Original Article

Moderate alcohol intake and renal function decline in women: a prospective study

Eric L. Knight¹,³, Meir J. Stampfer¹,², Eric B. Rimm¹,², Susan E. Hankinson¹,² and Gary C. Curhan¹,²

¹The Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, ²Department of Epidemiology, Harvard School of Public Health and ³Renal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Background. The impact of moderate alcohol consumption on renal function has important public health implications given the high prevalence of alcohol use. Experimentally, alcohol may adversely affect renal function, but clinical data are limited and no large, prospective studies have examined this issue.

Methods. In a prospective study of 1658 nurses enrolled in the Nurses’ Health Study, we sought to determine if there was an association between moderate alcohol consumption and rate of decline in renal function. Daily alcohol intake was measured in 1990, 1994 and 1998 using a detailed questionnaire. Maximum daily alcohol intake was measured in 1988. Creatinine, measured from blood samples provided in 1989 and 2000, was used to estimate glomerular filtration rate (GFR) and creatinine clearance (CCr).

Results. Compared to individuals with no alcohol intake, the odds ratios (ORs) for developing a ≥25% estimated GFR decline were: 0.98 (95% CI: 0.72–1.32) for 0.1–4.9 g/day, 0.83 (95% CI: 0.56–1.21) for 5–14.9 g/day and 0.81 (95% CI: 0.50–1.31) for 15–59.9 g/day. For women with hypertension (n = 726), the ORs for a ≥25% estimated GFR decline were: 0.98 (95% CI: 0.53–1.21) for 0.1–4.9 g/day, 0.62 (95% CI: 0.34–1.12) for 5–14.9 g/day and 0.53 (95% CI: 0.25–1.12) for 15–59.9 g/day.

Conclusions. Moderate alcohol consumption had no substantial adverse effect on renal function in women over an 11 year follow-up period.

Keywords: alcohol; creatinine clearance; glomerular filtration rate; renal function; renal insufficiency

Introduction

Despite the high prevalence of alcohol use throughout the world, the effect of alcohol consumption on renal function has not been well studied. A recent, large case-control study found significantly increased odds of developing end-stage renal disease (ESRD) in subjects who drank more than two alcoholic beverages per day [odds ratio (OR): 4.0; 95% confidence interval (CI): 1.2–13.0] [1]. However, to our knowledge, no prospective study has examined the impact of alcohol consumption on renal function decline. We hypothesized, based on the prior limited data, that moderate alcohol intake may be associated with increased renal function decline compared with no alcohol intake.

Some experimental evidence supports the hypothesis that chronic alcohol ingestion may have adverse renal effects. In a rodent model of immunoglobulin A nephropathy, intragastric whisky infusion was associated with mesangial deposits, proteinuria and haematuria [2]. Another rodent model found renal hypertrophy in response to chronic alcohol ingestion [3]. Heavy, chronic alcohol consumption has also been associated with hypertension [4], which may cause renal dysfunction [5]. However, there are also some autopsy data suggesting that alcohol may prevent renovascular disease [6]. There are sparse clinical data on the impact of moderate alcohol intake on renal function. Perneger et al. [1] found no association between alcohol intake of one or less alcoholic beverages per day and the odds of ESRD (OR: 1.1; 95% CI: 0.7–1.9), but reported a higher, though non-significant, odds for ESRD with an intake of one to two alcoholic beverages per day (OR: 1.6; 95% CI: 0.6–4.3). To address prospectively the association between moderate alcohol intake and decline in renal function, we studied this question in a subset of participants in the Nurses’ Health Study.

Correspondence and offprint requests to: Eric L. Knight, MD, MPH, Channing Laboratory, Nurses’ Health Study, 3rd Floor, 181 Longwood Avenue, Boston, MA 02115, USA.
Email: elknight@partners.org

© 2003 European Renal Association-European Dialysis and Transplant Association
Subjects and methods

Study population

The Nurses’ Health Study began in 1976, when 121700 female nurses, 30–55 years old, living in the USA, completed a detailed questionnaire regarding health-related information. Since then, questionnaires have been sent biennially. Information on lifestyle factors and new medical diagnoses is collected every 2 years and a detailed dietary questionnaire is mailed every 4 years.

The creatinine measurements used to estimate renal function were initially obtained as part of a study designed to assess the impact of analgesic use on renal function. Women from the Nurses’ Health Study were eligible for inclusion in this study if they answered the 1990 and 1992 biennial questionnaires, which had information on analgesic use, had a blood sample collected in 1989 and 2000 and had no history of cancer (except non-melanoma skin cancer) or cardiovascular disease (myocardial infarction, angina, stroke or transient ischaemic attack). From a total of 4238 eligible women, 3876 (91%) agreed to participate in the study and returned a supplementary analgesic use questionnaire. From these 3876 women, we selected 1769 women with lifetime consumption of at least 1501 tablets of one of the analgesics and a random sample of women with intake less than 1501 tablets.

From these 1769 women, we excluded 34 who reported a history of ‘abnormal kidney function’, 20 who were missing a creatinine value from either 1989 or 2000, four who had a creatinine < 0.4 mg/dl (35 μmol/l) in 1989, nine who reported a daily alcohol consumption > 60 g/day and 44 who were missing information on daily alcohol consumption. This left 1658 women for the primary analyses. There were no exclusions based on serum creatinine and only one woman had a baseline creatinine > 1.5 mg/dl. An additional 16 women were excluded from the analysis of maximum daily alcohol intake because they were missing this information. Compared with the whole Nurses’ Health Study cohort, the women in this sub-cohort were of similar age (56.5 ± 6.7 vs 56.5 ± 7.2 years) and weight (69.5 ± 15.0 vs 69.8 ± 14.1 kg) and had a similar prevalence of hypertension (29% vs 32%), diabetes (3% vs 5%) and hypercholesterolaemia (41% vs 38%), but these women were less likely to smoke (12% vs 18%). In terms of the distribution of body mass indices in this sub-cohort, 53% of women had a BMI < 25 kg/m² (optimal), 31% had a BMI 25–29.9 kg/m² (overweight) and 16% had a BMI ≥ 30 kg/m² (obese).

Assessment of alcohol intake

In 1990, 1994 and 1998, participants were asked to complete a semi-quantitative food frequency questionnaire that contained questions about alcohol consumption during the previous year. Specifically, the questionnaire asked about average use of beer (one glass, bottle or can), red and white wine (4 oz glass) and liquor (one drink or shot) over the past year. For each beverage, subjects were asked to choose one of the following frequency categories: (i) never or less than once per month, (ii) 1–3 per month, (iii) 1 per week, (iv) 2–4 per week, (v) 5–6 per week, (vi) 1 per day, (vii) 2–3 per day, (viii) 4–5 per day and (ix) 6+ per day. Total daily alcohol intake was calculated by adding the usual daily intake of alcohol, assuming the following alcoholic content of specific beverages: one 12 oz can of beer, 12.8 g; one 4 oz glass of wine, 11.0 g; one standard drink of spirits, 14.0 g [7]. Daily alcohol intake was classified as none, 0.1–4.9, 5–14.9 and 15–59.9 g/day. A previous validation study among a subset of participants demonstrated a high correlation between reported alcohol intake on the questionnaire and dietary records (r = 0.9) [8].

The 1988 questionnaire was used to assess maximal daily alcohol intake. The following question was asked, ‘In a typical month during the past year, what was the largest number of drinks of beer, wine and/or liquor you may have had in any one day?’ The possible response categories were: none, 1–2, 3–5, 6–9, 10–14 or 15+.

Assessment of other factors

Age, race, body mass index, diabetes, hypertension, smoking, hypercholesterolaemia, analgesic medication use and anti-hypertensive medication use were initially included as potentially important confounders. Age, race, body mass index, smoking status and analgesic use were obtained from the 1990 questionnaire. Age and body mass index were categorized as continuous variables, race was categorized as black or white, smoking was classified as current smoker, past smoker or non-smoker and acetaminophen, aspirin and non-steroidal anti-inflammatory use were classified based on number of days of use per month. Diabetes, hypertension and hypercholesterolaemia were recorded if a woman reported any of these diagnoses from 1976 to 1998. Information on antihypertensive medication use was obtained from the 1994 and 1996 questionnaires. These medications were classified as thiazide diuretic (yes/no), calcium channel blocker (yes/no), beta-blocker (yes/no), angiotensin-converting enzyme inhibitor (yes/no) or other antihypertensive (yes/no).

Estimation of renal function

Renal function was estimated using creatinine values from blood samples drawn and stored at −130°C in 1989 and 2000. All samples were analysed at the same time in 2001 at Boston Children’s Hospital. Twenty samples had insufficient quantity for analysis. Creatinine was measured by a Hitachi auto-analyser using the modified kinetic Jaffé reaction. The coefficient of variation for 371 interspersed masked samples that were included with the study samples was 10.0%.

The primary estimate of renal function was glomerular filtration rate (GFR) estimated by the simplified formula from the Modification of Diet in Renal Disease (MDRD) study [9–11]. This formula was empirically derived from 1070 patients with renal insufficiency using iothalamate GFR measurements and subsequently validated in 558 patients in the same study [9,10]. The simplified formula is:

\[ 186 \times \text{Creatinine}^{-1.154} \times \text{Age}^{0.203} \times 0.742 \]

and multiplied by a factor of 1.212 for black women, where creatinine is measured in mg/dl, age in years and the GFR units are ml/min/1.73 m² [9,10]. The second formula used was a modification of the Cockcroft–Gault formula for estimating creatinine clearance (CCr) [12]. This modified
formula to estimate CCr based on fat-free body mass has the advantage of attenuating the overestimation of CCr in obese individuals with the Cockcroft-Gault equation and provides similar results in average-weight women [13]. The formula for women is:

\[
 \text{CCr} = \frac{(146 - \text{Age}) \times [(0.287 \times \text{Weight}) + (9.74 \times \text{Height}^2)]}{(60 \times \text{Creatinine})}
\]

where age is measured in years, weight in kilograms, height in metres and creatinine in mg/dl, the units for CCr are ml/min. This formula has been validated compared with actual measurements of CCr [13,14]. We used 1989 weight to calculate the estimated 1989 CCr and 1998 weight to calculate the estimated 2000 CCr, since a simultaneous weight was unavailable.

**Statistical analyses**

Descriptive data were examined for all variables for the total cohort and for the different categories of alcohol consumption. For continuous variables, the mean, median and SD were calculated. Multivariate analyses were performed using logistic regression. The primary outcomes of interest were a decline in estimated GFR of ≥20%, ≥25% and ≥30%. We also examined these same cut points for estimated CCr.

The following pre-specified independent variables were included in all models: age, body mass index, alcohol intake, protein intake, hypercholesterolaemia, diabetes, hypertension and smoking status. Black race was excluded as a variable, because there were only 13 black women. Aspirin, non-steroidal anti-inflammatory, acetaminophen and antihypertensive medication use were eliminated from the final models, because their inclusion did not affect the point estimates of the main exposures of interest. We also performed analyses stratified by the presence or absence of hypertension and obesity. Daily average alcohol intake based on the 1990 questionnaire was used for the primary analyses and secondary logistic regression analyses were performed using the mean of the daily alcohol intake obtained from the 1990, 1994 and 1998 questionnaires. Additional logistic regression analyses were performed using information on maximum daily alcohol intake.

Two-tailed P-values and 95% CIs were calculated for each OR and parameter estimate. The methodology of Lemeshow and Hosmer [15] was used to assess model goodness-of-fit and there was no evidence of lack of goodness-of-fit at the chosen cut points of estimated GFR and CCr.

The correlations between alcohol intake in 1990, 1994 and 1998 were assessed using the Pearson's test.

All analyses were performed using SAS software (version 6.12; SAS Institute, Cary, NC, USA).

**Results**

Demographic, laboratory, dietary and disease-specific information for different categories of 1990 alcohol consumption (none, 0.1–4.9, 5–14.9 and 15–59.9 g/day) are presented in Table 1. Over the 11 year period, the estimated mean GFR for the total cohort fell 9.8 ml/min/1.73 m\(^2\) (0.89 ml/min/1.73 m\(^2\)/year) and there were similar declines across strata of alcohol use (Table 1). Alcohol intake in 1990 was highly correlated with intake in 1994 (\(r = 0.75, P < 0.001\)) and 1998 (\(r = 0.70, P < 0.001\)). In age-adjusted analyses, average quantity of daily alcohol intake was not significantly associated with decline in renal function (Table 2). In multivariate analyses, with different cut points of estimated GFR, we observed no statistically significant association between alcohol intake and decline in estimated renal function (Table 2) and the addition of potential confounders did not substantially affect the age-adjusted point estimates. We observed similar results when we examined decline in CCr at these same cut points.

![Table 1](image)

Demographic, laboratory, dietary and disease-specific information with mean values and 95% CIs for continuous variables (total \(n = 1658\))

<table>
<thead>
<tr>
<th></th>
<th>No alcohol ((n = 659))</th>
<th>Alcohol 0.1–4.9 g/day ((n = 532))</th>
<th>Alcohol 5–14.9 g/day ((n = 303))</th>
<th>Alcohol 15–59.9 g/day ((n = 164))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.2 ± 6.7</td>
<td>55.6 ± 6.7</td>
<td>55.2 ± 6.7</td>
<td>56.0 ± 6.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.6 ± 17.6</td>
<td>68.8 ± 17.1</td>
<td>65.9 ± 14.5</td>
<td>65.4 ± 14.7</td>
</tr>
<tr>
<td>Alcohol intake (g/day)</td>
<td>0</td>
<td>2.1 ± 1.2</td>
<td>9.8 ± 3.0</td>
<td>26.2 ± 9.2</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>0.75 ± 0.13</td>
<td>0.74 ± 0.14</td>
<td>0.74 ± 0.12</td>
<td>0.74 ± 0.14</td>
</tr>
<tr>
<td>2000</td>
<td>0.81 ± 0.16</td>
<td>0.79 ± 0.16</td>
<td>0.80 ± 0.17</td>
<td>0.79 ± 0.14</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73 m(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td>89.5 ± 18.3</td>
<td>89.6 ± 19.4</td>
<td>89.1 ± 17.7</td>
<td>90.3 ± 19.4</td>
</tr>
<tr>
<td>2000</td>
<td>78.5 ± 16.9</td>
<td>80.6 ± 17.3</td>
<td>80.4 ± 18.8</td>
<td>80.6 ± 17.0</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>76.9 ± 14.6</td>
<td>78.0 ± 12.9</td>
<td>75.5 ± 12.4</td>
<td>72.7 ± 10.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47%</td>
<td>44%</td>
<td>38%</td>
<td>43%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7%</td>
<td>4%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>60%</td>
<td>61%</td>
<td>58%</td>
<td>55%</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>9%</td>
<td>10%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>Past</td>
<td>31%</td>
<td>45%</td>
<td>52%</td>
<td>57%</td>
</tr>
</tbody>
</table>

To convert creatinine to from mg/dl to \(\mu\)mol/l, multiply by 88.4.
points (data not shown). The ORs for the association between mean alcohol intake from 1990, 1994 and 1998 and estimated GFR decline $\geq 25\%$ were: $0.83 \ (95\% \ CI: \ 0.61-1.14)$ for $0.1-4.9$ g/day, $0.69 \ (95\% \ CI: \ 0.45-1.04)$ for 5–14.9 g/day and $0.74 \ (95\% \ CI: \ 0.45-1.22)$ for $15-59.9$ g/day.

We also examined the impact of alcohol intake in women with hypertension ($n = 726$). For the women with hypertension, the ORs for $\geq 20\%$ estimated GFR decline were: $0.78 \ (95\% \ CI: \ 0.53-1.14)$ for $0.1-4.9$ g/day, $0.65 \ (95\% \ CI: \ 0.39-1.07)$ for $5-14.9$ g/day and $0.54 \ (95\% \ CI: \ 0.29-1.03)$ for $15-59.9$ g/day. The ORs for $\geq 25\%$ decline were: $0.98 \ (95\% \ CI: \ 0.53-1.21)$ for $0.1-4.9$ g/day, $0.62 \ (95\% \ CI: \ 0.34-1.12)$ for $5-14.9$ g/day and $0.53 \ (95\% \ CI: \ 0.25-1.12)$ for $15-59.9$ g/day. There were too few women with hypertension to examine the outcome of estimated GFR decline $\geq 30\%$. For women with hypertension who consumed alcohol in any quantity compared with abstainers, the ORs were: $0.66 \ (95\% \ CI: \ 0.46-0.94)$ for $\geq 20\%$ decline in estimated GFR and $0.77 \ (95\% \ CI: \ 0.51-1.15)$ for $\geq 25\%$ decline.

When we examined the impact of alcohol intake on change in estimated GFR in women without obesity ($n = 1399$), there were no material changes in our results.

We also examined the association between maximal alcohol intake and decline in estimated GFR. The ORs for $\geq 25\%$ decline in estimated GFR for different maximum daily alcohol intake categories compared with no alcohol intake were as follows: 1–2 drinks (OR: 0.79; 95\% CI: 0.59–1.07), 3–5 drinks (OR: 0.91; 95\% CI: 0.64–1.30) and $\geq 6$ drinks (OR: 0.34; 95\% CI: 0.12–0.98).

### Discussion

We found no material association between daily alcohol quantity or maximum daily alcohol intake and decline in renal function over an 11 year period. Overall, these results suggest that moderate alcohol intake has no long-term adverse effects on renal function. We also found that moderate alcohol intake may possibly have a renoprotective effect in women with hypertension.

This study differs from the study by Perneger et al. [1], which found a significant association between an average intake of more than two alcoholic beverages per day and the risk of ESRD. First, our population was different, since it was composed exclusively of women with very few blacks. It is possible that gender and race may influence the effects of alcohol, because Perneger et al. [1] found a stronger association between alcohol and ESRD in men compared with women and blacks compared with whites. Second, this was a prospective, observational study whereas the Perneger study used a case-control design. As the authors acknowledged, recall bias may have occurred in their study since alcohol consumption was assessed after the development of ESRD. Third, the adverse effects of alcohol seen in the Perneger study may be more reflective of very high alcohol consumption in the more than two drinks per day category, because in their study, prior to excluding moonshine drinkers, 58% of subjects in this category drank more than four drinks per day [1].

Alcohol may have both detrimental and salutatory effects on renal function. The adverse effects may include glomerular damage, especially in those with pre-existing renal disease [2,3]. Long-term, heavy alcohol use could also potentially lead to hypertension and hypertensive nephrosclerosis [4,5]. Therefore, we purposely excluded women with a history of abnormal renal function in order to examine the effect of alcohol on renal function in those without pre-existing renal disease.

The possible beneficial effects of alcohol on renal function may be similar to that seen with cardiovascular disease. Alcohol has beneficial effects on high-density lipoproteins, fibrinogen, insulin and haemostatic factors [6]. Therefore, chronic alcohol ingestion may help prevent renovascular disease. In support of this theory, Burchfiel et al. [6] found an inverse correlation between alcohol intake and hyalinization of renal arterioles at autopsy.

The finding that alcohol intake may possibly have a protective effect in individuals with hypertension may be explained by the fact that these individuals are at greater risk for renovascular disease and renal function decline, so we were more likely to observe a protective
effect in this population. However, we did not have serial blood pressure measurements over the course of the study and it is possible that abstainers may have had higher blood pressure recordings overall and been told to stop alcohol to improve blood pressure control or, conversely, moderate alcohol intake may lower blood pressure [17].

The overall lack of an adverse effect of alcohol on renal function in the population as a whole might also reflect the possibility that abstainers have higher rates of chronic diseases, leading to abstention from alcohol (this reasoning is analogous to the reasoning in the previous paragraph). However, we excluded women with cardiovascular disease and cancer. Also, studies of alcohol and cardiovascular disease that have excluded subjects who abstain from alcohol for health reasons have found a similar protective effect of chronic, moderate alcohol consumption [18,19].

There is no clear consensus in the literature on how best to estimate renal function using creatinine and other available information. The primary formula we used was one of the formulas derived from the MDRD trial [9–11]. The major strength of this formula is that it was empirically derived from iothalamate GFR measurements. Limitations of this formula include the fact that the MDRD study was limited to a select population with renal disease and excluded individuals with certain chronic medical conditions, including insulin-requiring diabetes and severe obesity (defined as >160% standard body weight). Traditionally, the Cockcroft–Gault formula has been used to estimate CCr and, by inference, GFR [12]. However, this formula does not accurately estimate GFR [20] and has been shown to overestimate CCr, especially in obese women [13]. Therefore, since we had many obese women in our cohort, we chose to use a modified version of this formula designed to reduce overestimation of CCr in these women.

This study has several limitations. Some women may have under-reported or denied their alcohol intake, despite the fact that self-reported alcohol intake has been separately validated [8]. However, the combination of the prospective study design and the study outcome has the advantage of eliminating recall bias based on knowledge of disease status. There was also a relatively narrow distribution of alcohol intake in this population. There were many non-drinkers and very few heavy drinkers. Therefore, our power to detect a difference in renal function among the heaviest drinkers compared with the rest of the population was limited. Another possible limitation is that we may have inadequately adjusted for potential confounders. For example, we did not have an accurate measure of mean blood pressure throughout the study period, though we did have information on diagnosis of hypertension. This study may also have limited generalizability. This study is generalizable to Caucasian women, but there were very few non-Caucasian women (2%) and estimates of risk among other ethnic groups of women and among men should be evaluated. Finally, we were unable to measure the development of specific end-points of chronic kidney disease, such as an estimated GFR <60 ml/min/1.73 m² [11], because this low level of renal function was rare in this cohort.

In conclusion, moderate alcohol intake was not associated with renal function decline in women over an 11 year period. Additional studies are needed to assess the impact of alcohol use on renal function in individuals with hypertension and other chronic diseases associated with accelerated renal function decline.

Acknowledgements. We thank the participants of the Nurse’s Health Study, Elaine Coughlin for a careful review of the statistical programming and manuscript content and Melissa Francis for help with manuscript preparation. This work was supported by grants T32DK0740, T32DK07791, DK52866, CA87969 and HL34594 from the National Institutes of Health.

Conflict of interest statement. None declared.

References

Received for publication: 8.11.02
Accepted in revised form: 6.3.03