Serum gamma-glutamyltransferase, daily alcohol consumption, and the risk of chronic kidney disease: the Kansai Healthcare Study

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Running Title: gamma-glutamyltransferase and CKD

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Abstract

Background: Serum gamma-glutamyltransferase has been recognized as the risk factor of cardiovascular and metabolic diseases. However, the association between serum gamma-glutamyltransferase and the risk of chronic kidney disease is not well known and no prospective studies have examined separately the relationship of serum gamma-glutamyltransferase with the risk of proteinuria versus that of low estimated glomerular filtration rate (eGFR).

Methods: We prospectively followed 9,341 Japanese men who did not have low eGFR, proteinuria, nor diabetes, and did not take antihypertensive medications at entry for the analysis of proteinuria, and 9,299 men for that of low eGFR. We defined “persistent proteinuria” if proteinuria was detected two or more times consecutively and persistently as ≥1+ on urine dipstick at the annual check-up until the end of follow-up. Low eGFR was defined as eGFR <60 mL/min/1.73 m².

Results: During the 11-year observation period, 151 men developed persistent proteinuria and 1,276 men low eGFR. In multivariate models, the highest quartile (≥71 IU/L) of serum gamma-glutamyltransferase was independently related to the development of persistent proteinuria (hazard ratio 3.39; 95% confidence interval, 1.92-5.97) compared with the lowest quartile (≤25 IU/L). In joint analysis of alcohol consumption and serum gamma-glutamyltransferase, non-drinkers with the highest tertile (≥58 IU/L) of serum
gamma-glutamyltransferase had the highest risk of persistent proteinuria. However, there was no association between serum gamma-glutamyltransferase and low eGFR.

**Conclusion:** In middle-aged Japanese men, elevated serum gamma-glutamyltransferase was independently associated with future persistent proteinuria, but not low eGFR.

**Keywords:** gamma-glutamyltransferase; proteinuria; chronic kidney disease; prospective cohort study; epidemiology
Introduction

Serum gamma-glutamyltransferase (GGT) has been widely known as a liver function test used for the assessment of liver disease and a biological marker of alcohol consumption. Previous epidemiological studies have shown that serum GGT might be a useful marker for oxidative stress. In addition, serum GGT has been reported to be related to the development of hypertension, stroke, and cardiovascular mortality.

Chronic kidney disease (CKD) is a global health problem and has been related to the development of end-stage renal disease and cardiovascular mortality. Only three prospective cohort studies have suggested that serum GGT level was related to the development of CKD. Two of these studies defined CKD as the composite endpoint which was defined as the presence of an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² or proteinuria, which might lead to an attenuation of the association between serum GGT level and the risk of CKD because higher eGFR was reported to be related to the development of proteinuria. Although the other study defined CKD as eGFR <60 mL/min/1.73 m², it did not examine the development of proteinuria. Only one prospective cohort study showed the relationship between serum GGT level and the incidence of microalbuminuria but it did not take into account the influence of participants with transient albuminuria because incident microalbuminuria was measured only one time. To our knowledge, studies examining separately the effect of serum GGT level on the risk of proteinuria versus that of low eGFR in
the same cohort are lacking.

GGT is a common marker for alcohol intake and correlates with alcohol intake.\textsuperscript{13,14} Although various prospective studies have shown the relationship between alcohol consumption and the risk of low eGFR and/or that of proteinuria or albuminuria,\textsuperscript{15-25} the results of these studies were inconclusive. Furthermore, as far as we know, there was no prospective study which had examined the joint relationship of serum GGT and alcohol consumption to the risk of low eGFR versus that of proteinuria.

Therefore, our specific purposes were: 1) to prospectively examine separately the relationship of serum GGT level with the risk of proteinuria versus that of low eGFR and 2) to prospectively investigate the joint relationship of serum GGT and alcohol consumption with the risk of these outcomes. To take into account the influence of transient proteinuria, the definition of persistent proteinuria was used.

Materials and Methods

Site and Setting

The Kansai Healthcare Study is an ongoing prospective cohort study designed to obtain information on the risk factors of cardiovascular and metabolic diseases. From April 2000 to March 2001, we enrolled 12,647 male workers aged 40-55 years of a company in the Kansai area of Japan. The details of this study have been mentioned previously.\textsuperscript{26,27} The protocol for
this research was approved by the Ethics Committee of Osaka City University Graduate School of Medicine.

The current investigation is composed of 10,019 men who had no proteinuria, an eGFR ≥60 mL/min/1.73 m², a fasting plasma glucose (FPG) <126 mg/dL, and were not taking hypoglycemic agents, insulin, or antihypertensive drugs at entry. We excluded 320 men who did not undergo annual medical examinations. Because there were missing covariates at baseline, we excluded 358 men for the analysis of examining the outcome of proteinuria and 400 men for that of low eGFR. Thus, a total 9,341 men remained for the analytic cohort for proteinuria and 9,299 men for low eGFR.

Data Collection and Measurements

The participants were examined on a medical history, anthropometric measurements, physical examination, self-administered questionnaires on lifestyle habits, and dipstick urinalysis. Serum GGT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), FPG, creatinine, total cholesterol, triglycerides, and high-density lipoprotein cholesterol were measured. Using the Friedewald formula, low-density lipoprotein cholesterol levels were calculated in participants who had triglycerides levels <400 mg/dL.28 Trained nurses carried out all of the measurements. Blood samples were collected after an overnight 12-hour fast. AST and ALT were measured using the International Federation of Clinical
Chemistry-recommended method.\textsuperscript{29,30} GGT was measured using the Japanese Society of Clinical Chemistry-transferable method.\textsuperscript{31} In general, serum creatinine was measured by an enzymatic method using a Hitachi 7350 automatic chemistry analyzer (Hitachi Ltd., Tokyo, Japan). In 1,799 participants, serum creatinine was measured by the Jaffe method. We recalibrated the Jaffe values to enzymatic values using the equation which had been described previously in detail.\textsuperscript{24,25} Then eGFR was calculated using the Modification of Diet in Renal Disease study equation for Japanese men as follows: eGFR = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094} (\text{mg/dL, enzymatic method}).\textsuperscript{32} Dipstick urinalysis was performed on clean-catch, mid-stream, and random urine specimens. The results of the urine dipstick test were recorded as negative, ±, 1+, 2+, 3+, or 4+. We measured blood pressure in a sitting position at the right arm with a standard automated sphygmomanometer (BP-203RV; Omron Colin, Tokyo, Japan, and Udex-super; ELK Osaka, Japan) after approximately 5 minutes of rest. Hypertension at baseline was defined if systolic blood pressure was $\geq$140 mm Hg or diastolic blood pressure was $\geq$90 mm Hg.\textsuperscript{33} Dyslipidemia was defined as triglycerides $\geq$150 mg/dL, high-density lipoprotein cholesterol $<40$ mg/dL, low-density lipoprotein cholesterol $\geq$140 mg/dL, or use of oral lipid-lowering medications. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m\textsuperscript{2}). Participants filled out self-administered questionnaires on the medication information and lifestyle factors such as smoking habits, alcohol consumption, and regular leisure-time
Regarding smoking habits, participants were divided into three groups: non-smokers, past smokers, and current smokers. As for drinking habit, the questionnaire consisted of the frequency of alcohol drinking per week and the usual amount of drinking per drinking day according to Japanese standard drinks. One Japanese standard drink is equivalent to 23 g of ethanol. Daily alcohol consumption (in grams of ethanol per day) was calculated as (the amount consumed per drinking day) × (the drinking frequency per week)/7.

We asked for regular leisure-time activity using the single-item questionnaire, which had three choices: rarely, sometimes, and regular (that is, at least once a week). After that, we categorized participants as engaging in leisure-time physical activity at least once a week or less than once a week. The validity of this questionnaire has been reported in detail previously.  

Outcomes

Proteinuria on urine dipstick was defined as ≥1+ (≥30 mg/dL) at the annual medical examination. In order to avoid the influence of participants with transient proteinuria, more definite definition of proteinuria, “persistent proteinuria”, were used: “persistent proteinuria” was defined if proteinuria was observed twice or more consecutively at the annual examination and persistently until the end of follow-up. Low eGFR was defined if eGFR was less than 60 mL/min/1.73 m² regardless of the presence of proteinuria.
Statistical Analyses

We used the Cox proportional hazards model to examine separately the relationship between serum GGT level and the development of two outcomes: persistent proteinuria and low eGFR. Follow-up of each participant was continued until the diagnosis of the outcome occurrence or until the 11-year follow-up examination from 1 April 2011 to 31 March 2012, whichever came first. The presence of non-linear effects of continuous independent variables was assessed by plotting the regression coefficients against the variables. We also assessed these effects using quadratic, square root, and log transformations. The proportional hazards assumption for covariates was assessed by the insertion of time-dependent covariates or by the Schoenfeld residuals plot and Schoenfeld residuals test. To test whether there was effect modification, the first-order interaction term between serum GGT and daily alcohol consumption was examined. In this study, this interaction term was not detected significantly. Multicollinearity was assessed using the variance inflation factor. We ensured lack of multicollinearity. Outliers were checked by plotting the likelihood displacement values and LMAX values of all independent variables. We did not detect outliers. To test for linear trends across quartiles of serum GGT, we modeled the median value of each quartile category as a continuous variable. We calculated the 95% confidence interval for each hazard ratio. All reported P-values were two-tailed. Statistical analyses were performed using Stata MP,
Results

Baseline Characteristics

The baseline characteristics of participants according to baseline serum GGT for analysis of the development of persistent proteinuria are shown in Table 1. Participants who had higher serum GGT quartiles had higher BMI, systolic blood pressure, diastolic blood pressure, AST, ALT, total cholesterol, triglycerides, FPG, and daily alcohol consumption. They had higher proportion of hypertension, dyslipidemia, and drinking habits and were less likely to have leisure-time physical activity. These characteristics of participants for incident low eGFR tended to be similar to those for incident persistent proteinuria (eTable 1).

Prospective Analysis

During the total follow-up of 84,587 person-years, 151 incident cases of persistent proteinuria were observed. Incidence rates and multivariate-adjusted hazards ratios are shown in Table 2. In Cox proportional hazards models, as relationships of BMI and daily alcohol consumption to the development of persistent proteinuria were nonlinear, we fitted models using these categorized variables. Therefore, the BMI was divided into the following four categories: BMI <18.5, 18.5 to <25.0, 25.0 to <30.0, and ≥30.0 kg/m² according to the World
Health Organization classification of obesity. As for drinking habits, except non-drinkers, participants were classified into tertiles of daily alcohol consumption levels. After adjustment for age, BMI categories, FPG, smoking habits, regular leisure-time activity, and hypertension, elevated serum GGT was related to the development of persistent proteinuria. In addition, even after adjustment for daily alcohol consumption, the results did not change. Compared to non-drinkers, participants who drank 16.5-42.7 g ethanol per day had the lowest risk of the development of persistent proteinuria (model 2 of Table 2). After further adjustment for baseline eGFR (model 3 of Table 2) or dyslipidemia (yes/no) (data not shown), these associations did not change.

During the total follow-up of 80,824 person-years, 1,276 incident cases of low eGFR were observed. Incidence rates and multivariate-adjusted hazards ratios are shown in Table 3. In Cox proportional hazards models, as relationships of BMI, FPG, daily alcohol consumption, and eGFR to the development of low eGFR were nonlinear, we fitted a model using these categorized variables. The manner of categorization of BMI and daily alcohol consumption was similar to that of Table 2. The FPG level was classified into the following two categories: FPG <100 and FPG ≥100 mg/dL in the model of Table 3. As for baseline eGFR, we divided the eGFR level into tertiles. In multivariable models of Table 3, elevated serum GGT was not associated with the incident low eGFR. On the other hand, participants who drank higher daily alcohol had a lower risk of the development of low eGFR compared
with non-drinkers in the models that included serum GGT and daily alcohol consumption simultaneously (models 2 and 3 of Table 3).

For sensitivity analysis, we excluded participants who had the upper 2.5th percentile value of GGT or participants who had systolic blood pressure \( \geq 140 \) mm Hg or diastolic blood pressure \( \geq 90 \) mm Hg in the baseline population. However, the results of examining separately the relationship of serum GGT with the development of persistent proteinuria and low eGFR did not change (data not shown). To avoid the influence of participants with liver dysfunction, we excluded participants with ALT \( \geq 40 \) IU/L. After excluding 1,595 of the 9,341 participants in the analytic cohort for proteinuria, the results did not change (data not shown).

The joint analysis of daily alcohol consumption and serum GGT in relation to the development of persistent proteinuria is shown in Figure 1. Using too many categories might cause too low incidence in each category. Therefore, apart from non-drinkers, we divided participants into two groups by median of daily alcohol consumption levels. In the joint analysis, participants who drank 0.1-24.6 g ethanol per day and had the lowest tertile of serum GGT had the lowest risk of the development of persistent proteinuria. Compared with this category, non-drinkers who had the highest tertile of serum GGT had the highest risk of the development of persistent proteinuria. In each GGT category, the relationship between daily alcohol consumption and the development of persistent proteinuria tended to be U-shaped. On the other hand, in each daily alcohol consumption category, the relationship
between serum GGT and the development of persistent proteinuria was a dose-response manner.

Discussion/Conclusion

These prospective data demonstrated that serum GGT was independently related to the development of persistent proteinuria. This association was independent of age, BMI categories, FPG, smoking habits, regular leisure-time physical activity, hypertension, daily alcohol consumption, and eGFR. According to joint categories of daily alcohol consumption and serum GGT, non-drinkers who had the highest tertile of serum GGT had the highest risk of the development of persistent proteinuria but participants who drank 0.1-24.6 g ethanol per day and had the lowest tertile of serum GGT had its lowest risk. In contrast, no association was found between elevated serum GGT and the risk of low eGFR.

Previous three prospective cohort studies have reported the association between serum GGT and the development of CKD.\(^8\)-\(^10\) Ryu et al.\(^8\) reported in 10,337 Korean male workers that elevated serum GGT was related to the development of CKD but the multivariate models were not adjusted for alcohol consumption. Shen et al.\(^9\) showed in 21,818 urban Han Chinese that the presence or absence of alcohol drinking was not related to the development of CKD and men, not women, with elevated serum GGT had an increased risk for CKD. As both studies\(^8\),\(^9\) defined CKD as the composite endpoint which was defined as the presence of an
eGFR of <60 mL/min/1.73 m² or proteinuria. The relationship of serum GGT level with the
risk of proteinuria versus that of low eGFR has not been examined separately. Kunutsor et
al. \(^{10}\) showed in 2,338 Finnish men that the relationship between serum GGT and the risk of
CKD defined as an eGFR of <60 mL/min/1.73 m² was a log-linear association in
age-adjusted analysis. However, the association did not remain statistically significant after
further adjustment including alcohol consumption. In their study, participants with an eGFR
<60 mL/min/1.73 m² at baseline were excluded but they did not consider the presence or
absence of proteinuria. Lee et al. \(^{12}\) reported in 2,478 black and white men and women that the
relationship between serum GGT and incident microalbuminuria was a U-shaped association
in nonhypertensive and nondiabetic participants in the multivariate models including alcohol
consumption. As incident microalbuminuria was measured only one time, they did not avoid
the influence of participants with transient albuminuria. Furthermore, their inconsistent
results with ours might be in part due to differences in ethnicity, age distribution, and GGT
distribution of study subjects. \(^{1}\)

On the other hand, a number of prospective studies have shown the relationship
between alcohol consumption and the risk of the development of CKD. \(^{15-25}\) Regarding the
development of low eGFR, four studies have reported that alcohol consumption was not
related to the risk of low eGFR or eGFR decline speed, \(^{15-18}\) whereas six studies have shown
that alcohol consumption reduced the risk of low eGFR. \(^{19-24}\) As for the development of
proteinuria or albuminuria, four prospective studies have reported the association between alcohol consumption and the incidence of proteinuria or albuminuria.\textsuperscript{20,22,23,25} Alcohol consumption was related to a reduced risk of the development of proteinuria or albuminuria in three studies,\textsuperscript{22,23,25} but it was related to an increased risk of the development of albuminuria in one study.\textsuperscript{20} In these studies, the multiple-adjusted models were not adjusted for serum GGT and the joint relationship of alcohol consumption and serum GGT to the development of low eGFR or proteinuria was not examined.

In the present study, we were unable to identify why elevated serum GGT was related to the development of persistent proteinuria but not to low eGFR. The association between elevated serum GGT and incident persistent proteinuria did not change after adjustment for alcohol consumption. Serum GGT is a biological marker of alcohol intake\textsuperscript{1} and we previously reported that the relationship between daily alcohol consumption and the development of proteinuria tended to be a U-shaped association.\textsuperscript{25} Therefore, we investigated the relationship of daily alcohol consumption and serum GGT to the development of persistent proteinuria using the joint categories. In the joint analysis, the relationship of daily alcohol consumption to the development of persistent proteinuria was a U-shaped association in each serum GGT category. Furthermore, even for non-drinkers, serum GGT was independently related to the development of persistent proteinuria and the relationship was a dose-response association.

Several epidemiological studies have shown that serum GGT level within its normal range
might be an early and sensitive enzyme associated with oxidative stress. Although it is known that reactive oxygen species play an essential role in the pathogenesis causing proteinuria in case of diabetic nephropathy, an experimental study has shown that reactive oxygen species may cause proteinuria in various clinical conditions related to high oxidative stress. The oxidant stress might have an important role of the relationship between serum GGT and the development of persistent proteinuria.

Notable strengths of our study was that we used the definition of persistent proteinuria to take into account the influence of participants who had transient proteinuria. In previous studies about the relationship of serum GGT to the development of CKD or albuminuria, urine samples have been collected only one time.

There were some limitations in our study. First, because the study participants were middle-aged Japanese men who worked at the same company, our results might not be generalizable to other populations. Second, as we measured proteinuria using a urinary dipstick test, the participants with incident proteinuria might include those with false-positive proteinuria and miss those with false-negative proteinuria. However, urinary dipstick testing is very convenient and easily available for clinical practice and large epidemiological studies. Additionally, the definition of persistent proteinuria was adopted to avoid overestimating false-positive proteinuria as far as possible.

In conclusion, higher serum GGT level was positively related to the incidence of
persistent proteinuria, but not to low eGFR, in middle-aged Japanese men independent of daily alcohol consumption. In joint analysis of serum GGT and alcohol consumption, non-drinkers who had the highest tertile of serum GGT had the highest risk of persistent proteinuria, and participants who drank 0.1-24.6 g ethanol per day and who had the lowest tertile of serum GGT had the lowest risk of development of persistent proteinuria. Further research to identify why non-drinkers with an elevated serum GGT had the higher risk of persistent proteinuria is necessary.

Acknowledgment

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Conflicts of interest: None declared.
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Figure legend

Figure 1. Multiple-adjusted hazard ratios for persistent proteinuria according to joint categories of daily alcohol consumption and serum GGT

Multiple-adjusted hazard ratios were calculated after adjustment for age, body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0), fasting plasma glucose, smoking habits (nonsmokers, past smokers and current smokers), regular leisure-time activity (yes/no), and hypertension (yes/no).

*: P <0.05, **: P<0.01.

Abbreviations: GGT, gamma-glutamyltransferase; CI, confidence interval.
Table 1. Baseline characteristics of study participants for incident persistent proteinuria according to quartile of baseline serum GGT

<table>
<thead>
<tr>
<th>Total</th>
<th>Quartile of serum GGT (IU/L)</th>
<th>Quartile 1 (5-25)</th>
<th>Quartile 2 (26-39)</th>
<th>Quartile 3 (40-70)</th>
<th>Quartile 4 (71-1,530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9,341</td>
<td>2,504</td>
<td>2,219</td>
<td>2,286</td>
<td>2,332</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.2 (4.2)</td>
<td>48.3 (4.2)</td>
<td>48.3 (4.2)</td>
<td>48.2 (4.2)</td>
<td>48.0 (4.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.2 (2.8)</td>
<td>22.2 (2.6)</td>
<td>23.2 (2.7)</td>
<td>23.8 (2.8)</td>
<td>23.9 (3.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127.6 (17.7)</td>
<td>122.6 (16.5)</td>
<td>125.9 (17.0)</td>
<td>129.3 (17.2)</td>
<td>133.0 (18.3)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.7 (11.8)</td>
<td>76.5 (11.2)</td>
<td>78.3 (11.4)</td>
<td>80.8 (11.6)</td>
<td>83.2 (11.9)</td>
</tr>
<tr>
<td>Hypertensiona (%)</td>
<td>28.1</td>
<td>18.5</td>
<td>24.4</td>
<td>31.1</td>
<td>39.2</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>22 (19-28)</td>
<td>19 (17-22)</td>
<td>21 (18-24)</td>
<td>24 (20-28)</td>
<td>28 (23-36)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>23 (17-34)</td>
<td>17 (14-23)</td>
<td>21 (16-28)</td>
<td>26 (19-36)</td>
<td>34 (25-48)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.6 (33.2)</td>
<td>198.4 (31.1)</td>
<td>204.1 (31.9)</td>
<td>206.5 (32.5)</td>
<td>209.9 (35.9)</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>139.7 (111.7)</td>
<td>105.4 (73.1)</td>
<td>126.3 (86.3)</td>
<td>143.0 (102.7)</td>
<td>186.0 (152.5)</td>
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<tr>
<td>High-density lipoprotein cholesterol (mg/dL)</td>
<td>56.5 (14.8)</td>
<td>56.0 (14.1)</td>
<td>55.8 (14.8)</td>
<td>56.1 (14.9)</td>
<td>58.2 (15.5)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterolb (mg/dL)</td>
<td>121.5 (31.1)</td>
<td>121.6 (28.9)</td>
<td>123.5 (30.0)</td>
<td>122.7 (30.8)</td>
<td>118.2 (34.2)</td>
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<tr>
<td>Dyslipidemiab,c (%)</td>
<td>50.4</td>
<td>39.7</td>
<td>48.1</td>
<td>52.8</td>
<td>61.8</td>
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<td>Fasting plasma glucose (mg/dL)</td>
<td>97.2 (9.2)</td>
<td>95.1 (8.8)</td>
<td>96.9 (8.8)</td>
<td>98.1 (9.2)</td>
<td>98.9 (9.6)</td>
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<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73 m²)</td>
<td>84.8 (14.1)</td>
<td>84.8 (14.4)</td>
<td>84.1 (13.9)</td>
<td>84.2 (13.8)</td>
<td>86.2 (14.1)</td>
</tr>
<tr>
<td>Daily alcohol consumptiond (g ethanol/day)</td>
<td>23.0 (3.3-46.0)</td>
<td>8.2 (0-23.0)</td>
<td>16.4 (3.3-32.9)</td>
<td>23.0 (14.8-46.0)</td>
<td>41.1 (23.0-46.0)</td>
</tr>
<tr>
<td>Drinking habit (%)</td>
<td>85.0</td>
<td>72.0</td>
<td>83.3</td>
<td>90.1</td>
<td>95.7</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>Non-smokers (%)</td>
<td>21.2</td>
<td>24.0</td>
<td>22.2</td>
<td>21.0</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Past smokers (%)</td>
<td>21.6</td>
<td>21.5</td>
<td>20.0</td>
<td>24.2</td>
<td>20.7</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>57.2</td>
<td>54.5</td>
<td>57.8</td>
<td>54.8</td>
<td>62.0</td>
</tr>
<tr>
<td>Regular leisure-time physical activity (%)</td>
<td>17.9</td>
<td>19.4</td>
<td>18.7</td>
<td>18.2</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Note: Values are the mean (SD), the median (interquartile range) or %.

Abbreviations: GGT, gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

aHypertension: Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
bLow-density lipoprotein cholesterol levels were calculated by the Friedewald formula for participants with triglyceride levels <400 mg/dL. We excluded 230 participants with triglyceride levels ≥400 mg/dL.
cDyslipidemia was defined as triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or use of oral lipid-lowering medications.
dDaily alcohol consumption: (the amount consumed per drinking day) × (the drinking frequency per week)/7.
<table>
<thead>
<tr>
<th>Serum GGT (IU/L)</th>
<th>Incidence rates&lt;sup&gt;a&lt;/sup&gt; (cases/person-years)</th>
<th>Multiple-adjusted hazard ratio (95% CI)</th>
<th>Model 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1 (5-25)</td>
<td>0.82 (19/23,249)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Quartile 2 (26-39)</td>
<td>1.65 (33/19,990)</td>
<td>1.73 (0.98-3.06)</td>
<td>1.88 (1.06-3.34)</td>
<td>1.89 (1.07-3.35)</td>
<td></td>
</tr>
<tr>
<td>Quartile 3 (40-70)</td>
<td>1.65 (34/20,638)</td>
<td>1.58 (0.89-2.79)</td>
<td>1.85 (1.03-3.31)</td>
<td>1.85 (1.03-3.33)</td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (71-1,530)</td>
<td>3.14 (65/20,710)</td>
<td>2.74 (1.62-4.63)</td>
<td>3.44 (1.95-6.05)</td>
<td>3.39 (1.92-5.97)</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily alcohol consumption</th>
<th>Incidence rates&lt;sup&gt;a&lt;/sup&gt; (cases/person-years)</th>
<th>Multiple-adjusted hazard ratio (95% CI)</th>
<th>Model 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinkers</td>
<td>1.92 (24/12,470)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1-16.4 g ethanol/day</td>
<td>1.75 (47/26,849)</td>
<td>0.80 (0.49-1.32)</td>
<td>0.80 (0.49-1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.5-42.7 g ethanol/day</td>
<td>1.49 (35/23,528)</td>
<td>0.52 (0.30-0.89)</td>
<td>0.50 (0.29-0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥42.8 g ethanol/day</td>
<td>2.07 (45/21,740)</td>
<td>0.59 (0.34-1.02)</td>
<td>0.58 (0.34-1.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GGT, gamma-glutamyltransferase; CI, confidence interval.

<sup>a</sup>Incidence rates are expressed as the incidence per 1,000 person-years.

<sup>b</sup>Model 1 was adjusted for age, body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0), fasting plasma glucose, smoking habits (nonsmokers, past smokers and current smokers), regular leisure-time physical activity (yes/no), and hypertension (yes/no).

<sup>c</sup>Model 2 was adjusted for all variables in model 1 of Table 2 plus daily alcohol consumption (nondrinkers, 0.1-16.4, 16.5-42.7, ≥42.8 g ethanol/day).

<sup>d</sup>Model 3 was adjusted for all variables in model 2 of Table 2 plus estimated glomerular filtration rate.
Table 3. Multivariate model of the incidence of low eGFR according to baseline serum GGT and alcohol consumption (n=9,299)

<table>
<thead>
<tr>
<th>Serum GGT (IU/L)</th>
<th>Incidence rates(^a) (cases/person-years)</th>
<th>Multiple-adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1(^b)</td>
</tr>
<tr>
<td>Quartile 1 (5-25)</td>
<td>16.4 (361/22,052)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Quartile 2 (26-39)</td>
<td>16.8 (319/19,005)</td>
<td>1.02 (0.87-1.19)</td>
</tr>
<tr>
<td>Quartile 3 (40-70)</td>
<td>15.6 (307/19,726)</td>
<td>0.92 (0.79-1.07)</td>
</tr>
<tr>
<td>Quartile 4 (71-1,530)</td>
<td>14.4 (289/20,041)</td>
<td>0.89 (0.76-1.05)</td>
</tr>
</tbody>
</table>

P for trend: 0.1 0.9 0.4

<table>
<thead>
<tr>
<th>Daily alcohol consumption</th>
<th></th>
<th>Model 1(^b)</th>
<th>Model 2(^c)</th>
<th>Model 3(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drinkers</td>
<td>19.3 (228/11,838)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0.1-16.4 g ethanol/day</td>
<td>17.5 (445/25,436)</td>
<td>0.92 (0.78-1.08)</td>
<td>0.96 (0.81-1.12)</td>
<td></td>
</tr>
<tr>
<td>16.5-42.7 g ethanol/day</td>
<td>14.5 (326/22,489)</td>
<td>0.74 (0.62-0.89)</td>
<td>0.84 (0.70-1.00)</td>
<td></td>
</tr>
<tr>
<td>≥42.8 g ethanol/day</td>
<td>13.2 (277/21,061)</td>
<td>0.70 (0.58-0.84)</td>
<td>0.77 (0.64-0.93)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GGT, gamma-glutamyltransferase; CI, confidence interval; eGFR, estimated glomerular filtration rate.

\(^a\)Incidence rates are expressed as the incidence per 1,000 person-years.
\(^b\)Model 1 was adjusted for age, body mass index (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0), fasting plasma glucose (<100, ≥100 mg/dL), smoking habits (nonsmokers, past smokers and current smokers), regular leisure-time physical activity (yes/no), and hypertension (yes/no).
\(^c\)Model 2 was adjusted for all variables in model 1 of Table 3 plus daily alcohol consumption (nondrinkers, 0.1-16.4, 16.5-42.7, ≥42.8 g ethanol/day).
\(^d\)Model 3 was adjusted for all variables in model 2 of Table 3 plus eGFR (<79.2, 79.3-90.7, ≥90.8 mL/min/1.73 m\(^2\)).
Figure 1. Multiple-adjusted hazard ratios for persistent proteinuria according to joint categories of daily alcohol consumption and serum GGT

<table>
<thead>
<tr>
<th>Serum GGT (IU/L)</th>
<th>Non-drinkers</th>
<th>0.1-24.6</th>
<th>≥24.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1 (5-29)</td>
<td>1.44 (0.62-3.39)</td>
<td>1.00 (reference)</td>
<td>1.21 (0.46-3.18)</td>
</tr>
<tr>
<td>Tertile 2 (30-57)</td>
<td>2.82 (1.25-6.33)</td>
<td>1.60 (0.79-3.23)</td>
<td>1.78 (0.87-3.64)</td>
</tr>
<tr>
<td>Tertile 3 (58-1,530)</td>
<td>3.41 (1.10-10.55)</td>
<td>2.27 (1.13-4.55)</td>
<td>2.56 (1.37-4.78)</td>
</tr>
</tbody>
</table>