Alcohol Consumption and the Risk of Renal Dysfunction in Apparently Healthy Men

Elke S. Schaeffner, MD, MSc; Tobias Kurth, MD, ScD; Paul E. de Jong, MD, PhD; Robert J. Glynn, PhD, ScD; Julie E. Buring, ScD; J. Michael Gaziano, MD, MPH

Background: Moderate alcohol consumption has been consistently associated with beneficial health effects on cardiovascular disease. In contrast, the association between alcohol consumption and renal dysfunction is less clear.

Methods: We conducted a prospective cohort study of 11,023 initially healthy men who provided blood samples 14 years after a baseline assessment of alcohol consumption. We categorized alcohol consumption into 1 or fewer, 2 to 4, 5 to 6, and 7 or more drinks per week. The main outcome measures were elevated creatinine levels (defined as ≥1.5 mg/dL [≥133 μmol/L]) and reduced estimated glomerular filtration rates (defined as ≤55 mL/min). We used logistic regression to calculate multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: After 14 years, 473 men (4.3%) had elevated creatinine levels and 1296 (11.8%) had reduced glomerular filtration rates. Compared with men who consumed no more than 1 drink per week, men who consumed 2 to 4 drinks weekly had a multivariable-adjusted OR of 1.04 (95% CI, 0.81-1.32), men who consumed 5 to 6 drinks per week had an OR of 0.92 (95% CI, 0.68-1.25), and men who consumed at least 7 drinks weekly had an OR of 0.71 (95% CI, 0.55-0.92) (P = .01 for trend across categories). Similar associations were observed between alcohol consumption and decreased glomerular filtration rates. Hypertension, diabetes mellitus, and cholesterol level did not attenuate these effects.

Conclusions: In this large cohort of apparently healthy men, alcohol consumption was not associated with an increased risk of renal dysfunction. Instead, these data suggest an inverse relationship between moderate alcohol consumption and the risk of renal dysfunction.

Arch Intern Med. 2005;165:1048-1053
the PHS have been described in detail previously.17,18 The Brigham and Women’s Hospital institutional review board approved the study. The trial population consisted of 22,071 apparently healthy male physicians without a history of CVD, cancer, current liver disease or renal dysfunction (defined as renal failure or insufficiency), or other major illnesses at baseline in 1982. Most of the participants (94.3%) were white; 2.8% were Asian, 0.7% were African American, and 2.2% were other ethnicity. Baseline information was self-reported and was collected using a mailed questionnaire that asked about many demographic, medical history, and lifestyle variables, including alcohol consumption. Every 6 months for the first year and annually thereafter, participants were sent follow-up questionnaires that asked about personal characteristics, medical history, and health behaviors during the study period.

BLOOD COLLECTION AND ANALYSIS

The method of blood collection was published in detail previously.19,20 Briefly, at baseline in 1982 and during follow-up in 1996, participants were invited to provide an EDTA blood sample. In 1996, a total of 11,360 blood samples were received. Creatinine could be analyzed in 11,104 of these samples; of those, 4,497 physicians had remaining blood samples from the baseline blood collection for which creatinine could be evaluated. Creatinine was analyzed at the same time in all blood samples, using an automated Jaffe rate method on a SYNCHRON LX20 autoanalyzer (Beckman Coulter, Fullerton, Calif) for quantification of creatinine. Plasma creatinine is stable in chilled next-day whole blood samples preserved with EDTA.21 To assess quality control, masked duplicate split samples were submitted; the coefficient of variation for these masked split samples was 7.1%. The difference in mean (SD) between the study samples and the repeated quality control samples was 0.018 (0.67) mg/dL (2.59 µmol/L). Intraday coefficients of variation on internal quality control runs were 1.4% to 3.6%.

INFORMATION ON ALCOHOL CONSUMPTION

Information about alcohol consumption was collected at baseline and on the 84-month questionnaire. Answer categories included “rarely/never,” “1 to 3 drinks per month,” “1 drink per week,” “2 to 4 drinks per week,” “5 to 6 drinks per week,” “daily,” and “2 or more drinks per day.” We a priori combined the 3 lowest categories and the 2 highest categories and categorized alcohol consumption into 4 groups (<1 drink per week, 1-4 drinks per week, 5-6 drinks per week, and ≥7 drinks per week).

OUTCOMES

Our primary outcome was elevated creatinine level, defined as 1.5 mg/dL or greater (≥133 µmol/L) at the time of follow-up blood sample collection in 1996. We also examined reduced glomerular filtration rate (GFR), estimated using the Cockcroft-Gault equation:23 GFR=[(140–age) × (weight in kilograms)]/ [72 × (creatinine in milligrams per deciliter)]. A reduced GFR was defined as 55 mL/min or less. Because the best measure of renal function in large-scale epidemiologic studies has not been determined,23 we also evaluated the change in creatinine concentration in participants for whom baseline and follow-up blood creatinine measurements were available (n = 4,497). We evaluated several different cutoff values for increases in creatinine concentration (ranging from ≥0.3 to ≥0.6 mg/dL [≥27 to ≥33 µmol/L]).

STATISTICAL ANALYSIS

Information on alcohol intake at baseline was missing for 81 of the 11,104 physicians with creatinine measurements in 1996, leaving a sample of 11,023 participants for this analysis. We compared the characteristics of participants with respect to alcohol consumption category using general linear models (SAS version 8.2; SAS Institute Inc, Cary, NC) to compare continuous measurements adjusted for age. We used direct standardization to adjust categorical variables for age in 5-year age groups. We used logistic regression to analyze the association between alcohol intake and elevated creatinine levels, low GFRs, and change in creatinine concentration. We calculated age- and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs). We made a distinction in the multivariable models between variables considered potential confounders and those considered potential intermediate markers, that is, variables known to be affected by alcohol consumption and suspected to contribute to renal dysfunction. However, because it was considered desirable to measure the contribution of alcohol to renal dysfunction separate from the intermediary variables, analyses were performed separately with and without controlling for these variables.

In the first multivariable model (model 1), we controlled for age in 5-year increments (<45, 45-49, 50-54, 55-59, 60-64, 65-69, and ≥70 years), body mass index at baseline (quartiles), smoking (never, past, and current), physical activity (none, <5 times per week, and ≥5 times per week), history of diabetes mellitus at baseline, parental history of myocardial infarction before age 60 years, and randomized treatment assignment (aspirin and beta carotene). In the second model (model 2), we controlled for all the variables in the first model plus a self-reported history of hypertension at baseline (defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use at baseline regardless of blood pressure); the development of hypertension, diabetes mellitus, or CVD (defined as myocardial infarction, stroke, angina, or coronary artery bypass graft) during follow-up; and a history of an elevated cholesterol level at baseline.

RESULTS

Of the 11,023 study participants, 4,259 (38.6%) reported alcohol consumption of 1 or fewer drinks per week, 2,582 (23.4%) of 2 to 4 drinks per week, 1,474 (13.4%) of 5 to 6 drinks per week, and 2,708 (24.6%) of 7 or more drinks per week. The age-adjusted characteristics of the study participants according to alcohol consumption categories are summarized in Table 1. Men who consumed at least 7 drinks per week were older, were leaner, had higher systolic and diastolic blood pressures, were more likely to develop hypertension during follow-up, and smoked more frequently. On the other hand, they exercised less and were less likely to have developed CVD and diabetes mellitus during follow-up. After a mean of 14.2 years of follow-up, 473 men (4.3%) had elevated creatinine levels (≥1.5 mg/dL [≥133 µmol/L]). A total of 1,126 men (11.8%) had decreased GFRs (≤55 mL/min) based on the Cockcroft-Gault estimation.

The age- and multivariable-adjusted ORs of elevated creatinine levels for the categories of alcohol consumption are summarized in Table 2. The multivariable-adjusted OR of developing an elevated creatinine level of 1.5 mg/dL or greater (≥133 µmol/L) declined with increasing alcohol intake. Compared with men who con-
used no more than 1 drink per week, men who consumed 2 to 4 drinks per week had a multivariable-adjusted OR of 1.04 (95% CI, 0.81-1.32), men who consumed 5 to 6 drinks per week had an OR of 0.92 (95% CI, 0.68-1.25), and men who consumed 7 or more drinks per week had an OR of 0.71 (95% CI, 0.55-0.92). There was a significant inverse trend across increasing alcohol intake categories (P < .001). Additional adjustments for potential intermediate variables (model 2) only slightly changed the ORs of the association between the highest alcohol consumption group and creatinine levels. When we separated the highest alcohol intake group into categories of 7 drinks per week and 8 or more drinks per week, this trend continued (P = .008) (Figure).

The multivariable ORs for reduced GFRs demonstrated the same tendencies (Table 3). There was a significant inverse trend across alcohol consumption categories with respect to decreased GFRs (≥55 mL/min). Men who consumed 7 or more drinks per week had a multivariable-adjusted OR of 0.76 (95% CI, 0.64-0.91) compared with men who consumed 1 or fewer drinks per week. There was also a significant trend across alcohol intake categories (P = .002). Model 2 yielded similar results.

Adjustments for categories of blood pressure did not appreciably change the effect estimate between alcohol intake and renal function. We also considered different ethnicities as a potential confounding variable, in particular African American. However, because most PHS participants were white (94.3%) and only a small proportion were African American (0.7%), inclusion of an indicator for African American or other ethnic categories did not yield materially different results for the association between alcohol consumption and risk of renal dysfunction. We did not find different effects of the association between alcohol consumption and risk of renal disease in stratified analyses based on tertiles of baseline GFR.

The association between alcohol consumption and change in creatinine concentration depended on the chosen cutoff value. Of the 4497 participants for whom creatinine measurements were available in 1982 and 1996, no association was observed between alcohol consumption and a creatinine level increase of 0.3 mg/dL or greater (P = .09 for trend). However, raising the cutoff value for increased creatinine level revealed an inverse association. With a cutoff value of 0.6 mg/dL or greater (≥27 µmol/L), men who consumed at least 7 drinks per week had an age-adjusted OR of 0.49 (95% CI, 0.25-0.96; P = .04 for trend) compared with those who never or rarely drank. Multivariable adjustments (model 1) increased the OR to 0.54 (95% CI, 0.27-1.07; P = .09 for trend).

In addition, we evaluated the association between alcohol consumption as reported on the 84-month questionnaire and elevated creatinine level (≥1.5 mg/dL [≥133 µmol/L]) in 1996. Compared with men who consumed 1

---

**Table 1. Age-Adjusted Baseline Characteristics of 11 023 Men in the Physicians’ Health Study According to Alcohol Consumption Categories**

<table>
<thead>
<tr>
<th>Alcohol Consumption Category</th>
<th>1 wk (n = 4259)</th>
<th>2-4 wk (n = 2582)</th>
<th>5-6 wk (n = 1474)</th>
<th>≥7 wk (n = 2708)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SE), y</td>
<td>52.4 (0.13)</td>
<td>52.0 (0.17)</td>
<td>52.5 (0.22)</td>
<td>54.6 (0.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, mean (SE), kg/m²</td>
<td>25.1 (0.04)</td>
<td>24.9 (0.06)</td>
<td>24.7 (0.08)</td>
<td>24.6 (0.06)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SE), mm Hg</td>
<td>124.6 (0.18)</td>
<td>124.7 (0.23)</td>
<td>125.2 (0.31)</td>
<td>126.1 (0.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SE), mm Hg</td>
<td>78.2 (0.12)</td>
<td>78.0 (0.15)</td>
<td>78.5 (0.21)</td>
<td>79.0 (0.15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension, %‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>65.5</td>
<td>66.1</td>
<td>62.9</td>
<td>59.5</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.1</td>
<td>13.1</td>
<td>21.6</td>
<td>23.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Follow-up</td>
<td>14.4</td>
<td>14.8</td>
<td>15.5</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>92.9</td>
<td>95.6</td>
<td>95.1</td>
<td>95.4</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.8</td>
<td>1.2</td>
<td>1.4</td>
<td>1.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Follow-up</td>
<td>4.2</td>
<td>3.2</td>
<td>3.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease during follow-up, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>15.1</td>
<td>14.2</td>
<td>13.6</td>
<td>11.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>64.2</td>
<td>50.8</td>
<td>44.9</td>
<td>37.7</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>29.4</td>
<td>41.2</td>
<td>46.3</td>
<td>49.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current</td>
<td>6.4</td>
<td>8.0</td>
<td>8.8</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>Physical activity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rarely</td>
<td>15.0</td>
<td>16.3</td>
<td>18.2</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>&lt;5 times per week</td>
<td>70.2</td>
<td>74.6</td>
<td>73.5</td>
<td>70.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥5 times per week</td>
<td>14.8</td>
<td>9.1</td>
<td>8.3</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Parental history of myocardial infarction, %§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>8.9</td>
<td>10.3</td>
<td>9.9</td>
<td>9.7</td>
<td>.20</td>
</tr>
<tr>
<td>History of elevated cholesterol level (≥240 mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[≥6.2 mmol/L], %</td>
<td>11.5</td>
<td>11.4</td>
<td>12.9</td>
<td>13.6</td>
<td>.005</td>
</tr>
</tbody>
</table>

†The P values are from generalized linear models for continuous variables and from the Mantel-Haenszel χ² test using row mean score differences for categorical variables.

‡Hypertension was self-reported (defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or current antihypertensive medication use regardless of blood pressure).

§Parental history of myocardial infarction before age 60 years.
The results of this large prospective cohort study do not indicate that alcohol consumption is associated with an increased risk of renal dysfunction in apparently healthy men. Instead, the data suggest an inverse relationship between moderate alcohol consumption and the subsequent risk of renal dysfunction in men. Men who consumed at least 7 drinks per week had an OR of 0.80 (95% CI, 0.59-1.09), and men who consumed at least 7 drinks per week had an OR of 0.66 (95% CI, 0.49-0.87). The trend test across alcohol intake categories after 84 months of follow-up was also significant (P = .003). The inclusion of potential intermediate variables did not substantially change these estimates. The ORs for decreased GFRs were similar.

### COMMENT

Moderate alcohol consumption has been observed to have a favorable effect on several diseases in numerous studies during the past 20 years. Individuals who consume small to moderate amounts of alcohol are at decreased risk for CVD, including myocardial infarction, peripheral arterial disease, angina pectoris, and ischemic stroke, and have a decreased risk of dying. Beneficial effects of moderate alcohol consumption on renal function are plausible; in recent years, traditional risk factors for CVD have been associated with an increased risk of developing renal dysfunction. Furthermore, autopsy data suggested potential beneficial effects of alcohol consumption on the hyalinization in renal arterioles. In a prediction model for new-onset renal disease, several traditional CVD risk factors showed significant associations. In this study, however, alcohol consumption was not considered. In addition, there is evidence that the consumption of light to moderate amounts of alcohol decreases the risk of type 2 diabetes mellitus and has preventive effects on the development of arteriosclerosis in patients with type 2 diabetes mellitus.
A recent prospective cohort study found no statistically significant association between alcohol consumption and risk of decline in renal function among 1658 apparently healthy women. This study, however, suggested beneficial effects of moderate alcohol consumption on renal function, with an approximately 20% risk reduction. The sample size of this study might have been too small to detect any statistically significant association.

Our finding stands in contrast to those of previously published retrospective studies. A population-based case-control study reported an approximately 4-fold increase in the risk of end-stage renal disease among individuals who consumed more than 2 alcoholic drinks per day after adjustment for potential confounders. Another case-control study also concluded that individuals who consumed 2 or fewer drinks per day had higher serum creatinine concentrations than matched controls who did not drink alcohol. This study, however, provided evidence that drinkers in higher alcohol intake categories had reduced creatinine levels compared with their nondrinking controls. These differences may be explained by the different study designs or by the fact that alcohol might have different effects on future renal function in healthy individuals than in those with preexisting renal disease.

It has been argued that alcohol consumption may result in renal disease because of alcohol-induced hypertension. Indeed, in our study, the prevalence and incidence of hypertension was statistically significantly higher among participants who consumed 7 or more alcoholic drinks per week. However, this group had a decreased risk of renal dysfunction. Men with the highest amounts of alcohol intake also had the highest high-density lipoprotein (HDL) cholesterol levels compared with men who rarely or never consumed alcohol. This result is consistent with earlier experimental studies showing that moderate drinking increases several HDL cholesterol subfractions. Besides some antithrombotic properties, an alcohol-induced increase in HDL cholesterol subfractions has been discussed to be the major mechanism for the cardiovascular benefit of moderate alcohol consumption. Because it has been shown that low HDL cholesterol levels (\( <40 \text{ mg/dL} \)) increases the risk of renal dysfunction, it is plausible that an alcohol-related increase in HDL cholesterol may explain the potential beneficial effect seen in our analysis of renal dysfunction. The potential beneficial effect of alcohol intake on renal function observed in our study could also be mediated by the positive effect of moderate drinking on the incidence of diabetes mellitus and the protective effect on atherosclerosis among patients with type 2 diabetes mellitus. Heavy alcohol consumption or intoxication has been linked to acute renal failure via rhabdomyolysis. This specific question, however, could not be studied in our cohort because heavy alcohol consumption was uncommon.

The strengths of this study include its large size, its long follow-up of more than 14 years, its prospective method of data collection, and the relatively homogeneous nature of the cohort, which reduces confounding by several variables, including access to medical care, educational attainment, and socioeconomic status. Furthermore, we evaluated the association between alcohol consumption and risk of renal dysfunction using several different outcomes, including change in creatinine levels.

This study has several limitations that should be considered. Men who participated in the PHS may differ in many ways from the general population. Thus, our results may not necessarily be extended to women or other populations. Regarding the specifics of our study, there is currently little biological basis to postulate that the mechanism by which alcohol may affect renal function would be materially different between PHS participants and other populations. Regarding ethnicity, recent studies provided evidence that the most striking difference between African Americans and whites was not the prevalence of moderate-to-severe chronic kidney disease but rather the more frequent progression to kidney failure among African Americans. Indeed, there is a higher prevalence of major risk factors for renal dysfunction among African Americans. However, inclusion of an indicator variable for African American in our multivariable models did not yield different results (data not shown). Because of the low numbers, we could not evaluate whether a different association between alcohol consumption and renal disease exists in African Americans. In support of generalizability, the association between alcohol consumption and CVD found in other PHS analyses follows the findings of other population-based research. The GFR estimated using the Cockcroft-Gault equation has been criticized. However, when we repeated the analyses using the simplified version of the Modification of Diet in Renal Disease Study equation to estimate GFR, the results were similar (data not shown).

Another consideration in evaluating studies of alcohol and disease is that drinking habits can change with time. However, in a sensitivity analysis using information on alcohol consumption from the 84-month follow-up questionnaire, the results were similar. As in most other alcohol-oriented epidemiologic studies, we relied on self-reported levels of alcohol consumption. Other studies of health professionals have demonstrated that this population provides reliable reports of alcohol use. In addition, the prospective method of exposure collection would lead to random misclassification and thus to a potential underestimation of the association between alcohol consumption and renal dysfunction. In addition, blood samples were available only for a subsample of the PHS cohort, and for only a smaller fraction were baseline and follow-up creatinine levels measured. Finally, confounding remains a possible alternative explanation for our finding; however, multiple covariate adjustments did not materially alter the results.

In summary, this large prospective cohort study shows that moderate alcohol consumption is not associated with an increased risk of renal dysfunction in men. Instead, our data suggest an inverse relationship between moderate alcohol consumption and the risk of developing renal dysfunction.

Accepted for Publication: January 18, 2005.
Correspondence: Tobias Kurth, MD, ScD, Division of Preventive Medicine, Brigham and Women’s Hospital, 900 Commonwealth Ave E, Boston, MA 02215-1204 (tkurth@rics.bwh.harvard.edu).
Funding/Support: This work was supported by grants CA 34944, CA 40360, HL 26490, and HL 34595 from the National Institutes of Health, Bethesda, Md.

Previous Presentation: The study was presented in part at the American Society of Nephrology meeting; November 14, 2003; San Diego, Calif.

Acknowledgment: We thank the participants in the PHS for their outstanding commitment and cooperation and the entire PHS staff for their expert and unfailing assistance.

REFERENCES


