1 drink per day), and daily (≥1 drink per day). For each physician, person-years of follow-up were counted from the date the enrollment questionnaire was returned until January 31, 1988, or, in case of death, the date of death. We calculated proportions and means of baseline risk factors for the 4 levels of alcohol use and used proportional hazards models to compute age-adjusted and multivariable-adjusted relative risk and 95% confidence intervals for each category of alcohol use compared with the reference category. Multivariate models were adjusted for potential confounders by including terms for age, smoking (never, past, current [<20 cigarettes/d, or 20 or more cigarettes/d]), exercise (at least once per week), body mass index, current aspirin use (at enrollment), history of angina, hypertension (reported systolic blood pressure of ≥160 or diastolic blood pressure of ≥95 or history of treatment for high blood pressure), and high cholesterol (reported blood cholesterol level of ≥260 or history of treatment for high cholesterol). Initially, we did not adjust for history of hypertension and high cholesterol in our models because these variables may be considered predictors of death affected by alcohol consumption.18,19 We did, however, add them in our analyses because this did not materially change the results. Analyses were repeated excluding the first 2 years of follow-up to determine if there was any possible confounding of the association between alcohol and death caused by changes in alcohol consumption resulting from terminal stages of illness. We tested linear trends across the categories of alcohol consumption by using alcohol intake as an ordinal variable in the model. We also examined the association of alcohol with incident CHD in the subgroup of the enrollment cohort subsequently randomized in the PHS.

Results
At baseline, about one quarter (29%) of the study population reported alcohol use of <1 drink per week; almost half (46%) reported weekly alcohol use (1 to 6 alcoholic beverages per week); and the remaining 25% reported daily alcohol use. Overall, alcohol consumption was light to moderate, with only 3% of the members of this cohort reporting alcohol consumption of >1 drink per day. Baseline characteristics of the subjects with and without diabetes are presented in Table 1. Men who reported higher levels of alcohol intake tended to be older, were more likely to be former or current smokers, and tended to report more physical activity, a history of hypertension, and higher aspirin intake. Of the 87,938 respondents, 2790 (3.2%) reported having diabetes mellitus. As expected, among those with diabetes, the distribution of alcohol consumption was somewhat different, with 43% reporting alcohol use of <1 drink per week, 35% reporting weekly consumption, and the remaining 22% reporting daily consumption. At study entry, those with diabetes were slightly older, were more likely to be former or current smokers, were less physically active, and had a higher prevalence of angina, hypertension, and high cholesterol than those with no diagnosis of diabetes at baseline.

During an average follow-up period of 5.5 years (a total of 480,876 person-years), 3093 deaths were identified. CHD was the reported cause of death in 850 cases: 717 among nondiabetics and 133 among diabetics. The CHD deaths included 353 deaths from ischemic heart disease and 497 from myocardial infarction. Relative risks for CHD mortality are presented in Table 2. Overall, there was a decreasing risk of CHD mortality with increasing levels of alcohol intake (P<0.0001). Men reporting daily consumption of alcohol were observed to have a 40% decreased risk of CHD mortality compared with those reporting rarely or never drinking alcohol.

When examining the association between alcohol use and CHD mortality by diabetes status, similar relations between alcohol use and CHD were observed in both groups. For participants with no diabetes at baseline, the relative risks were 1.00 (referent), 1.02, 0.82, and 0.61 (95% CI 0.49 to 0.78; P for trend <0.0001) for those consuming alcohol rarely, monthly, weekly, and daily, respectively, after adjusting for age, aspirin use, smoking, physical activity, body mass index, history of angina, hypertension, and high cholesterol. For those reporting diabetes at baseline, the relative risks were 1.00 (referent), 1.11, 0.67, and 0.42 (95% CI 0.23
to 0.77; \( P \) for trend=0.0019) for increasing level of alcohol intake after adjusting for the same variables (Table 2). No significant interaction was observed when we examined possible modifications of this association by age (>60 years of age versus ≤60), body mass index (≥27.8 versus <27.8), cigarette smoking (ever versus never), aspirin intake at baseline, or physical activity (at least once per week versus less than once per week) among men with diabetes.

Because the enrollment cohort was followed for mortality only, we could not determine the relative risk for CHD incidence. We were able, however, to examine this association in a subset of the enrollment cohort: physicians who were randomized into the PHS. In this group of 21 852 men, the overall relative risks for any CHD diagnosis (defined as cases of myocardial infarction plus cases of coronary artery bypass graft or percutaneous transluminal coronary angioplasty procedures) for the same 4 categories of alcohol use were 1.00 (referent), 0.93, 0.89, and 0.67 (95% CI 0.57 to 0.78; \( P \) for trend, 0.0001) after an average follow-up of 12 years and adjustment for age, randomized treatment, smoking, physical activity, body mass index, parental history of myocardial infarction before age 60 years, and personal history of angina.

### TABLE 1. Baseline Characteristics by Level of Alcohol Consumption Among Nondiabetic and Diabetic Samples (Enrollment Cohort)

<table>
<thead>
<tr>
<th>Frequency of Alcohol Consumption</th>
<th>No Diabetes</th>
<th>Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely/Never (n=14 091)</td>
<td>55.4 (10.8)</td>
<td>59.0 (10.2)</td>
</tr>
<tr>
<td>Monthly (n=9757)</td>
<td>52.8 (10.1)</td>
<td>59.0 (10.2)</td>
</tr>
<tr>
<td>Weekly (n=39 542)</td>
<td>53.1 (9.7)</td>
<td>56.1 (10.4)</td>
</tr>
<tr>
<td>Daily (n=21 758)</td>
<td>57.3 (10.3)</td>
<td>60.1 (10.2)</td>
</tr>
<tr>
<td>Rarely/Never (n=799)</td>
<td>63.1 (10.0)</td>
<td>60.1 (10.2)</td>
</tr>
<tr>
<td>Monthly (n=396)</td>
<td>60.1 (10.2)</td>
<td>61.4 (9.8)</td>
</tr>
<tr>
<td>Weekly (n=986)</td>
<td>61.4 (9.8)</td>
<td>63.8 (9.1)</td>
</tr>
<tr>
<td>Daily (n=609)</td>
<td>63.8 (9.1)</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2. Relative Risk of CHD Mortality by Level of Alcohol Consumption (Enrollment Cohort)

<table>
<thead>
<tr>
<th></th>
<th>Rarely/Never</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily</th>
<th>( P ) Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (87 938)</td>
<td>14 890</td>
<td>10 153</td>
<td>40 528</td>
<td>22 367</td>
<td></td>
</tr>
<tr>
<td>Cases (850)</td>
<td>220</td>
<td>106</td>
<td>304</td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>80 397</td>
<td>55 528</td>
<td>222 871</td>
<td>122 080</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>0.95 (0.76–1.20)</td>
<td>0.71 (0.60–0.85)</td>
<td>0.61 (0.51–0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>1.04 (0.81–1.34)</td>
<td>0.80 (0.65–0.97)</td>
<td>0.59 (0.48–0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stratified by diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes (85 148)</td>
<td>14 091</td>
<td>9757</td>
<td>39 542</td>
<td>21 758</td>
<td></td>
</tr>
<tr>
<td>Cases (717)</td>
<td>166</td>
<td>83</td>
<td>267</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>76 386</td>
<td>53 468</td>
<td>217 665</td>
<td>118 902</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>0.97 (0.74–1.26)</td>
<td>0.80 (0.66–0.97)</td>
<td>0.70 (0.57–0.86)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>1.02 (0.77–1.36)</td>
<td>0.82 (0.66–1.02)</td>
<td>0.61 (0.49–0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (2790)</td>
<td>799</td>
<td>396</td>
<td>986</td>
<td>609</td>
<td></td>
</tr>
<tr>
<td>Cases (133)</td>
<td>54</td>
<td>23</td>
<td>37</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>4012</td>
<td>2060</td>
<td>5205</td>
<td>3178</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>0.99 (0.60–1.61)</td>
<td>0.59 (0.39–0.90)</td>
<td>0.44 (0.26–0.74)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>1.11 (0.66–1.89)</td>
<td>0.67 (0.42–1.07)</td>
<td>0.42 (0.23–0.77)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Multivariate model adjusted for age, aspirin use, smoking, physical activity, body mass index, history of angina, hypertension, high cholesterol, and diabetes mellitus (in overall models).
hypothesis, high cholesterol, and diabetes (Table 3). Similar associations were observed among the non-diabetic men in this group. Among the relatively small number of randomized PHS participants who reported having diabetes at baseline (n=510), those reporting daily alcohol consumption had a relative risk for CHD incidence of 0.66 (95% CI 0.38 to 1.16) compared with those reporting rarely or never drinking alcohol. These relative risks, however, did not reach statistical significance, perhaps because of the small sample size of diabetics within this subpopulation.

Discussion
These prospective data indicate that low-to-moderate consumption of alcohol is associated with a decreased risk of CHD mortality in men with diabetes, just as it is among men without diabetes, and that there are comparable risk reductions for CHD mortality in both groups.

Despite the prevalence of diabetes and the impact of CHD among people with diabetes, few studies have examined the possible relation between alcohol and CHD in diabetic populations. One case-control study of risk factors for CHD among diabetics reported alcohol consumption as a predictor of CHD.\(^2\) However, alcohol consumption data were not clearly reported and were included in the models as a binary variable only. In contrast, a small (n=232) prospective population study of the impact of cardiovascular risk factors on CHD mortality among diabetic men reported no association between alcohol abuse and CHD.\(^3\) Our findings are consistent with 2 more recent studies. A preliminary report from Switzerland regarding 287 patients with type 2 diabetes mellitus recruited for a multinational study of vascular disease in diabetes sponsored by the World Health Organization showed that alcohol intake was associated with decreased risk of death from ischemic heart disease among men with type 2 diabetes (Exp[Coef]: 0.90 (95% CI 0.81 to 0.995; P=0.039) (P. Diem et al, data presented at 59th Scientific Session of American Diabetes Association, 1999). In addition, data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed a 55% to 75% reduction in risk of death caused by CHD in people with older-onset diabetes and who consumed ≥14 g of alcohol per day (≥1 drink per day).\(^2\)

Our findings are also consistent with those from the Nurses’ Health Study, in which an approximately 50% reduction in risk of CHD was observed among diabetic participants of that large cohort (C. Solomon, personal communication).\(^2\) Several plausible biological mechanisms have been proposed to explain the inverse association between alcohol and CHD among general populations. In addition to increasing the levels of HDL cholesterol and its subfractions, hyperinsulinemia, which is common among diabetics, has been implicated as an important risk factor for CHD.\(^2\) Alcohol has also been shown to decrease platelet aggregation and increase fibrinolytic activity. These hypothesized mechanisms could be even more important in a diabetic population, in which dyslipidemia and coagulation disorders are more prevalent than they are in a general population. In addition, hyperinsulinemia, which is common among diabetics, has been implicated as an important risk factor for CHD. Low to moderate alcohol consumption has been reported to lower fasting insulin levels and light to moderate alcohol consumption has been reported to lower fasting insulin levels.

Our study has several strengths. Its large sample size provides sufficient power to detect true differences. The prospective design minimizes differential misclassification of exposure status, and the relatively homogeneous group minimizes confounding by factors such as socioeconomic status, educational background, and access to and quality of medical care.

Potential limitations of the study also must be considered. Misclassification of outcome is possible when using death...
certificate data to determine cause of death. However, the end points in this study were ascertained without prior knowledge of alcohol use, making nonrandom misclassification unlikely. As in most other alcohol-related studies, we used self-reported alcohol consumption; other approaches are generally not practical in large cohort studies such as this. Health professionals generally provide reliable reports of alcohol use, though random misclassification of alcohol intake is possible if the physicians in this study generally underreported or underestimated their alcohol intake. This type of misclassification could have led to underestimation of any true protective association of light to moderate alcohol intake and CHD if heavier drinkers underreported to a greater extent than light or moderate drinkers. We used a single measure of alcohol consumption and did not account for any change in alcohol intake over time. This could also lead to some misclassification, although drinking patterns among middle-aged and older subjects tend to be stable over time. We did not collect information on type of alcoholic beverage consumed and thus cannot compare separately the risks and benefits of wine, beer, or liquor consumption. Moreover, if healthier subjects tended to consume light to moderate amounts of alcohol, or if alcohol consumption was a marker of overall healthy behavior, a “healthy worker effect” cannot be ruled out.

It has been suggested that the reduced risk of cardiovascular disease observed among drinkers in studies of alcohol consumption can be partly explained by increased risk among ex-drinkers who stopped drinking because of comorbid conditions and who are included with the nondrinkers. Although we were unable to exclude recent ex-drinkers, we did exclude any physician who reported a history of myocardial infarction, stroke, cancer, or liver disease. Furthermore, studies of alcohol and cardiovascular mortality have reported no difference in results with and without excluding recent ex-drinkers.

Another potential limitation of our study is generalizability. The study participants were relatively healthy men who consumed low-to-moderate amounts of alcohol. Therefore, results may not be generalizable to other populations with less healthy risk factor profiles or to those consuming higher amounts of alcohol. Although our results are not generalizable to women, this concern is minimized by findings similar to ours from the Nurses’ Health Study, a large cohort of women. Finally, residual confounding is possible but unlikely because adjustment for potential confounders did not materially change the results.

In the PHS enrollment cohort, distribution of alcohol consumption among all participants and those with diabetes showed a greater proportion of diabetic participants reporting rarely/never drinking alcohol, suggesting that the participants may have changed their alcohol consumption in response to diabetes. It is also possible that some clinicians may routinely discourage low-to-moderate alcohol consumption among those with diabetes. This may be due to a potential risk of alcohol-induced hypoglycemia, which can be minimized by consuming alcohol in moderation and in conjunction with meals. Current guidelines from the American Diabetes Association state that “[i]f [if] used in moderation and with food, however, blood glucose levels are not affected by the ingestion of alcohol when diabetes is well controlled.”

In conclusion, results from this prospective cohort study suggest that light to moderate alcohol consumption is associated with a similar degree of reduction in risk of CHD mortality among men with diabetes as it is among men in the general population. Our results are limited to those consuming low-to-moderate amounts of alcohol and cannot be generalized to those consuming heavy amounts. Furthermore, these results should be interpreted with caution and require confirmation in other cohorts of diabetics. In light of major clinical and public health problems associated with heavy drinking, recommendations regarding alcohol use must be made on an individual basis after carefully assessing the risks and benefits of any changes in drinking behavior.

Acknowledgments

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