

## $\gamma$ -Glutamyltransferase and Risk of Sudden Cardiac Death in Middle-Aged Finnish Men: A New Prospective Cohort Study

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**Background**— $\gamma$ -Glutamyltransferase (GGT) has been linked to an increased risk of several cardiovascular outcomes; however, the relationship of GGT with sudden cardiac death (SCD) has not been investigated previously. We aimed to assess the association of GGT with risk of SCD.

**Methods and Results**—Serum GGT activity was assessed at baseline in the Kuopio Ischemic Heart Disease prospective cohort of 1780 men, and 136 SCDs were recorded during 22 years of follow-up. Correction for within-person variability was made using data from repeated measurements taken several years apart. The regression dilution ratio of  $\log_e$  GGT adjusted for age was 0.68 (95% CI 0.61–0.74). Serum GGT was log-linearly associated with risk of SCD. The hazard ratio for SCD per 1 SD higher baseline  $\log_e$  GGT values (2-fold higher) was 1.30 (95% CI 1.10–1.54;  $P=0.002$ ) after adjustment for several established risk factors and remained consistent with further adjustment for alcohol consumption, resting heart rate, lipids, and C-reactive protein (hazard ratio 1.26, 95% CI 1.05–1.50;  $P=0.014$ ). The corresponding hazard ratios were 1.48 (95% CI 1.15–1.89;  $P=0.002$ ) and 1.40 (95% CI 1.07–1.82;  $P=0.014$ ) after correction for within-person variability. Hazard ratios remained unchanged after accounting for incident coronary events and did not vary importantly by levels or categories of prespecified conventional risk factors.

**Conclusions**—GGT is positively, log-linearly, and independently associated with future risk of SCD in the general male population. Further research is needed to replicate these findings. (*J Am Heart Assoc.* 2016;5:e002858 doi: 10.1161/JAHA.115.002858)

**Key Words:**  $\gamma$ -glutamyltransferase • risk factor • sudden cardiac death

The majority of sudden cardiac deaths (SCDs) occur in the general population and outside of the hospital, with few or no early warning signs.<sup>1</sup> Coronary heart disease (CHD) with its sequelae (eg, scarring from previous myocardial infarction, heart failure) is the most common pathology underlying SCD, especially for persons aged >40 years.<sup>2,3</sup> Despite a progressive decline in CHD over past decades due to major advances in treatment and prevention, SCD remains a vast public health problem accounting for 15% to 20% of all deaths.<sup>4,5</sup> In a large percentage of persons, SCD is usually the first manifestation of cardiac disease.<sup>6</sup> Out-of-hospital SCD is an unrecognized but major contributor to overall SCD. Risk factors for SCD

include atherosclerotic cardiovascular disease (CVD) risk factors, especially among middle-aged and older persons.<sup>7</sup> Although these established risk factors explain a large proportion of the risk of SCD,<sup>8</sup> its pathogenesis is still not fully established because multiple factors appear to be involved. These established risk factors are often absent in a large proportion of those who have SCD,<sup>9</sup> making identification of persons at increased risk a difficult undertaking.

There is a need to further assess potential risk factors that may have causal or predictive relevance to SCD (in- and out-of-hospital SCD) and that will help tailor preventive and therapeutic interventions.  $\gamma$ -Glutamyltransferase (GGT), a biomarker that is routinely used in clinical practice to help indicate potential hepatic or biliary disease, has been shown to be positively and independently associated with CHD,<sup>10,11</sup> stroke,<sup>10,11</sup> CVD,<sup>11,12</sup> cardiac arrhythmias,<sup>13</sup> and congestive heart failure.<sup>14,15</sup> The proposed mechanistic pathways underpinning these associations include the pro-oxidant and proinflammatory activities<sup>16</sup> of GGT. GGT may be linked to the risk of SCD; however, there has been no previous prospective evaluation of its association with SCD. We aimed to evaluate, in detail, the nature and magnitude of the prospective association of GGT with risk of SCD in a population-based cohort of 1780 apparently healthy men from eastern Finland. Repeated measurements of GGT were

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performed in a subset of men to help quantify within-person variability in GGT values. In subsidiary analysis, we assessed the associations with out-of-hospital SCD and non-SCD.

## Methods

### Study Population

The study population consisted of a representative sample of men living in the city of Kuopio and its surrounding rural communities in eastern Finland. These men were participants in the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a longitudinal population-based study designed to investigate risk factors for CVD and related outcomes.<sup>17</sup> Men were aged 42 to 61 years during baseline examinations performed between March 1984 and December 1989. Of 3433 potentially randomly eligible and randomly selected men, 2682 (78%) volunteered to participate; 186 did not respond to the invitation, and 367 declined to give informed consent. The final cohort for the present analysis included 1780 men who were not missing information on serum GGT, covariates, and outcomes. The research ethics committee of the University of Eastern Finland approved the study, and each participant gave written informed consent.

### Ascertainment of Outcomes

All SCDs that occurred from study enrollment through 2012 were included. There were no losses to follow-up. In the KIHD study, participants are under continuous surveillance for the development of new CVD events, including incident cases and deaths.<sup>18</sup> The sources of information on outcomes were based on a comprehensive review of national hospital discharge records, inpatient physician claims data, study ECGs, death certificate registers, and medical-legal reports. Deaths were coded according to the International Classification of Diseases, 9th or 10th revision codes. The diagnostic classification of events was based on symptoms, ECG findings, cardiac enzyme elevations, autopsy findings (80% of all cardiac deaths), and history of CHD. A death was determined to be an SCD when it occurred within 1 hour of the onset of an abrupt change in symptoms or within 24 hours after the onset of symptoms, including unwitnessed cases when clinical and autopsy findings did not reveal a noncardiac cause of sudden death.<sup>19</sup> The witnessed participant was to have been alive and symptom free within 1 hour before the event. SCDs that occurred under out-of-hospital conditions were also defined as events that occurred in places that had been reported accurately in hospital documents. The deaths due to aortic aneurysm rupture; cardiac rupture or tamponade; and pulmonary embolism, cancer, or other noncardiac comorbidities were not included as SCDs.

Documents were cross-checked in detail by 2 physicians. Non-SCDs were also carefully documented using standardized criteria. Cardiac deaths that did not lead to death during the 24 hours following the onset of symptoms were considered non-SCDs. The independent events committee of the KIHD study, masked to clinical data, performed classification of outcomes.

### Measurement of Risk Factors

Collection of blood specimens and measurement of serum lipids, lipoproteins, and glucose have been described previously.<sup>20,21</sup> Blood samples were taken between 8 and 10 AM. In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days and from smoking for at least 12 hours before assessment. The serum samples were stored frozen at  $-80^{\circ}\text{C}$  for 0.2 to 2.5 years. The cholesterol content of lipoprotein fractions and serum triglycerides were measured enzymatically (Boehringer Mannheim).<sup>22</sup> Fasting plasma glucose was measured by the glucose dehydrogenase method (Merck) after protein precipitation by trichloroacetic acid. Serum GGT activity was measured using the kinetic method (Thermo Fisher Scientific) and C-reactive protein (CRP) with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; Diagnostic Products Corp). Serial measurements of GGT were performed at 4 and 11 years after baseline measurements over a 22-year period in a random subset of participants. Smoking, alcohol consumption, and blood pressure were assessed, as described previously.<sup>20</sup> Body mass index was computed as the ratio of weight in kilograms to the square of height in meters. Standard resting 12-lead ECG was also recorded. The ECG criterion for left ventricular hypertrophy was based on either the Sokolow-Lyon or Romhilt-Estes point score.<sup>23–25</sup>

### Statistical Analysis

Values of skewed variables (GGT, CRP, and triglycerides) were log-transformed to achieve approximately symmetrical distributions. We performed descriptive analyses summarizing the baseline characteristics of the participants. Cross-sectional associations of GGT with various risk markers were assessed using linear regression models adjusted for age. Time-to-event analyses were conducted using Cox proportional hazards models after confirming proportional hazards assumptions using Schoenfeld residuals.<sup>26</sup> To quantify and correct for within-person variability in levels of GGT, that is, the extent to which an individual person's GGT measurements vary around a long-term average level of exposure ("usual levels"),<sup>27</sup> adjusted regression dilution ratios were estimated by regressing available repeated measurements on baseline values.<sup>28</sup> To characterize the shape of the association between GGT and

SCD risk, hazard ratios (HRs) were calculated within quartiles of baseline GGT values and plotted against mean GGT values within each quartile. Floating variances were used to calculate 95% CIs for the log HR in each group, including the reference group, to allow for comparisons across the groups, regardless of the arbitrarily chosen reference category (bottom quartile).<sup>26</sup> Because the association showed a log-linear shape, HRs were calculated per 1 SD higher log<sub>e</sub> GGT values. The SD of baseline log<sub>e</sub> GGT was 0.63 (equivalent to ≈2-fold higher circulating GGT, e<sup>0.63</sup>=1.88). HRs were adjusted for age, body mass index, systolic blood pressure, prevalent CHD, smoking status, history of diabetes mellitus, left ventricular hypertrophy, history of hypertension, use of medications (antihypertensive agents and lipid-lowering drugs), alcohol consumption, resting heart rate, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and CRP. We performed subgroup analyses using interaction tests to assess statistical evidence

of any differences in hazards across levels or categories of prespecified individual-level characteristics, including age at survey, smoking status, history of diabetes mellitus, history of hypertension, left ventricular hypertrophy, body mass index, systolic blood pressure, and CRP. To minimize biases as a result of including cases with prevalent but undetected CHD, heart failure, and cardiac arrhythmias, sensitivity analysis involved excluding the first 5 years of follow-up. All statistical analyses were conducted using Stata version 14 (Stata Corp).

## Results

### Baseline Characteristics and Correlates of GGT

Table 1 summarizes baseline characteristics of the 1780 men in the current study. The mean age was 53 years (SD 5 years).

**Table 1.** Baseline Participant Characteristics

	Overall (N=1780) Mean (SD) or n (%)	Without SCD (n=1644) Mean (SD) or n (%)	With SCD (n=136) Mean (SD) or %	P Value
Log <sub>e</sub> GGT, U/L	3.11 (0.63)	3.09 (0.61)	3.39 (0.76)	<0.0001
Questionnaire/prevalent conditions				
Age at survey, y	52.6 (5.0)	52.5 (5.1)	54.0 (3.8)	0.002
Alcohol consumption, g/week	76.1 (140.2)	74.0 (140.1)	103.9 (140.1)	0.023
History of diabetes	82 (4.6)	68 (4.1)	14 (10.3)	0.001
Current smokers	577 (32.4)	515 (31.3)	62 (45.6)	0.001
Left ventricular hypertrophy	19 (1.1)	17 (1.0)	2 (1.5)	0.634
History of hypertension	517 (29)	473 (28.8)	44 (32.4)	0.377
History of CHD	391 (22.0)	334 (20.3)	57 (41.9)	<0.001
Use of antihypertensives	325 (18.3)	287 (17.5)	38 (27.9)	0.002
Medication for dyslipidemia	11 (0.6)	11 (0.7)	0 (0.0)	0.339
Physical measurements				
BMI, kg/m <sup>2</sup>	26.8 (3.5)	26.7 (3.5)	28.1 (4.2)	<0.0001
SBP, mm Hg	133.9 (16.6)	133.6 (16.5)	138.6 (18.0)	0.001
DBP, mm Hg	89.0 (10.5)	88.9 (10.5)	91.0 (10.3)	0.031
Resting heart rate, bpm	62.5 (10.7)	62.4 (10.6)	63.9 (11.1)	0.122
Lipid markers				
Total cholesterol, mmol/L	5.93 (1.10)	5.91 (1.09)	6.21 (1.13)	0.004
HDL-C, mmol/L	1.29 (0.30)	1.30 (0.30)	1.23 (0.26)	0.015
Log <sub>e</sub> triglycerides, mmol/L	0.09 (0.50)	0.08 (0.49)	0.19 (0.55)	0.020
Metabolic and inflammatory markers				
Fasting plasma glucose, mmol/L	5.33 (1.21)	5.30 (1.14)	5.77 (1.94)	<0.0001
Serum creatinine, μmol/L	89.4 (22.5)	89.2 (13.4)	91.7 (70.7)	0.251
Log <sub>e</sub> CRP, mg/L	0.29 (0.96)	0.26 (0.95)	0.69 (1.01)	<0.0001

BMI indicates body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; SCD, sudden cardiac death.

**Table 2.** Cross-Sectional Correlates of GGT

	Pearson Correlation <i>r</i> (95% CI) <sup>†</sup>	Percentage Difference (95% CI) in GGT Levels Per 1 SD Higher or Compared With Reference Category of Correlate <sup>‡</sup>
Log <sub>e</sub> GGT, U/L	—	—
Questionnaire/prevalent conditions		
Age at survey, y	−0.03 (−0.08 to 0.02)	−2% (−5 to 1)
Alcohol consumption, g/week	0.27 (0.23–0.31) <sup>***</sup>	19% (15–22) <sup>***</sup>
History of diabetes		
No	—	Ref
Yes	—	47% (28–69) <sup>***</sup>
Smoking status		
Other	—	Ref
Current	—	11% (4–18) <sup>**</sup>
Left ventricular hypertrophy		
No	—	Ref
Yes	—	−4% (−28 to 28)
History of hypertension		
No	—	Ref
Yes	—	27% (20–36) <sup>***</sup>
History of CHD		
No	—	Ref
Yes	—	17% (9–25) <sup>***</sup>
Use of antihypertensives		
No	—	Ref
Yes	—	24% (15–34) <sup>***</sup>
Medication for dyslipidemia		
No	—	Ref
Yes	—	25% (−14 to 81)
Physical measurements		
BMI, kg/m <sup>2</sup>	0.34 (0.30–0.38) <sup>***</sup>	24% (21–27) <sup>***</sup>
SBP, mm Hg	0.21 (0.17–0.26) <sup>***</sup>	14% (11–18) <sup>***</sup>
DBP, mm Hg		
Resting heart rate, bpm	0.14 (0.10–0.19) <sup>***</sup>	9% (6–13) <sup>***</sup>
Lipid markers		
Total cholesterol, mmol/L	0.10 (0.05–0.14) <sup>***</sup>	6% (3–9) <sup>***</sup>
HDL-C, mmol/L	−0.04 (−0.09 to 0.01)	−2% (−5 to 0)
	0.26 (0.21–0.30) <sup>***</sup>	18% (14–21) <sup>***</sup>

Continued

**Table 2.** Continued

	Pearson Correlation <i>r</i> (95% CI) <sup>†</sup>	Percentage Difference (95% CI) in GGT Levels Per 1 SD Higher or Compared With Reference Category of Correlate <sup>‡</sup>
Log <sub>e</sub> triglycerides, mmol/L		
Metabolic and inflammatory markers		
Fasting plasma glucose, mmol/L	0.21 (0.16–0.25) <sup>***</sup>	14% (11–17) <sup>***</sup>
Serum creatinine, μmol/L	0.00 (−0.04 to 0.05)	0% (−3 to 3)
Log <sub>e</sub> CRP, mg/L	0.27 (0.22–0.31) <sup>***</sup>	18% (15–21) <sup>***</sup>

BMI indicates body mass index; CHD, coronary heart disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; GGT, γ-glutamyltransferase; Ref, reference.

Asterisks indicate the level of statistical significance: \*\**P*<0.01; \*\*\**P*<0.001.

<sup>†</sup>Pearson correlation coefficients between log<sub>e</sub> GGT and the row variables.

<sup>‡</sup>Percentage change in GGT levels per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean GGT levels for the category vs the reference) adjusted for age.

Median GGT value was 20 U/L (interquartile range 15–32 U/L). During a mean follow-up of 22 years, there were 136 SCDs (annual rate 3.50 per 1000 person-years at risk; 95% CI 2.96–4.14). Of the total SCDs, 108 occurred out of the hospital. There were 66 non-SCDs. Serum GGT values were weakly to moderately and positively correlated with physical measures (body mass index, blood pressure, and resting heart rate) and with several lipid, metabolic, and inflammation (CRP) markers. Weak inverse correlations were observed for age (*r* = −0.03) and high-density lipoprotein cholesterol (*r* = −0.04). Baseline GGT values were higher in men with diabetes compared with men without diabetes, in men with a history of hypertension compared with men without a history of hypertension, and in current smokers compared with nonsmokers (Table 2).

### Correction for Within-Person Variability

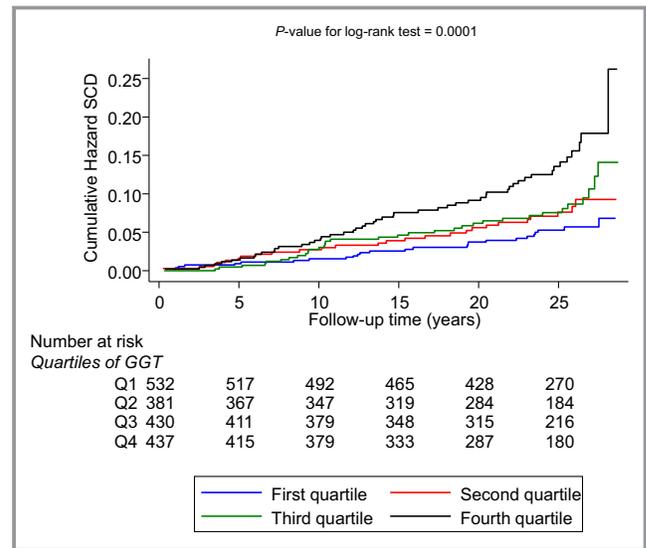
Serial measurements of GGT taken at 4 and 11 years after baseline over 22 years were available in a random sample of 624 men, providing a total of 1143 repeated measurements of GGT. The regression dilution ratio of log<sub>e</sub> GGT, adjusted for age, was 0.68 (95% CI 0.61–0.74), suggesting that the associations using single or baseline measurements of GGT with SCD could underestimate the association by [(1/0.68) − 1] × 100 = 47%.

### GGT and Risk of SCD

SCD rates per 1000 person-years of follow-up across quartiles of GGT were 5.67 (95% CI 4.31–7.46) for the fourth quartile, 3.54 (95% CI: 2.52–4.98) for the third quartile, 3.09 (95% CI 2.10–4.354) for the second quartile, and 2.14 (95% CI: 1.46–3.15) for the first quartile. Cumulative hazard curves demonstrated a greater risk of SCDs among men in the top quartile of GGT levels compared with those in the bottom quartile ( $P=0.0001$  for log-rank test) (Figure 1). Baseline and usual GGT values were log-linearly associated with risk of SCD in analyses adjusted for conventional risk factors (age, body mass index, systolic blood pressure, prevalent CHD, smoking status, history of diabetes mellitus, left ventricular hypertrophy, history of hypertension, use of antihypertensive agents and lipid-lowering drugs) (Figure 2). The age-adjusted HR per 1-SD change in baseline  $\log_e$  GGT value was 1.56 (95% CI 1.34–1.82;  $P<0.001$ ), which was somewhat attenuated following further adjustment for established risk factors (HR 1.30, 95% CI 1.10–1.54;  $P=0.002$ ). The results remained consistent on further adjustment for alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HR 1.26, 95% CI 1.05–1.50;  $P=0.014$ ) and further for CRP (HR 1.23, 95% CI 1.02–1.47;  $P=0.028$ ). The corresponding HRs per 1-SD change in usual  $\log_e$  GGT values were 1.93 (95% CI 1.55–2.41;  $P<0.001$ ), 1.48 (95% CI 1.15–1.89;  $P=0.002$ ), 1.40 (95% CI 1.07–1.82;  $P=0.014$ ), and 1.35 (95% CI 1.03–1.77;  $P=0.028$ ), respectively. The HRs remained materially unchanged after further adjusting for incident coronary events (Table 3). HRs did not vary importantly by levels or categories of prespecified conventional risk factors ( $P$  for interaction  $>0.10$  for each) (Figure 3), and the main results remained the same in analyses that excluded the first 5 years of follow-up (data not shown). In separate analyses for out-of-hospital SCD and non-SCD, the initial positive associations of GGT with out-of-hospital SCD and non-SCD in analyses adjusted for several established risk factors were less robust on further adjustment for potential confounders (Table 3). To put the strength of the association of GGT with risk of SCD into context, comparisons were made to the associations of GGT with the combined outcome of SCDs plus resuscitated sudden cardiac arrests. The associations were similar compared with those observed for GGT and SCD (Table 4).

### Discussion

In this population of middle-aged and older men without a history of heart failure and cardiac arrhythmias at baseline, we have assessed—for the first time—the shape, magnitude, and independence of the prospective association of both

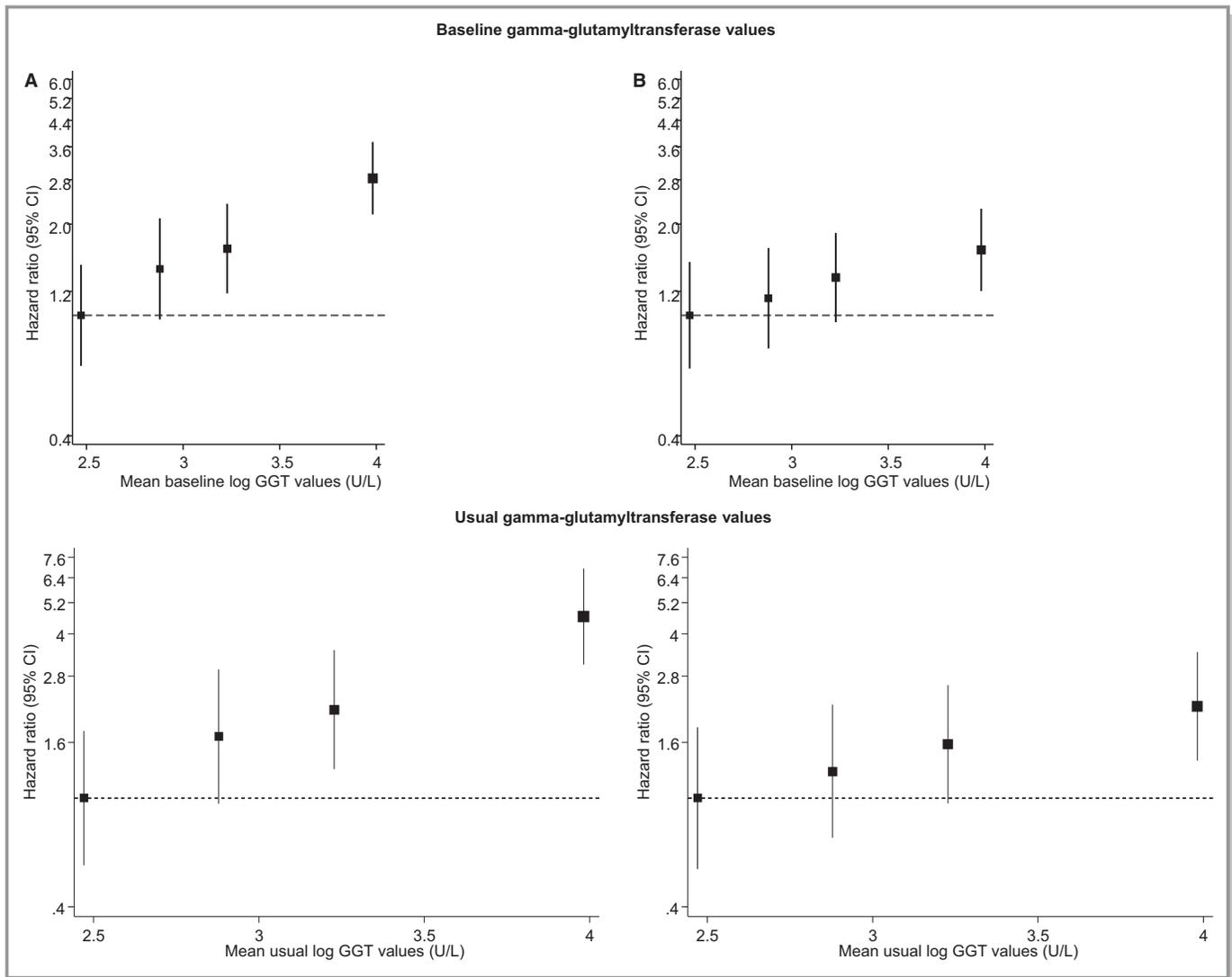


**Figure 1.** Cumulative hazard curves for sudden cardiac death by quartiles of GGT. The median GGT level was 12.0 IU/L (range 11–14 IU/L) for the lowest quartile; 18.0 IU/L (range 16–19 IU/L) for the second quartile; 25.0 IU/L (range 23–29 IU/L) for the third quartile; and 46.0 IU/L (range 38–68 IU/L) for the top quartile. GGT indicates  $\gamma$ -glutamyltransferase; Q, quartile; SCD, sudden cardiac death.

baseline and usual values of GGT with risk of SCD. There were weak to modest correlations of GGT values with several conventional cardiovascular risk factors. In analyses adjusted for age and established risk factors, we observed an approximately log-linear association of GGT with risk of SCD. The association remained persistent on further adjustment for a comprehensive panel of potential confounders and on accounting for incident coronary events during follow-up. The overall findings remained consistent across several subgroups and levels of cardiovascular risk markers. Significant associations with out-of-hospital SCD and non-SCD were observed in analyses adjusted for several established risk factors but were less robust after further adjustment for potential confounders.

### Possible Explanations for Findings

Several studies have demonstrated GGT levels to be associated with a variety of CVD end points; however, no study has evaluated the specific end point of SCD. The finding of a positive and log-linear association of GGT with SCD is consistent with that observed for GGT and CVD,<sup>11,12</sup> thereby highlighting important clues regarding the mechanistic pathways underlying the association between GGT and SCD. The most likely culprits are the proinflammatory activities of GGT<sup>16</sup> and the direct involvement of GGT in atheromatous plaque formation.<sup>29,30</sup> Given the length of time between baseline measurements of GGT and subsequent occurrence of



**Figure 2.** Hazard ratios for sudden cardiac death, by quartiles of baseline and usual values of GGT. A, Adjusted for age. B, Adjusted for age, body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs). GGT indicates  $\gamma$ -glutamyltransferase.

SCD in our study (>20 years), there is a likelihood that the effects of inflammation on SCD are mediated through a chronic process, which is most likely to be the development and progression of coronary atherosclerosis.<sup>7</sup> Indeed, pathological signs of inflammation are evident in the coronary atherosclerotic lesions and vulnerable plaques that are found in the majority of cases of SCD.<sup>31,32</sup> The GGT–SCD association observed in our study remained robust after adjusting for CRP. This was unexpected, given that elevated levels of GGT may reflect chronic subclinical inflammation, a state characterized by elevated levels of CRP, which is also secreted by the liver and is directly and strongly correlated with levels of GGT<sup>12</sup> (as demonstrated in the current study). The persistent association on further adjustment for CRP reflects the possibility that other pathways apart from

inflammatory processes may also play a role in the etiology between GGT and SCD. Our data showed that the joint association of elevated GGT and CRP levels was associated with a stronger risk of SCD, but the estimate was imprecise and was not statistically significant because of the small number of SCDs in each category (data not shown). Other likely pathways include the involvement of GGT in impairing antioxidant defense systems and promoting oxidative stress<sup>16</sup> and underlying fatty liver,<sup>16</sup> which is also associated with insulin resistance and oxidative stress,<sup>33,34</sup> all known to be associated with increased risk of CVD.<sup>35–37</sup> Through its involvement in atheromatous plaque formation,<sup>29,30</sup> GGT may also cause acute myocardial ischemia, which is the most common trigger for fatal arrhythmias.<sup>38</sup> It is difficult to place our findings in the context of previous population-

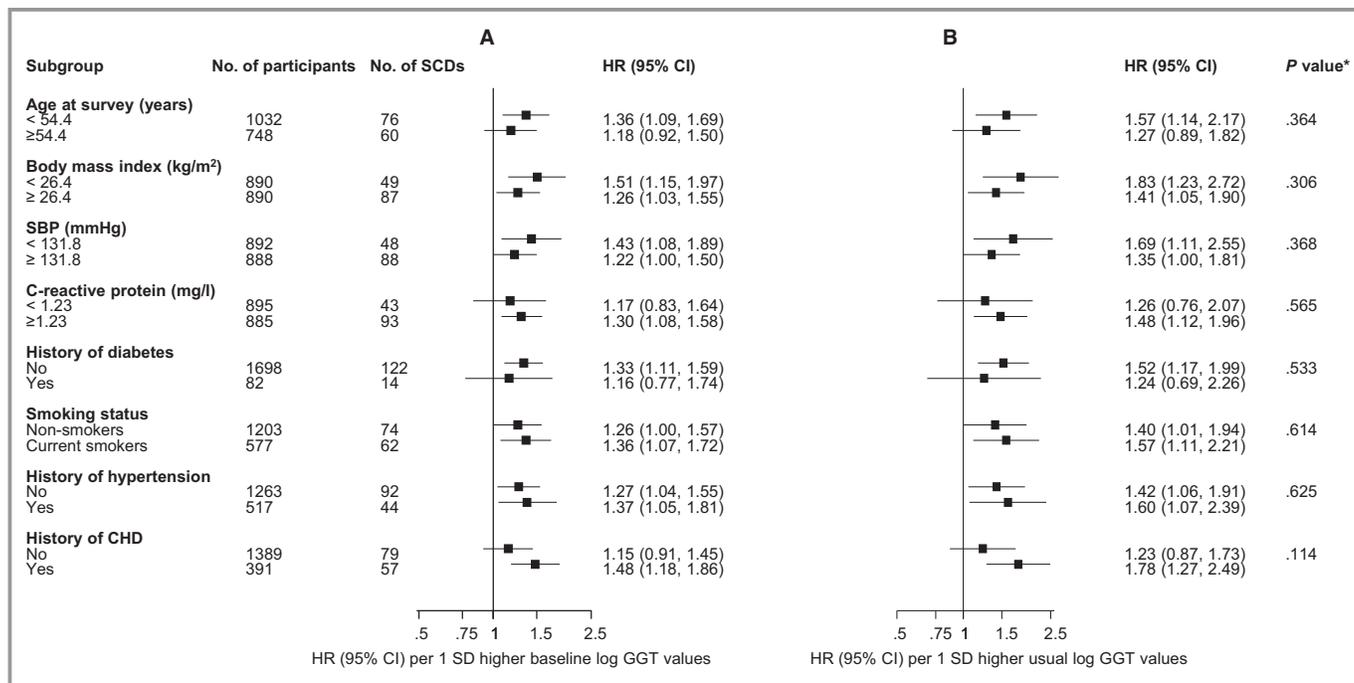
**Table 3.** Associations of Baseline and Usual Levels of GGT With SCDs, Out-of-Hospital SCDs, and Non-SCDs

Models	SCD		Out-of-Hospital SCD		Non-SCD	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
	n=136/1780		n=108/1780		n=66/1780	
<b>Baseline GGT</b>						
Model 1	1.56 (1.34–1.82)	<0.001	1.47 (1.24–1.74)	<0.001	1.46 (1.16–1.83)	0.001
Model 2	1.30 (1.10–1.54)	0.002	1.23 (1.01–1.49)	0.038	1.34 (1.04–1.72)	0.022
Model 3	1.26 (1.05–1.50)	0.014	1.17 (0.95–1.44)	0.139	1.29 (0.99–1.68)	0.059
Model 4	1.23 (1.02–1.47)	0.028	1.16 (0.95–1.43)	0.152	1.27 (0.97–1.67)	0.077
Model 5	1.23 (1.03–1.48)	0.025	1.17 (0.95–1.44)	0.149	1.29 (0.99–1.68)	0.065
<b>Usual GGT</b>						
Model 1	1.93 (1.55–2.41)	<0.001	1.76 (1.37–2.27)	<0.001	1.74 (1.24–2.43)	0.001
Model 2	1.48 (1.15–1.89)	0.002	1.35 (1.02–1.79)	0.038	1.53 (1.06–2.21)	0.022
Model 3	1.40 (1.07–1.82)	0.014	1.26 (0.93–1.70)	0.139	1.46 (0.99–2.15)	0.059
Model 4	1.35 (1.03–1.77)	0.028	1.25 (0.92–1.70)	0.152	1.43 (0.96–2.12)	0.077
Model 5	1.36 (1.04–1.78)	0.025	1.25 (0.92–1.70)	0.149	1.45 (0.98–2.14)	0.065

Model 1: Adjusted for age. Model 2: Model 1 plus body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs). Model 3: Model 2 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol. Model 4: Model 3 plus C-reactive protein. Model 5: Model 4 plus incident coronary heart disease as a time-dependent covariate. HRs are reported per 1-SD increase in log<sub>e</sub> GGT levels; 1 SD higher log<sub>e</sub> GGT was approximately equivalent to 2-fold higher GGT levels. GGT indicates γ-glutamyltransferase; HR, hazard ratio; SCD, sudden cardiac death.

based prospective studies because we were unable to locate any previously published articles exploring the prospective association between serum GGT and the specific

cardiovascular end point of SCD. Further research is needed to help unravel the mechanistic pathways of GGT in the pathogenesis of SCD.



**Figure 3.** HRs for baseline and usual levels of GGT and SCD risk by several participant-level characteristics. A, Baseline levels of GGT. B, Usual levels of GGT. HRs were adjusted for age, body mass index, SBP, prevalent CHD, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs). \*, P value for interaction. CHD indicates coronary heart disease; GGT, γ-glutamyltransferase; HR, hazard ratio; SCD, sudden cardiac death; SBP, systolic blood pressure.

**Table 4.** Associations of Baseline and Usual Levels of GGT With the Combined Outcome of Sudden Cardiac Deaths and Resuscitated Sudden Cardiac Arrests

	HR (95% CI)	P Value
	n=158/1780	
<b>Baseline GGT levels</b>		
Model 1	1.53 (1.33–1.77)	<0.001
Model 2	1.30 (1.11–1.52)	0.001
Model 3	1.26 (1.06–1.49)	0.008
Model 4	1.23 (1.03–1.46)	0.019
Model 5	1.24 (1.04–1.46)	0.016
<b>Usual GGT levels</b>		
Model 1	1.87 (1.52–2.31)	<0.001
Model 2	1.47 (1.16–1.85)	0.001
Model 3	1.40 (1.09–1.80)	0.008
Model 4	1.35 (1.05–1.74)	0.019
Model 5	1.36 (1.06–1.75)	0.016

Model 1: Adjusted for age. Model 2: Model 1 plus body mass index, systolic blood pressure, prevalent coronary heart disease, smoking status, history of diabetes, left ventricular hypertrophy, history of hypertension, and use of medications (antihypertensive agents and lipid-lowering drugs). Model 3: Model 2 plus alcohol consumption, resting heart rate, triglycerides, total cholesterol, and high-density lipoprotein cholesterol. Model 4: Model 3 plus C-reactive protein. Model 5: Model 4 plus incident coronary heart disease as a time-dependent covariate. HRs are reported per 1-SD increase in log<sub>e</sub> GGT levels; 1 SD higher log<sub>e</sub> GGT was approximately equivalent to 2-fold higher GGT levels. GGT indicates  $\gamma$ -glutamyltransferase; HR, hazard ratio.

### Implications of Findings

Our findings highlight a clear and independent link between serum GGT and the risk of SCD and may have clinical implications. Given the long-term association between baseline levels of GGT and risk of SCD, assays for GGT (which are sensitive, well standardized, simple, quick, inexpensive, commonly measured as part of routine liver function panels, and do not require a fasting state prior to venipuncture) may have the potential to be used in the identification of persons at high risk of SCD. In addition, early intervention in the development of the disease process will be important for prevention of SCD events. Although the causal nature of this association remains to be investigated, there is a possibility that lowering levels of GGT may decrease the risk of future SCD. Those with elevated GGT levels might benefit from nutritional and lifestyle modifications (eg, weight loss and physical activity<sup>39</sup>) that decrease GGT levels. Formal risk assessment analyses are warranted to assess the role of GGT in the prediction of SCD.

### Strengths and Limitations

The notable strengths of this study include a large sample that was selected to be a nationally representative population-based

sample of middle-aged men, that was well characterized, and that involved high response, and there were no losses during follow-up, reducing the risk of selection bias. Participants were monitored prospectively using established databases for hospital admissions, including out-of-hospital outcome events, supplemented with reliable data on a comprehensive panel of lifestyle and biological markers to allow adequate adjustment for potential confounding, enabling reliable assessments of the associations. The mean follow-up period in this study was sufficiently long to ascertain the risk for SCD in the general-population setting. Serial measurements of GGT made within a subset of men over time were available, enabling quantification of the extent of within-person variability over the long period of follow-up. The KIID study made such a correction on the basis of 2 repeated measurements, indicating an independent association of GGT with SCD. Nevertheless, studies are needed with repeated measurements of GGT in larger numbers of participants to assess GGT variability in greater detail. The reliability of the data was also confirmed by our ability to replicate the independent association of GGT with other cardiovascular outcomes.<sup>11</sup> Our study had a number of limitations in addition to the several strengths listed. We included a relatively small number of SCDs; therefore, these findings need to be confirmed in larger scale studies with more SCD events. Measurements of other liver function enzymes were not made in the KIID study, preventing comparison of the separate and joint associations of different liver function enzymes with SCD risk. Participants in the current study were not suitable for risk prediction analysis because we did not have complete measurements of risk factors used in standard risk-prediction algorithms for SCD. The KIID study involved prolonged blood storage, which could cause underestimation of the associations; however, GGT is not known to be influenced by prolonged storage or repeated freeze–thaw cycles.<sup>40</sup> The KIID study included only middle-aged white men from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases. The annual rate of SCDs of 3.50 per 1000 person-years at risk reflects the high rate of CHD mortality in the study region, which has the highest rate in the world.<sup>41,42</sup> Consequently, our findings cannot necessarily be extrapolated to women, young persons, elderly persons, and other populations. Although a comprehensive panel of confounders was taken into account to ensure the validity of our results, potential residual confounding due to errors in risk-marker measurements and other unmeasured confounders cannot be entirely ruled out.

### Conclusions

GGT activity is positively and log-linearly associated with future risk of SCD in the general male population. Further

research is needed to replicate these findings and to assess the potential clinical utility of GGT as a risk assessment tool or validated causal therapeutic target for SCD.

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### Disclosures

None.

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