Alcohol Consumption and Risk of Type 2 Diabetes Mellitus Among US Male Physicians

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Objective: To examine the association between low to moderate alcohol consumption and the incidence of type 2 diabetes mellitus (DM) in men.

Design: Prospective cohort study.

Subjects and Methods: Over an average period of 12.1 years, we evaluated 20,951 participants in the Physicians’ Health Study between ages 40 and 84 years who were free of cardiovascular disease, cancer, and diabetes and provided data on alcohol consumption at baseline.

Main Outcome Measure: Type 2 DM diagnosed after randomization.

Results: Among 20,951 physicians, 766 cases of incident DM were reported over an average follow-up period of 12.1 years. After adjustment for age, randomized treatment assignment, smoking, physical activity, and body mass index, the relative risk estimates and 95% confidence intervals for those reporting alcohol use of rarely/never, 1 to 3 drinks per month, 1 drink per week, 2 to 4 drinks per week, 5 to 6 drinks per week, and 1 or more drinks per day were 1.00 (referent), 1.03 (0.80-1.33), 0.89 (0.70-1.14), 0.74 (0.59-0.93), 0.67 (0.51-0.89), and 0.57 (0.45-0.73), respectively (linear trend, \( P < .001 \)). Additional adjustment for baseline history of hypertension, high cholesterol level, or parental history of myocardial infarction or family history of diabetes (data collected at 9 years) did not materially alter the results. These associations persisted in analyses stratified by age, smoking status, body mass index, physical activity, and family history of DM.

Conclusion: These data indicate that apparently healthy men who self-select for light to moderate alcohol consumption have a decreased subsequent risk of type 2 DM.

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TYPE 2 (non–insulin-dependent) diabetes mellitus (DM) is a relatively common condition affecting approximately 15 million individuals and is the seventh leading cause of death in the United States among those older than 45 years. The public health burden of this disease is further increased by higher rates of cardiovascular disease, renal failure, and blindness caused by retinopathy, resulting in economic costs of over $90 billion in direct medical and indirect expenditures. Although a family history of diabetes and genetic predisposition are established risk factors, lifestyle factors also play an important role in the etiology of diabetes. Alcohol consumption is common in the United States and may be related to risk for type 2 DM through its effects on insulin secretion and sensitivity.

Studies exploring the association between alcohol intake and the risk for type 2 DM have reported conflicting results. Several large-scale epidemiological studies have suggested an inverse association between moderate alcohol consumption and reduced risk for type 2 DM, while others have reported null or even positive associations. We assessed whether low to moderate alcohol consumption is associated with type 2 DM among participants in the Physicians’ Health Study during an average period of 12.1 years.

Table 1 shows the distribution of baseline characteristics and possible risk factors according to categories of alcohol intake. At study entry, approximately 25% of the study population reported alcohol consumption of less than 1 drink per week, almost 50% reported alcohol consumption of 1 to 6 drinks per week, and the remaining 25% reported alcohol consumption of 1 or more drinks per day. Overall,
SUBJECTS AND METHODS

STUDY POPULATION

The Physicians' Health Study was a randomized, double-blind, placebo-controlled trial of low-dose aspirin and beta carotene for the primary prevention of cardiovascular disease and cancer. In 1981, all 261,248 US male physicians between ages 40 and 85 years were invited to participate in the trial. Approximately half responded, and of these, 59,283 were willing to participate. After exclusion of those with a history of myocardial infarction, stroke, transient ischemic attack, cancer (except nonmelanoma skin cancer), current liver or renal disease, peptic ulcer, gout, or contraindication to or current use of trial treatments, a total of 33,223 eligible participants were enrolled in an 18-week “run-in” phase. At the end of the run-in phase, using a 2 × 2 factorial design, 22,071 physicians were randomly assigned to receive aspirin, beta carotene, both active agents, or both placebo. A detailed description of subjects and methods has been previously published. For this report, we excluded participants with missing baseline data on alcohol consumption (n = 195) and those who reported a history of diabetes prior to randomization (n = 603). Furthermore, those with any history of cardiovascular disease (angina and/or coronary revascularization) or cancer prior to randomization (n = 376) were also excluded, since these diagnoses could have altered their alcohol intake. These criteria were not mutually exclusive; therefore, this report includes 20,951 participants who provided complete information on alcohol consumption at baseline; had no diabetes, cardiovascular disease, or cancer at study entry; and were followed up through October 1995.

BASELINE DATA

Information about usual alcohol consumption and several other risk factors was collected at baseline. Participants were asked “How often do you usually consume alcoholic beverages?” The response categories listed were as follows: “rarely/never,” “1-3/month,” “1/week,” “2-4/week,” “5-6/week,” “daily,” and “2/day.” The responses were interpreted as the number of drinks consumed in the specified period. Information was also collected about age, cigarette smoking, parental history of myocardial infarction, physical activity, height, weight, history of diabetes, angina, history of hypertension or treatment of hypertension, and history of high cholesterol level or treatment for a high cholesterol level.

FOLLOW-UP DATA

Every 6 months for the first year and annually thereafter, the participants were mailed brief questionnaires asking about their compliance with the randomized treatment and the occurrence of new medical diagnoses, including diabetes. Participants were asked about their family history of diabetes (including parents and siblings) at 9 years. Because the participants were physicians, medical records were not requested to confirm the self-reports of diagnosed diabetes. Although type 1 diabetes can occur at any age, it is rare above age 40 years. All participants were 40 years or older at study entry; therefore, all incident cases of diabetes during the study period were classified as type 2 DM.

DATA ANALYSIS

The study population was primarily low to moderate consumers of alcohol. Since only 3% of participants (n = 674) reported alcohol use of 2 or more drinks per day, these men were combined with those reporting 1 drink per day. Incident cases of type 2 DM were allocated to the alcohol consumption categories with the follow-up period from study entry to the date of diagnosis of diabetes, date of death, or October 1995, whichever came first. Incidence rates of diabetes were calculated by dividing the number of incident cases by person-years in each category of alcohol consumption. Cox proportional hazards models using the SAS PHREG procedure were used to assess the independent contribution of alcohol consumption to the risk of diabetes. The lowest category of alcohol consumption (rarely/never) was used as the reference category for relative risk (RR) computation. Crude estimates of association were derived by adjusting for effects of age and randomized treatments (aspirin and beta carotene). To adjust for other potential confounders in the multivariate models, indicator terms were added for smoking status at baseline (never, former, light current [smoking < 20 cigarettes per day], heavy current [smoking ≥ 20 cigarettes per day]), body mass index (BMI) (calculated as the weight in kilograms divided by the square of the height in meters: weight [kg]/[height (m)]², in quartiles), physical activity (reported vigorous exercise of less than once per week, once per week, 2-4 times per week, or 5 or more times per week), history of hypertension (reported systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 95 mm Hg, or history of treatment for high blood pressure [yes/no]), history of high cholesterol level (reported serum cholesterol level ≥ 6.72 mmol/L [260 mg/dL] or history of treatment for high cholesterol level [yes/no]), and parental history of myocardial infarction before age 60 years (yes/no). The proportionality assumption for the Cox regression model was tested by including an interaction term for alcohol and follow-up time in a time-varying analysis. No violation of the proportionality assumption was observed. Secondary analyses were performed excluding any diagnosis of diabetes in the first 2 years of follow-up to address the possibility of any undiagnosed preexisting diabetes or glucose intolerance present at baseline. Data were also analyzed controlling for family history of diabetes reported at the 9-year follow-up (yes/no). To evaluate if the association differs by smoking status (possible effect modification), analyses were performed separately for those who were never smokers and those who were either former or current smokers at baseline. Similarly, analyses stratified by age, BMI, level of physical activity, and family history of DM were also performed. For each RR, a 2-tailed P value and 95% confidence interval (CI) were computed.
COMMENT

These prospective data from the Physicians’ Health Study indicate an inverse association between light to moder-
reported among nurses and in other studies, BMI was inversely associated with type 2 DM. We did not have enough heavy drinkers in this population to assess this group separately. The association persisted after adjustment for possible risk factors for diabetes, as well as after control for all available coronary risk factors and health habits.

Our findings of an inverse association between regular alcohol consumption and subsequent risk of type 2 DM are consistent with reports from several other large prospective cohort studies. The Nurses' Health Study, evaluating 85,000 women aged 34 to 59 years for 4 years with 526 incident cases of type 2 DM, suggested that there was a reduced risk of diabetes among women who consumed moderate amounts of alcohol compared with nondrinkers. Although an inverse association between BMI and alcohol consumption has been reported among nurses and in other studies, BMI was only marginally related to drinking habits in our study and was not a strong confounder. In the large-scale Health Professionals' Follow-up Study of over 41,000 men between age 40 and 75 years, a similar inverse association between alcohol consumption and diabetes was reported during 6 years of follow-up. This study reported an RR of 0.61 (95% CI, 0.44-0.91) for moderate amounts of alcohol consumption, which is similar to our findings. A report from the British Regional Heart Study observing 7577 men aged 40 to 59 years for an average duration of 12.8 years revealed a shallow U-shaped relationship between alcohol intake and risk of type 2 DM. In this study, moderate drinkers had an age- and BMI-adjusted RR of 0.64 (95% CI, 0.42-0.96) compared with occasional drinkers. Although, the risk estimates in our study were similar, the absence of an indication of a nonlinear relationship between alcohol consumption and type 2 DM in our data can be explained by a comparatively low range of alcohol intake reported in our

### Table 3. Relative Risks (RRs) for Type 2 Diabetes Mellitus by Alcohol Consumption Level (Excluding First 2 Years of Follow-up)*

<table>
<thead>
<tr>
<th>Alcohol Consumption, No. of Drinks</th>
<th>Rarely/Nevert</th>
<th>1-3/mo (n = 2263)</th>
<th>1/wk (n = 2300)</th>
<th>2-4/wk (n = 4729)</th>
<th>5-6/wk (n = 2678)</th>
<th>≥1/d (n = 5150)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, No.</td>
<td>132</td>
<td>87</td>
<td>108</td>
<td>136</td>
<td>75</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>30,495</td>
<td>23,206</td>
<td>29,889</td>
<td>49,140</td>
<td>27,717</td>
<td>52,251</td>
<td></td>
</tr>
<tr>
<td>Crude RR (95% CI)†‡</td>
<td>1.00 (Referent)</td>
<td>0.94 (0.72-1.23)</td>
<td>0.91 (0.71-1.18)</td>
<td>0.69 (0.54-0.87)</td>
<td>0.65 (0.49-0.87)</td>
<td>0.54 (0.42-0.69) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% CI)§</td>
<td>1.00 (Referent)</td>
<td>0.89 (0.68-1.18)</td>
<td>0.86 (0.67-1.12)</td>
<td>0.70 (0.55-0.90)</td>
<td>0.69 (0.52-0.92)</td>
<td>0.54 (0.42-0.70) &lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†For linear trend.
‡Adjusted for age and randomized treatment assignment.
§Adjusted for age, randomized treatment assignment, smoking status, body mass index, and physical activity.

### Table 4. Multivariate Relative Risks (RRs) for Type 2 Diabetes Mellitus by Alcohol Consumption Level Within Subgroups*

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Rarely/Nevert</th>
<th>1-3/mo</th>
<th>1/wk</th>
<th>2-4/wk</th>
<th>5-6/wk</th>
<th>≥1/d</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td></td>
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<td></td>
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<tr>
<td>&lt;60</td>
<td>1.00 (Referent)</td>
<td>0.98 (0.73-1.33)</td>
<td>0.91 (0.68-1.21)</td>
<td>0.67 (0.51-0.90)</td>
<td>0.69 (0.49-0.97)</td>
<td>0.67 (0.50-0.89) &lt;.002</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1.00 (Referent)</td>
<td>1.19 (0.76-1.59)</td>
<td>0.85 (0.53-1.35)</td>
<td>0.90 (0.61-1.33)</td>
<td>0.61 (0.37-1.01)</td>
<td>0.44 (0.30-0.66) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>BMI (median, 24.4 kg/m²)§</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Below median</td>
<td>1.00 (Referent)</td>
<td>1.07 (0.65-1.76)</td>
<td>0.79 (0.47-1.32)</td>
<td>0.68 (0.43-1.08)</td>
<td>0.30 (0.15-0.59)</td>
<td>0.55 (0.35-0.86) &lt;.002</td>
<td></td>
</tr>
<tr>
<td>At or above median</td>
<td>1.00 (Referent)</td>
<td>0.98 (0.73-1.31)</td>
<td>0.92 (0.69-1.21)</td>
<td>0.77 (0.59-1.00)</td>
<td>0.83 (0.61-1.13)</td>
<td>0.58 (0.44-0.77) &lt;.001</td>
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<tr>
<td>Ever smoked cigarettes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1.00 (Referent)</td>
<td>1.08 (0.75-1.55)</td>
<td>1.10 (0.78-1.54)</td>
<td>1.04 (0.75-1.43)</td>
<td>0.59 (0.36-0.95)</td>
<td>0.62 (0.42-0.92) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00 (Referent)</td>
<td>0.95 (0.67-1.35)</td>
<td>0.71 (0.50-1.01)</td>
<td>0.54 (0.39-0.76)</td>
<td>0.64 (0.45-0.92)</td>
<td>0.50 (0.37-0.68) &lt;.001</td>
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<tr>
<td>Physical activity¶</td>
<td></td>
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<tr>
<td>Vigorous exercise less than once a week</td>
<td>1.00 (Referent)</td>
<td>0.99 (0.67-1.45)</td>
<td>0.92 (0.63-1.35)</td>
<td>0.76 (0.52-1.10)</td>
<td>0.59 (0.36-0.96)</td>
<td>0.60 (0.41-0.87) &lt;.002</td>
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<tr>
<td>Vigorous exercise once a week or more</td>
<td>1.00 (Referent)</td>
<td>1.05 (0.75-1.45)</td>
<td>0.88 (0.64-1.21)</td>
<td>0.73 (0.54-0.98)</td>
<td>0.71 (0.50-1.00)</td>
<td>0.56 (0.41-0.75) &lt;.001</td>
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<tr>
<td>Family history of DM#</td>
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</tr>
<tr>
<td>No</td>
<td>1.00 (Referent)</td>
<td>1.07 (0.70-1.63)</td>
<td>1.19 (0.81-1.75)</td>
<td>0.81 (0.56-1.19)</td>
<td>0.71 (0.45-1.12)</td>
<td>0.65 (0.45-0.96) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.00 (Referent)</td>
<td>1.07 (0.76-1.51)</td>
<td>0.75 (0.52-1.08)</td>
<td>0.78 (0.56-1.07)</td>
<td>0.74 (0.50-1.10)</td>
<td>0.69 (0.49-0.97) .03</td>
<td></td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; DM, diabetes mellitus. All values are RR (95% confidence interval).
†For linear trend.
¶P = .004 for interaction term.
§P = .95 for interaction term.
P = .79 for interaction term.
||P = .83 for interaction term.
||P = .55 for interaction term.

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cohort. As mentioned above, only 3% of this cohort reported consumption of more than 1 drink per day compared with 12% of men participating in the Health Professionals’ Follow-up Study who consumed at least 2 to 4 drinks per day and 37% of participants in the British Regional Heart Study who consumed at least 2.3 to 6 U of alcohol per day.

Some studies have not found a statistically significant association between alcohol consumption and the risk of type 2 DM, while others have reported a positive association. A prospective study evaluating 766 men for over 13 years reported a possible nonsignificant trend toward greater alcohol consumption among those who subsequently developed diabetes. However, no clear association between alcohol consumption and the risk of diabetes was observed.8 Equivocal findings were reported from a cross-sectional study of 3 populations at high risk.9 In over 8700 subjects from Micronesian and Mariotai populations, alcohol intake had no association with prevalence of impaired glucose tolerance or type 2 DM. In a small prospective substudy conducted in 1982 among 287 Nauruans with normal glucose tolerance, the odds ratio for developing type 2 DM was 0.65 (95% CI, 0.33-1.31) among alcohol users. In a small survey among male self-defense officials in Japan, no statistically significant association was observed between alcohol consumption and type 2 DM.10 However, the data were compatible with a possible inverse association between moderate alcohol consumption and diabetes, with the odds ratio below unity. The statistical power of the study was limited. On the other hand, among 221 men and 303 women observed for 14 years in a Rancho Bernardo, Calif, cohort, high levels of alcohol consumption in the past 24 hours and high intake in the past week were associated with a 50% increased risk of non–insulin-dependent DM among men only. No association was observed among women in this cohort.11 Finally, the Paris Prospective Study found a 2.5-fold increased risk of diabetes among subjects with “very abnormal livers” during clinical examination,12 and an increased risk of diabetes among men with an alcohol consumption level of more than 20 g/d compared with abstainers.12 In these studies, relatively small sample sizes, as well as the small number of cases and the differences in the measurement of alcohol consumption levels (e.g., usual alcohol consumption vs recent alcohol consumption or average alcohol consumption over the past year vs alcohol consumption within the past 24 hours or past week), may explain some of the results. Also, larger amounts of alcohol and alcoholism have been shown to aggravate insulin resistance and cause liver disease, resulting in type 2 DM and even death.18-20 Our study population primarily consisted of low to moderate drinkers; therefore, we could not study the effects of larger amounts of alcohol consumption.

Plausible mechanisms mediating the association between alcohol intake and glucose tolerance have been hypothesized. Studies have suggested that moderate consumption of alcohol may increase insulin sensitivity21,22 and lower fasting insulin resistance.23 Increased insulin secretory responses and enhanced glucose disposal rates have been observed after moderate alcohol ingestion in subjects without diabetes as well as in subjects with type 2 diabetes.24-27 This increased secretory response could be a result of the alcohol-induced stimulation of insulin secretion by gastrointestinal secretagogues28 or an insulinogenic effect of corticotropin peptides present in cells of the gastroentero-pancreatic systems.27-29

Our study had several important strengths and limitations. The possibility of differential reporting of alcohol consumption according to disease status was minimized by the prospective design of this study. Alcohol consumption data were collected prior to diagnosis of diabetes; therefore, drinking habits and the recall of alcohol intake could not have been influenced by disease status. It is possible, however, that physicians at high risk for diabetes because of family history may have altered their alcohol consumption. Data about family history of diabetes among parents and siblings were collected at 9-year follow-up; therefore, data were available for only a subset of the study population. Adjustment for family history of diabetes did not change our results, and similar findings were reported from other studies.30 Moreover, we relied on self-reported alcohol consumption data in our study, as did most other alcohol-related epidemiological studies, since it has been reported that other approaches are not practical in large cohort studies.30 Furthermore, the usefulness of simple self-administered questionnaires to reliably estimate alcohol consumption, especially among health professionals, has been demonstrated.31 However, random misclassification of alcohol intake is possible if physicians generally underreported or underestimated their alcohol intake. If present, this type of misclassification could have led to underestimation of the true effect. Although our measurement of alcohol consumption lacks sufficient precision to evaluate dose response, other investigations in this population have demonstrated a protective effect for cardiovascular disease end points among those with low to moderate alcohol consumption levels, providing reassurance for our quantification methods and support for the construct validity of our alcohol categorization.32,33 The follow-up rate of our study was extremely high (>99%) and comparable across categories of alcohol intake; thus, these results cannot be biased by losses to follow-up. The study population was not screened for glucose tolerance; therefore, underascertainment of diabetes is possible. Although we do not have data regarding medical contact for the study population, all participants were physicians and were expected to have a high level of overall medical care. If present, the ascertainment bias is unlikely to be different by alcohol consumption level. Finally, the socioeconomic homogeneity of the study population offers advantages for the study of alcohol-disease association, since potential biases from confounding variables correlated with alcohol consumption, as described by Shaper et al,34 are minimized.

In conclusion, these prospective data from the Physicians’ Health Study support the hypothesis that there is an inverse association between light to moderate alcohol consumption and the subsequent risk for type 2 DM. The biological mechanisms behind this apparent ef-
fect, in particular the long-term effects of low to moderate alcohol consumption on insulin and glucose metabolism, remain to be elucidated. These results are limited to apparently healthy individuals consuming light to moderate amounts of alcohol. Caution should be exercised in assessing the individual health risks and benefits of any changes in drinking behavior in light of major clinical and public health problems associated with heavy drinking.

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