ORIGINAL ARTICLE

Serum \(\gamma\)-glutamyltransferase and the risk of heart failure in men and women in Finland

Yujie Wang,1,2,3 Jaakko Tuomilehto,4,5 Pekka Jousilahti,5 Veikko Salomaa,5 Bin Li,3 Riitta Antikainen,6 Markku Mähönen,4 Peter T Katzmarzyk,1 Gang Hu1

ABSTRACT

Objectives To evaluate the association of serum \(\gamma\)-glutamyltransferase (GGT) levels with heart failure (HF) risk in the Finnish population.

Design Prospective population-based cohort study.

Setting The present study, which is a part of FINRISK study, was carried out in Finland.

Subject study cohorts included 18,353 Finnish men and 19,726 women who were 25–74 years of age and free of HF at baseline.

Main outcome measures HF (636 men and 445 women) during a mean follow-up of 14.5 years.

Results Baseline measurement of different levels of serum GGT was used to predict incident HF. The multivariable-adjusted (age, sex, study area, study year, smoking, education, alcohol consumption, physical activity, valvular heart disease, body mass index (BMI), systolic blood pressure, total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up) HRs of HF at five GGT groups (using the 25th, 50th, 75th and 90th percentiles) were 1.00, 1.16 (95% CI: 0.97 to 1.38), 1.20 (1.00 to 1.45), 1.29 (1.04 to 1.60) and 1.82 (1.45 to 2.29) (Ptrend<0.001). Stratification by smoking status, alcohol consumption and BMI gave similar results, while stronger association was observed among subjects aged <60 years (P trend=0.001) compared with subjects 60+ years of age (P trend=0.173).

Conclusions Moderate to high levels of serum GGT (from the 50th to the 90th percentiles) were significantly associated with incident HF in men and women in Finland, and the predictive power was stronger in subjects aged <60 years.

INTRODUCTION

Heart failure (HF) is a worldwide epidemic which is associated with high morbidity and mortality. In addition to its high prevalence, HF has created heavy economic burdens on society. In the US alone, HF costs were over US$33 billion in 2007 according to the estimation of the American Heart Association.1 In response to this severe situation, increasing attention has been drawn to identifying the risk factors of HF. Serum \(\gamma\)-glutamyltransferase (GGT), a widely used index of liver dysfunction, was found to be positively associated with incident cardiovascular disease (CVD), including coronary heart disease (CHD),2 3 stroke3 and HF,4 and also mortality from CVD,2 5–7 including CHD,2 5–7 stroke,3 5–7 as well as congestive HF.5–7 It has been proposed that the pro-oxidant effects of GGT, which result from the production of reactive oxygen species superoxide anion and hydrogen peroxide during the process of glutathione hydrolysis by GGT, might be the biological mechanism linking GGT to various cardiovascular events.8 This is supported by the findings that GGT activity has been detected in atheromatous plaques of carotid and coronary arteries where a catalytically active enzyme has been identified.9 So far, very limited information is available on the role of GGT in predicting incident HF. Thus, the aim of this study is to examine the association between GGT and the risk of incident HF.

METHODS

Participants Five independent cross-sectional population-based health examination surveys were carried out in six geographic areas of Finland in 1982, 1987, 1992, 1997 and 2002.10 The original random sample was stratified by area, gender and 10-year age group according to WHO Monitoring Trends and Determinants of Cardiovascular Disease protocol.11 The participation rate varied by year from 65% to 88%.10 The participants included in the five surveys were 25–64 years old, and the 1997 and 2002 surveys also included individuals 65–74 years old. Subjects who participated in more than one survey were included only in the first survey cohort. The total sample size of the five surveys was 38,737. The final sample comprised 18,353 men and 19,726 women after excluding the participants with a history of HF (n=457) at baseline, and those with incomplete data on any variables required for this analysis (n=201). The participants gave an informed consent (verbal consents in 1982–1992, and signed consents in 1997 and 2002). These surveys were conducted according to the ethical rules of the National Public Health Institute, and the investigations were conducted in accordance with the Declaration of Helsinki.

Measurements A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. The questionnaire included questions on medical history, socioeconomic factors, physical activity, smoking habits and alcohol consumption. Education level, measured as the total number of school years, was divided into birth and cohort-specific tertiles. Information on occupational, commuting and leisure-time physical activity was merged and regrouped into three categories: low, moderate and high.12 13 Participants were
classified as never, ex-smokers and current smokers. Alcohol consumption was categorised into four groups: none, 1–34, 35–209, ≥210 g per week in men; none, 1–34, 35–139, ≥140 g per week in women. Data on diabetes and myocardial infarction at baseline and during follow-up were obtained from the questionnaire and completed by the National Hospital Discharge Register and National Social Insurance Institution’s Drug Register (diabetes only). Data on the history of valvular heart disease at baseline were collected by hospital discharge register. Data on liver cirrhosis at baseline and during follow-up were collected by the National Hospital Discharge Register. At the survey site, specially trained research nurses measured participants’ height and weight by using a standardised protocol. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in metres. Blood pressure was measured from the right arm after 5 min of sitting using a mercury sphygmomanometer in each survey. After blood pressure measurement, a venous blood specimen was taken. The serum total cholesterol level was determined by an enzymatic method (CHOD-PAP, Boehringer MANNHEIM, Mannheim, Germany). GGT was determined from fresh venous blood serum samples using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) based on the recommendation of the European Committee for Clinical Laboratory Standards. All samples were analysed in the same central laboratory at the National Public Health Institute.

Prospective follow-up
Follow-up information was from the Finnish Hospital Discharge Register and the National Social Insurance Institution’s Register on special reimbursement for HF drugs for non-fatal outcomes and the Finnish Causes of Death Register for fatal outcomes by record linkage using the personal identification numbers assigned to every citizen of Finland. The International Classification of Diseases (ICD) codes 427.00 and 427.10 (ICD-8), 428, 4029B (hypertensive heart disease with HF) and 4148A-X (ischemic HF with chronic CHD) (ICD-9), and I 50, 111.0 (hypertensive heart disease with HF), I 13.0 and I 13.2 (hypertensive heart and renal disease with HF) (ICD-10) were used to identify HF cases in any one of the above mentioned national databases. A HF diagnosis was made by the treating physicians, based on a clinical assessment and examinations as considered relevant by the clinician in charge of treatment. Follow-up of each cohort member continued until the date of the diagnosis of HF from the Hospital Discharge Register, Causes of Death Register or from the National Social Insurance Institution’s Drug Reimbursement Register, or death resulting from causes other than HF, or 31 December 2007. The overall positive predictive value of HF diagnosis in this FINRISK study was 85.9% (negative predictive value 97.9%).

Statistical analyses
Serum GGT levels were classified into five groups using the 25th, 50th, 75th and 90th percentiles as cut-points (quartiles with the top quartile split). The cut-points were 17.1, 25.7, 40.1 and 68.0 U/l among men, and 11.0, 15.1, 22.1 and 35.0 U/l among women for the categories of GGT used, respectively. Differences in risk factors based on different levels of serum GGT were tested using General Linear Models after adjustment for age and study year. Cox proportional hazards regression models were used to analyse the association of serum GGT level with the risk of incident HF. All proportionality assumptions were appropriate. The analyses were first carried out adjusting for age, study area and study year at baseline, then for smoking, education, alcohol consumption and physical activity at baseline, and further for BMI, history of valvular heart disease, systolic blood pressure and total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up. Diabetes and myocardial infarction at baseline and during follow-up were used as time-dependent covariates in Cox models. To avoid a potential bias due to severe disease at baseline, additional analyses were carried out excluding the subjects who died during the first 2 years of follow-up (n=289), and subjects who were diagnosed with liver cirrhosis at baseline and during follow-up (n=223). Statistical analyses were performed with PASW for Windows, V19.0 (IBM SPSS Inc, Chicago, Illinois, USA).

RESULTS
During a mean follow-up period of 14.5 years, 636 men and 443 women developed HF. General characteristics of the study population by different levels of GGT at baseline are presented in table 1. High levels of GGT were strongly associated with alcohol consumption. The age-adjusted, study area-adjusted and study year-adjusted partial correlations were 0.22 in men (p<0.001), and 0.11 in women (p<0.001) for GGT and alcohol consumption.

The age-adjusted, study area-adjusted and study year-adjusted HRs of HF at five GGT groups (using the 25th, 50th, 75th and 90th percentiles) were 1.00, 1.46, 1.60, 2.09 and 3.13 (Ptrend<0.001) among men, and 1.00, 1.12, 1.64, 1.92 and 2.79 (Ptrend<0.001) among women (table 2). Considering the strong associations between serum GGT and many CVDs, we presented a model further adjusting for smoking, education, alcohol consumption and physical activity at baseline, and not adjusting any clinical variable in order to avoid over-adjustment. Like the previous model, serum GGT predicted incident HF even in the normal range. Further adjustment for other clinical risk factors (history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline, myocardial infarction and diabetes at baseline and during follow-up) attenuated this relationship; however, the highest category of GGT was still associated with a higher risk of HF in both men (HR 1.79; 95% CI 1.31 to 2.43) and women (HR 1.76; 95% CI 1.25 to 2.48). When men and women were combined, the sex-adjusted and multivariable-adjusted HRs of HF across categories of GGT were 1.00, 1.16 (95% CI 0.97 to 1.38), 1.20 (95% CI 1.00 to 1.45), 1.29 (95% CI 1.04 to 1.60), and 1.82 (95% CI 1.45 to 2.29) (Ptrend<0.001), which suggested that the risk of HF significantly increased from the 50th to the 90th percentiles. Exclusion of the participants who died during the first 2 years of follow-up (n=289), and subjects who were diagnosed with liver cirrhosis at baseline and during follow-up (n=223), did not appreciably change the results above (data not shown).

When stratified by age at 60 years, the association between serum GGT and HF risk was only observed among subjects <60 years; the multivariable-adjusted HRs of HF across categories of GGT were 1.00, 1.36 (95% CI 1.09 to 1.71), 1.30 (95% CI 1.02 to 1.66), 1.41 (95% CI 1.07 to 1.86) and 1.90 (95% CI 1.42 to 2.55) (Ptrend=0.001) (table 3). Stratification by smoking status, alcohol consumption and BMI gave similar results to the pooled multivariable-adjusted HRs in table 2. The interaction between age and GGT was significant (p=0.014), while no significant interactions between GGT and other stratification variables were found. Of note, after stratification by alcohol consumption, the positive association between the highest category of serum GGT and HF risk was observed in both non-drinkers and drinkers.
## Table 1  General characteristics of study subjects at baseline*

<table>
<thead>
<tr>
<th>Baseline GGT level</th>
<th>&lt;25%</th>
<th>25 to &lt;50%</th>
<th>50 to &lt;75%</th>
<th>75 to &lt;90%</th>
<th>≥90%</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n=18,353)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>4659</td>
<td>4517</td>
<td>4593</td>
<td>3954</td>
<td>2739</td>
<td>1845</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>44.3</td>
<td>46.3</td>
<td>48.1</td>
<td>47.8</td>
<td>48.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0</td>
<td>26.2</td>
<td>27.4</td>
<td>28.4</td>
<td>29.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>81</td>
<td>83</td>
<td>86</td>
<td>88</td>
<td>90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>138</td>
<td>139</td>
<td>142</td>
<td>143</td>
<td>147</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.53</td>
<td>5.72</td>
<td>5.93</td>
<td>6.14</td>
<td>6.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.6</td>
<td>10.5</td>
<td>10.5</td>
<td>10.4</td>
<td>10.5</td>
<td>0.538</td>
</tr>
<tr>
<td>Alcohol drinker (%)</td>
<td>55.5</td>
<td>62.5</td>
<td>67.9</td>
<td>73.6</td>
<td>76.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>28.4</td>
<td>35.0</td>
<td>38.0</td>
<td>42.0</td>
<td>45.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low physical activity (%)</td>
<td>6.6</td>
<td>6.9</td>
<td>9.2</td>
<td>11.5</td>
<td>13.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>3.9</td>
<td>3.9</td>
<td>3.4</td>
<td>4.4</td>
<td>5.2</td>
<td>0.011</td>
</tr>
<tr>
<td>History of valvular heart disease (%)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.755</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>2.4</td>
<td>2.3</td>
<td>3.0</td>
<td>2.9</td>
<td>4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women (n=19,726)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>4598</td>
<td>5572</td>
<td>4756</td>
<td>3479</td>
<td>2799</td>
<td>2007</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>41.7</td>
<td>44.3</td>
<td>47.2</td>
<td>49.9</td>
<td>51.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7</td>
<td>25.4</td>
<td>26.4</td>
<td>27.6</td>
<td>28.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78</td>
<td>79</td>
<td>81</td>
<td>82</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132</td>
<td>134</td>
<td>136</td>
<td>138</td>
<td>140</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.60</td>
<td>5.68</td>
<td>5.72</td>
<td>5.81</td>
<td>5.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.2</td>
<td>11.2</td>
<td>11.1</td>
<td>11.0</td>
<td>10.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol drinker (%)</td>
<td>39.5</td>
<td>44.6</td>
<td>47.9</td>
<td>50.2</td>
<td>52.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>13.5</td>
<td>18.9</td>
<td>23.3</td>
<td>25.6</td>
<td>29.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low physical activity (%)</td>
<td>7.1</td>
<td>7.9</td>
<td>9.7</td>
<td>11.0</td>
<td>14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction (%)</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
<td>1.6</td>
<td>1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>History of valvular heart disease (%)</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.0</td>
<td>0.3</td>
<td>0.005</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>1.4</td>
<td>1.7</td>
<td>1.8</td>
<td>2.8</td>
<td>5.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Baseline characteristics represent mean or percentage; adjusted for age, study area and study year.

## Table 2  HRs of heart failure according to different levels of serum GGT

<table>
<thead>
<tr>
<th>Baseline GGT level</th>
<th>&lt;25%</th>
<th>25 to &lt;50%</th>
<th>50 to &lt;75%</th>
<th>75 to &lt;90%</th>
<th>≥90%</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence case (n)</td>
<td>149</td>
<td>153</td>
<td>151</td>
<td>100</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>83542</td>
<td>63716</td>
<td>58828</td>
<td>34195</td>
<td>20886</td>
<td></td>
</tr>
<tr>
<td>Age, area and study years adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.46 (1.16 to 1.84)</td>
<td>1.60 (1.27 to 2.02)</td>
<td>2.09 (1.61 to 2.71)</td>
<td>3.13 (2.37 to 4.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)*</td>
<td>1.00</td>
<td>1.41 (1.12 to 1.77)</td>
<td>1.51 (1.19 to 1.91)</td>
<td>1.92 (1.47 to 2.51)</td>
<td>2.70 (2.02 to 3.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)†</td>
<td>1.00</td>
<td>1.25 (1.00 to 1.58)</td>
<td>1.18 (0.92 to 1.50)</td>
<td>1.32 (1.00 to 1.74)</td>
<td>1.79 (1.31 to 2.43)</td>
<td>0.006</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence case (n)</td>
<td>98</td>
<td>115</td>
<td>102</td>
<td>63</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>91860</td>
<td>86478</td>
<td>58944</td>
<td>32512</td>
<td>22844</td>
<td></td>
</tr>
<tr>
<td>Age, area and study years adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.12 (0.85 to 1.46)</td>
<td>1.64 (1.24 to 2.18)</td>
<td>1.92 (1.39 to 2.66)</td>
<td>2.79 (2.02 to 3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)*</td>
<td>1.00</td>
<td>1.13 (0.86 to 1.48)</td>
<td>1.59 (1.20 to 2.11)</td>
<td>1.83 (1.32 to 2.54)</td>
<td>2.60 (1.88 to 3.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)†</td>
<td>1.00</td>
<td>0.98 (0.75 to 1.29)</td>
<td>1.19 (0.89 to 1.59)</td>
<td>1.21 (0.86 to 1.70)</td>
<td>1.76 (1.25 to 2.48)</td>
<td>0.006</td>
</tr>
<tr>
<td>Men and women combined†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence case (n)</td>
<td>247</td>
<td>268</td>
<td>253</td>
<td>163</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>175403</td>
<td>150193</td>
<td>117772</td>
<td>66707</td>
<td>43729</td>
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</tr>
<tr>
<td>Age, area and study years adjusted HR (95% CI)</td>
<td>1.00</td>
<td>1.33 (1.12 to 1.59)</td>
<td>1.64 (1.37 to 1.97)</td>
<td>2.05 (1.67 to 2.50)</td>
<td>3.08 (2.49 to 3.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)*</td>
<td>1.00</td>
<td>1.30 (1.09 to 1.55)</td>
<td>1.57 (1.31 to 1.88)</td>
<td>1.91 (1.55 to 2.34)</td>
<td>2.74 (2.21 to 3.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariable adjustment HR (95% CI)†</td>
<td>1.00</td>
<td>1.16 (0.97 to 1.38)</td>
<td>1.20 (1.00 to 1.45)</td>
<td>1.29 (1.04 to 1.60)</td>
<td>1.82 (1.45 to 2.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusting for age, study area, smoking, education, alcohol consumption, physical activity. 
†Further adjusting for history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline and myocardial infarction, diabetes at baseline and during follow-up.
‡Adjusted also for sex.

GGT, γ-glutamyltranspeptidase.
is often measured as a marker of liver health, this study provides evidence that it may also be useful in the identification of patients at elevated risk of CVD and HF. Future studies are required to determine the clinical utility of serum GGT in monitoring subjects at risk of developing HF.

### DISCUSSION

The present study suggested a positive association between serum GGT and the risk of HF. This association was more pronounced among subjects aged <60 years, which is in line with the finding of our previous study which evaluated the association between serum GGT and incident CHD with the FINRISK dataset. A similar trend was also observed in two other studies on the association between serum GGT and the risk of HF in men and women in Finland, especially in those aged <60 years, and this association is often measured as a marker of liver health, this study provides evidence that it may also be useful in the identification of patients at elevated risk of CVD and HF. Future studies are required to determine the clinical utility of serum GGT in monitoring subjects at risk of developing HF.

#### Table 3  HRs of heart failure according to different levels of serum GGT stratified by age, smoking status, alcohol consumption and BMI

<table>
<thead>
<tr>
<th>Baseline GGT level</th>
<th>Cases (n)</th>
<th>&lt;25%</th>
<th>25 to &lt;50%</th>
<th>50 to &lt;75%</th>
<th>75 to &lt;90%</th>
<th>≥90%</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at baseline (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–60</td>
<td>655</td>
<td>1.00</td>
<td>1.36 (1.09–1.71)</td>
<td>1.30 (1.02–1.66)</td>
<td>1.41 (1.07–1.86)</td>
<td>1.90 (1.42–2.55)</td>
<td>0.001</td>
</tr>
<tr>
<td>60–74</td>
<td>426</td>
<td>1.00</td>
<td>0.93 (0.70–1.24)</td>
<td>1.10 (0.82–1.48)</td>
<td>1.03 (0.73–1.47)</td>
<td>1.43 (0.99–2.08)</td>
<td>0.173</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or ever</td>
<td>737</td>
<td>1.00</td>
<td>1.02 (0.83–1.26)</td>
<td>1.14 (0.92–1.42)</td>
<td>1.21 (0.93–1.57)</td>
<td>1.67 (1.26–2.20)</td>
<td>0.004</td>
</tr>
<tr>
<td>Current</td>
<td>344</td>
<td>1.00</td>
<td>1.48 (1.06–2.08)</td>
<td>1.37 (0.97–1.95)</td>
<td>1.51 (1.02–2.25)</td>
<td>2.29 (1.51–3.46)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never drinker</td>
<td>614</td>
<td>1.00</td>
<td>1.13 (0.89–1.39)</td>
<td>1.13 (0.88–1.43)</td>
<td>1.50 (1.13–2.00)</td>
<td>1.99 (1.47–2.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol drinker</td>
<td>467</td>
<td>1.00</td>
<td>1.20 (0.89–1.60)</td>
<td>1.32 (0.99–1.76)</td>
<td>1.15 (0.82–1.60)</td>
<td>1.80 (1.28–2.52)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>239</td>
<td>1.00</td>
<td>1.21 (0.85–1.72)</td>
<td>1.60 (1.10–2.33)</td>
<td>1.99 (1.24–3.20)</td>
<td>3.28 (2.02–5.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25–29.9</td>
<td>448</td>
<td>1.00</td>
<td>1.13 (0.88–1.47)</td>
<td>1.06 (0.80–1.41)</td>
<td>1.15 (0.83–1.60)</td>
<td>1.58 (1.10–2.26)</td>
<td>0.161</td>
</tr>
<tr>
<td>≥30</td>
<td>394</td>
<td>1.00</td>
<td>1.13 (0.80–1.61)</td>
<td>1.15 (0.81–1.63)</td>
<td>1.24 (0.85–1.82)</td>
<td>1.66 (1.12–2.45)</td>
<td>0.094</td>
</tr>
</tbody>
</table>

*Adjusting for age, study area, study year, smoking, education, alcohol consumption, physical activity, history of valvular heart disease, BMI, systolic blood pressure, total cholesterol at baseline and myocardial infarction, diabetes at baseline and during follow-up.

GGT, γ-glutamyltransferase.
Contributors GH had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YW, GH. Analysis and interpretation of data: YW, GH, JT, PJ, VS, RA, MM, PTK, BL. Drafting of the manuscript: YW, GH. Critical revision of the manuscript for important intellectual content: YW, GH, JT, PJ, VS, RA, MM, PTK, BL. Study supervision: GH.

Funding This work was supported by grants from the Finnish Academy (108297 and 118065), and Special Research Funds of the Social Welfare and Health Board, City of Oulu.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES