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Serum Gamma Glutamyl Transferase and Risk of Heart Failure in the Community

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Abstract

Objective—To examine the association of serum gamma glutamyl transferase (GGT) to incident heart failure.

Methods and Results—We related serum GGT to the incidence of heart failure in 3544 (mean age 44.5yrs; 1833 women) Framingham Study participants who were free of heart failure and myocardial infarction. On follow-up (mean 23.6yrs), 188 participants (77 women) developed new-onset heart failure. In multivariable Cox models adjusting for standard risk factors and alcohol consumption as time-varying covariates (updated every 4 years), each standard deviation increase in log-GGT was associated with a 1.39-fold risk of heart failure (95% confidence intervals [CI] 1.20-1.62). The linearity of the association was confirmed by multivariable-adjusted splines and the relations remained robust upon additional adjustment for hepatic aminotransferases and C-reactive protein. Participants with serum GGT ≥median had a 1.71-fold risk of heart failure (95% CI 1.21-2.41) compared to individuals with GGT concentrations below the median. GGT marginally increased the model c-statistic from 0.85 to 0.86, but improved the risk reclassification modestly (net reclassification index 5.7%, p=0.01).

Conclusions—In our prospective study of large community-based sample higher serum GGT concentrations within the 'normal' range were associated with greater risk of heart failure and incrementally improved prediction of heart failure risk.

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Introduction

In clinical practice, serum gamma glutamyl transferase (GGT) is measured as a marker of excessive alcohol consumption or of hepatic disease.[1,2] Researchers over the past 3 decades have reported that GGT is not only secreted by liver but also by several other tissues including the kidneys and vascular pericytes in the brain.[3,4] Indeed, GGT has a primary role in glutathione metabolism, and acts as an antioxidant in the metabolism of amino acids to maintain intracellular glutathione levels.[5] Experimentally, GGT may also have a pro-oxidant activity by promoting the generation of free radical species in presence of free metal ions such as iron.[6] Overall, evidence from epidemiologic studies show that higher serum GGT concentrations within the so-called 'normal' range are associated with greater risk of hypertension,[7] incident diabetes,[8-10] metabolic syndrome,[10,11] cardiovascular disease (CVD),[11-14] CVD mortality [15,16] and all-cause mortality.[17] These associations of GGT with adverse sequelae were independent of alcohol consumption.

More recently, investigators have focused on serum GGT concentrations in heart failure. Limited data indicate that GGT concentrations are higher in patients with prevalent heart failure[18,19] and are a marker of increased mortality risk.[15] However, the association of serum GGT concentrations with the incidence of heart failure has not been elucidated. Therefore, in the present study we evaluated the association of serum GGT concentrations with the incidence of heart failure prospectively in a large community-based sample of individuals who were free of heart failure and myocardial infarction.

Methods

Study Participants

The Framingham Heart Study began in 1948 with the enrollment of 5209 participants into the Original cohort. In 1972, the children (and their spouses) of the original cohort participants were enrolled into the Framingham Offspring Study (n=5124).[20] All participants from Framingham Offspring Study who attended the second examination cycle (1978-1982; n=3792) with available data on serum GGT concentrations were eligible for the present investigation (n=3696). Additionally, we excluded participants with prevalent heart failure or a previous myocardial infarction yielding a final sample of 3544 individuals (1833 women) for the present study. All participants provided written informed consent, and the study protocol was approved by Institutional Review Board of the Boston University Medical Center.

Measurement of risk factors

At each Heart Study visit, attendees undergo a medical history and a physical examination (by a Heart Study physician), anthropometry, and laboratory assessment of vascular risk factors. For the present investigations, hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of anti-hypertensive medications.[21] Participants who smoked cigarettes regularly during the year preceding the Heart Study visit were considered 'current' smokers. Alcohol intake was assessed by averaging the self-reported weekly consumption of alcoholic drinks. Valve disease was defined as the presence of any diastolic murmur, or of a systolic murmur ≥3/6 on physical examination. Diabetes was defined as a fasting blood sugar level of ≥126mg/dL or the use of any hypoglycemic agent.

Measurement of GGT and other biomarkers

After an overnight fast, participants underwent phlebotomy, the blood was immediately centrifuged, plasma and serum separated and stored under −20°Celcius until assayed. GGT

activity was measured in plasma by spectrophotometry (Quest Diagnostics, [MetPath]) as described previously.[11] The interassay coefficient of variation for GGT measured using spectrophotometry is less than 6%.[22]

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and alkaline phosphatase levels were measured using standardized assays. High sensitivity C-reactive protein (hsCRP) was measured using Dade Behring BN100 nephelometer (Deerfield, Illinois).

Assessment of Heart Failure on Follow-up

The follow-up period for the current investigation was from the second examination (1979-1982) through December 2007. All Heart Study participants are under continuous surveillance for the development of new cardiovascular disease events including heart failure. A team of three physician investigators reviews all medical records (Heart Study examinations, physician office visits and hospitalization records) for adjudicating possible heart failure events. A diagnosis of heart failure In the Framingham Heart Study is based on the presence of two major, or of one major and two minor criteria. Briefly, the major criteria include the presence of paroxysmal nocturnal dyspnea, jugular venous distension, orthopnea, hepatojugular reflux, pulmonary rales, acute pulmonary edema, third heart sound, cardiomegaly on a chest radiograph, central venous pressure of >16cm of water and weight loss of >4.5 kg during first 5 days of treatment for suspected heart failure. Minor criteria include bilateral ankle edema, exertional dyspnea, nocturnal cough, hepatomegaly, pleural effusion and heart rate >120 beats/minute. A detailed description of the adjudication of heart failure events has been published previously.[23]

Statistical Analyses

The baseline characteristics of the study sample were assessed according to sex. We first calculated the age-adjusted cumulative incidence of heart failure for values of GGT below versus at or above the median level using Poisson regression. Cumulative incidence curves were constructed for these two groups and the incidence of heart failure compared using the log-rank test. Then, after confirming that the assumption of proportionality of hazards was met, we used multivariable Cox regression models to relate serum GGT concentrations to the incidence of heart failure. GGT concentrations were sex- pooled and natural logarithmically transformed to normalize the skewed distribution. Serum GGT was also modeled as a binary variable comparing categories ≥ median levels with <median concentrations (that served as the referent category). All models were adjusted for the following covariates in a hierarchical fashion:

- **a.** age and sex;
- **b.** age, sex, BMI, diabetes mellitus, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total/HDL cholesterol ratio, valve disease and history of myocardial infarction;
- **c.** all covariates as in model b above were updated every 4 years as time-dependent covariates
- **d.** all covariates as in model c and with additional adjustment for AST, ALT and hsCRP (all measured at the baseline examination).

Secondary Analyses

To assess for any potential non-linearity of relations between serum GGT and incidence of heart failure we examined multivariable generalized additive models using penalized

splines,[24,25] adjusting for all the covariates as in our multivariable model b (see above). We also evaluated for effect modification by age, BMI, hypertension and alcohol intake by incorporating interaction terms in the multivariable models examining the association of serum GGT (log-transformed) with heart failure risk. We examined the incidence of heart failure using Cox models by comparing heart failure incidence in the two groups defined by the sex-specific median cut-point for GGT level (as opposed to using the sex-pooled median threshold used in our primary analyses)

We also assessed the incremental contribution of GGT levels to the prediction of CHF risk by estimating the increment in the model c-statistic (comparing multivariable models without and with GGT), by calculating the proportion of people at risk reclassified appropriately (risk reclassification), and calibration indices.[26] Since risk reclassification requires categorization of longitudinal risk (in this instance 20-year risk of heart failure), we empirically (in the absence of an accepted grouping of risk) defined 'low', 'intermediate' and 'high' risk categories as: 0-<2%, 2-8%, >8% for both outcomes.

All analyses were performed using SAS 9.1 (Cary, NC), and S-plus (Version 8.0) was used for plotting regression splines. A two-sided P value <0.05 was considered statistically significant. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics of study participants are displayed in Table 1 according to sex. Median GGT concentrations in our young-middle-aged sample ranged from 9 (women) to 16 U/L (men). As reported previously,[11] the clinical correlates of circulating GGT included age, male sex, smoking, alcohol consumption, body mass index, low density lipoprotein cholesterol concentration, triglyceride levels, diastolic blood pressure and use of antihypertensive medications.

On follow-up (mean 23.6 yrs, range 0-28.2 years), 188 participants (77 women) developed heart failure. Age and sex-adjusted incidence rates of heart failure were about 75% higher for participants with serum GGT ≥median (compared to those with concentration below the median, Table 2).

Continuous increase in serum GGT concentration and heart failure risk

In age- and-sex adjusted Cox models, each standard deviation (SD) increase in log- GGT was associated with a 49% higher risk of heart failure (Table 3). In multivariable models, each SD increase in log-GGT was associated with a 26 -36% higher risk of heart failure in models with baseline covariates and those with time-varying covariates, respectively. These results remained unchanged after adjustment for hsCRP, and other liver enzymes (aminotransferases). Additional adjustment for alkaline phosphatase also did not change our primary results (HR per SD increase in log-GGT 1.31, 95% CI 1.09-1.57). Penalized splines demonstrated a graded linear increase in the risk of heart failure with rising serum GGT concentrations (Figure 1). Additionally, when individuals with serum GGT above the normal levels (>40 U/L in women and >50 U/L in men) were excluded (n=3162), the association of higher log-GGT with incident heart failure remained robust (HR 1.36, CI 1.08 –1.67, p = 0.007).

Serum GGT concentration above versus below the median and heart failure risk

Cumulative incidence curves demonstrated a greater risk of new-onset heart failure among individuals with serum GGT concentration at or above the median compared to those with levels below the median (p value for log rank test<0.0001; Figure 2). In Cox regression

models adjusting for age- and sex, participants with ≥ median serum GGT concentration had a >2-fold risk of heart failure compared to individuals with concentrations below the median (Table 3). After adjustment for baseline covariates, the risk of heart failure was attenuated, with a 55% higher risk in those with GGT concentrations ≥ median. These results remained robust when covariates were updated every 4 years, and after adjusting for liver enzymes and hsCRP (Table 3).

Secondary Analyses

We did not observe any effect modification by age, sex, hypertension, BMI or alcohol intake in the relations of log-GGT to incident heart failure (all p values for interaction terms were >0.05). When individuals were dichotomized using the sex-specific median concentrations of serum GGT, the association of GGT with heart failure risk remained robust (HR 1.68, 95% CI 1.20-2.34, compared to those with levels below the median, results for models adjusted for time-varying covariates as in model c [see above]).

The addition of GGT to a multivariable model incorporating baseline covariates increased the c-statistic from 0.85 to 0.86, and improved the risk reclassification (net reclassification index 5.7%, p=0.01; Figure 3).

Discussion

Principal findings

Our results were 3-fold. Within the so-called normal range of serum GGT, higher concentrations were associated with greater risk of heart failure in a graded fashion. Values above the median level of serum GGT were associated with a 55-71% greater risk of heart failure compared to individuals with less than median levels. Second, relations of higher serum GGT to heart failure risk were maintained in models adjusting for MI and other covariates on follow up, and upon adjustment for AST/ALT and hsCRP. Third, GGT modestly improved prediction of heart failure risk as judged by an improvement in the c-statistic and risk reclassification.

In prior studies, higher serum GGT concentration has been associated cross-sectionally with impaired coronary reserve flow in hypertensive [27] and cardiomyopathy patients,[28] and longitudinally with greater mortality in heart failure patients.[15] To our knowledge, the present study is the first to examine the relations of serum GGT and risk of developing heart failure in a community-based sample.

Mechanisms

Several mechanisms are postulated in relations to serum GGT with greater CVD risk, which may also be implicated in the development of heart failure. Higher serum GGT activity has been reported in atherosclerotic plaques and foam cells.[29] Because higher serum GGT levels have been associated with greater incidence of metabolic syndrome and incident diabetes,[10] it has been postulated that GGT may also reflect the development of fatty liver and greater insulin resistance. However, our results were independent of the development of MI or diabetes on follow up, and remained robust in analysis adjusting for other liver enzymes and hsCRP.[30,31]

Serum GGT has also been associated with production of reactive oxygen species and subsequent oxidation of lipids,[32] nucleic acids and transcription factor proteins. These findings have suggested that GGT levels may be a marker of greater oxidative stress,[33] which has also been postulated as a mechanism for the development of heart failure.[34] In addition, serum GGT levels are inversely associated with several antioxidants such as beta

carotene, lycopene and vitamin C,[35] and positively related to other biomarkers of oxidative stress such as F-2 isoprostanes.[8] Hence, it is plausible that serum GGT concentrations reflect systemic oxidative stress and therefore can predict the development of heart failure. Another possible explanation of these relations could be due to the association of serum GGT with inflammation and atherogenesis.[14,29,30] Lastly, hepatic congestion due to heart failure could raise serum GGT levels although this would likely happen in chronic heart failure patients.[19,36,37] Currently, it is unclear whether first episode of heart failure (as opposed to chronic heart failure) would have significant hepatic sinusoidal injury and would elevate serum GGT levels.[37,38]

Overall, the exact mechanism of GGT to predict the incidence of heart failure remains unclear. However, GGT does provide incremental risk prediction and the current information may warrant testing this biomarker in relation to other ones (such as BNP, GDF-15) for the prediction of heart failure using a multimarker approach.[39,40]

Strengths and Limitations

The present study has several strengths, including the community-based sample of men and women, a prospective design with a long follow up time, comprehensive adjustment for covariates at baseline, and accounting for myocardial infarction on follow-up as a time-varying covariate, and consistency of results in multiple analyses. However, there are several limitations that must be noted. We did not measure other biomarkers that reflect oxidative stress (such as isoprostanes), which may have enabled us to elucidate the mechanisms underlying the observed association. Given the long follow-up, we were unable to characterize separately the association of GGT with incidence of heart failure with reduced versus preserved ejection fraction. Also, participants in our study were white Americans of European descent, which limits the generalizability of our results to other ethnic groups.

Conclusion

In a community based sample, higher concentrations of serum GGT within the normal range were associated with greater risk of developing heart failure in individuals without a prior history of MI. Additional studies are needed to confirm our findings and to elucidate the underlying pathogenetic mechanisms.

Condensed abstract

We related serum GGT to incident heart failure in 3544 Framingham participants. In multivariable models, participants with serum GGT ≥median had a 1.71-fold risk of heart failure compared to individuals with GGT concentrations <median. Higher serum GGT concentrations within the ‘normal’ range were associated with greater risk of heart failure.

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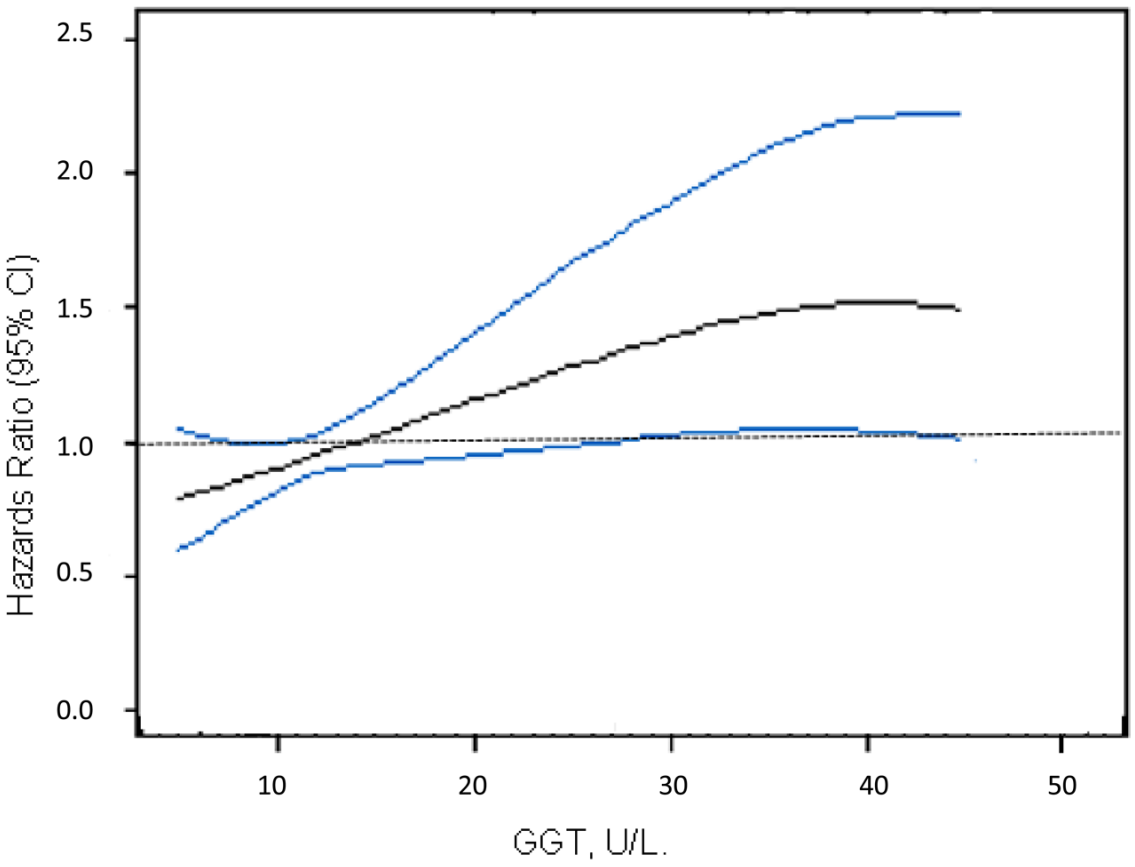
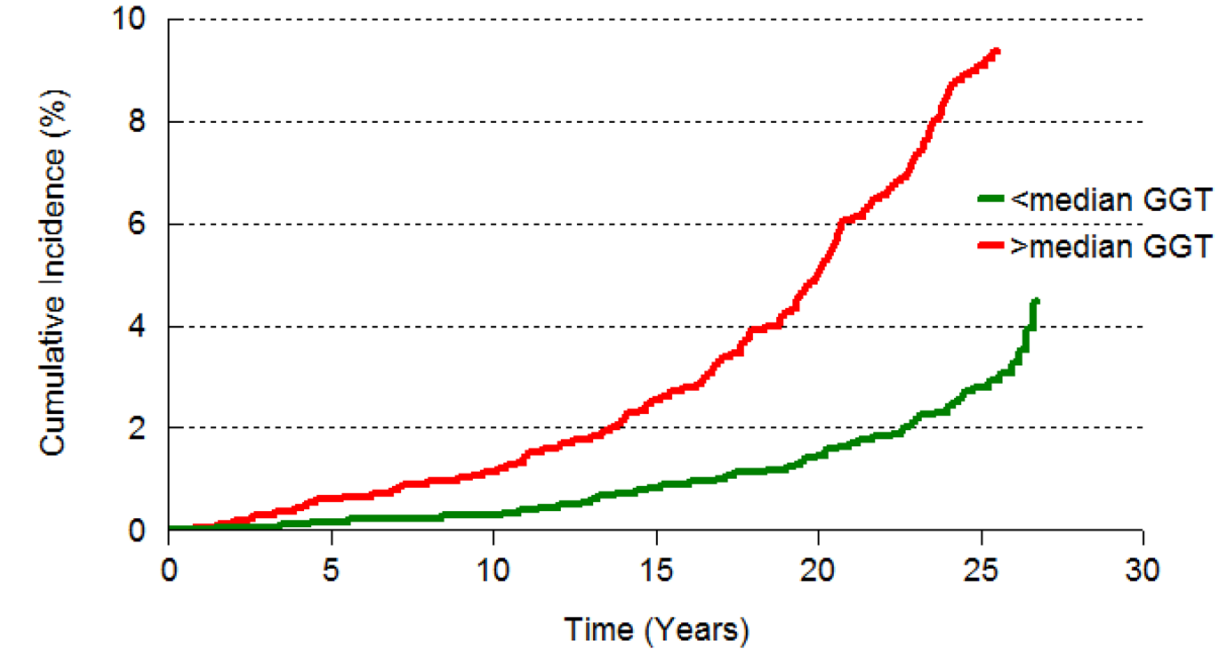


Figure 1.
Regression spline curve based on multivariable models (adjusted for all baseline covariates - see text) examining relations of serum GGT to the incidence of heart failure on follow-up. Figure shows estimated multivariable hazard ratios for heart failure (Y axis) in relation to serum GGT (X axis) as a function of penalized regression splines.



No. At Risk

<Median	1830	1797	1752	1693	1108
>Median	1650	1601	1505	1378	847

Figure 2.
Age and sex-adjusted cumulative incidence of heart failure by serum GGT median levels (above and below median)

Event= CHF

20-Yr Probability of Event with GGT Included

20-Yr Initial Probability of Event	Case / Non-Case	0-2 %	2-8 %	> 8 %	Total
	0-2 %	41 / 1592	7 / 67	0 / 0	48 / 1659
	2-8 %	1 / 94	62 / 1033	7 / 70	70 / 1197
	>8 %	0 / 0	3 / 57	67 / 443	70 / 500
	Total	42 / 1686	72 / 1157	74 / 513	188 / 3356

Figure 3.

Risk reclassification table with and without serum GGT incorporation into model on follow up using ‘low’, ‘intermediate’ and ‘high’ risk GGT categories with 0-<2%, 2-8% and >8% respectively.

Table 1

Baseline Characteristics of Study Participants

Characteristic	Men (N=1717)	Women (N= 1833)
Age, yrs	44.7 (10.3)	44.3 (9.9)
Height, inches	68.9 (2.7)	63.4 (2.5)
Weight, pounds	182 (27)	142 (29)
Body mass index, kg/m^2	26.9 (3.7)	24.9 (4.8)
Systolic blood pressure, mmHg	126 (16)	119 (17)
Diastolic blood pressure, mm Hg	81 (9)	75 (9)
Hypertension, %	28.0	17.2
Treatment for hypertension, %	10.3	8.5
Diabetes, %	6.0	2.7
Smoking, %	35.4	36.8
Alcohol, drinks/week	5.1 (6.2)	2.2 (3.1)
Valve disease*, %	0.3	0.7
Laboratory parameters		
Total/HDL cholesterol, mmol/L	5.1 (1.6)	4.0 (1.3)
Aspartate amino transferase, IU/L	24 (12)	19 (11)
Alanine amino transferase, IU/L	31 (19)	21 (15)
hs CRP, mg/dL	2.7 (5.3)	2.3 (4.4)
GGT, U/L median (Q1-Q3)	16 (11-25)	9 (7-14)
Log GGT	2.8 (0.6)	2.3 (0.6)

* Valve disease was defined as the presence of any diastolic murmur, or a systolic murmur ≥3/6 on physical examination

All values are mean (standard deviation) unless specified otherwise

hsCRP is high sensitivity C-reactive protein. Q1=0.43, Q3=2.46mg/L

Table 2

Age-Adjusted Cumulative Incidence Rates of Heart Failure According to Serum GGT.

Serum GGT	No. Events	No. at Risk	Age and Sex-adjusted Incidence Rates of Heart Failure per 1000 Pyrs (95% CI)*
Serum GGT < median	53	1845	1.93 (1.45, 2.53)
Serum GGT ≥ median	135	1699	3.35 (2.81, 3.96)

* Poisson confidence intervals

Median cut points for serum GGT concentrations were 12 U/L

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Table 3

Cox Proportional Hazard Models Examining the Relations of Serum GGT Concentration to the Incidence of Heart Failure

Model	Age- and sex-adjusted		Multivariable 1		Multivariable 2 †		Multivariable 3 ‡	
	Hazards Ratio (95% CI)	P value	Hazards Ratio (95% CI)	P value	Hazards Ratio (95% CI)	P value	Hazards Ratio (95% CI)	P value
Log GGT, per SD increment	1.49 (1.30, 1.69)	<0.0001	1.26 (1.09, 1.46)	0.002	1.39 (1.20, 1.62)	<0.0001	1.36 (1.15, 1.62)	0.0005
Categorical model								
< median	Referent		Referent		Referent		Referent	
≥ median	2.19 (1.57, 3.01)	<0.0001	1.55 (1.09, 2.20)	0.02	1.71 (1.21, 2.41)	0.003	1.57 (1.08, 2.30)	0.02

*Multivariable 1 models are adjusted for age, sex, BMI, diabetes mellitus, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total/HDL cholesterol ratio, valve disease and history of myocardial infarction.

†Multivariable 2 models are adjusted for all covariates as in multivariable 1 model in time-varying fashion (updating every 4 years) except age and sex

‡Multivariable 3 models are adjusted for all covariates as in multivariable 2 and additionally for aspartate amino transferase, alanine amino transferase and high sensitivity C - reactive protein.