γ-Glutamyltransferase as a Risk Factor for Cardiovascular Disease Mortality : An Epidemiological Investigation in a Cohort of 163 944 Austrian Adults

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An Epidemiological Investigation in a Cohort of 163 944 Austrian Adults

Elfriede Ruttmann, MD; Larry J. Brant, PhD; Hans Concin, MD; Günter Diem, MD; Kilian Rapp, MD; Hanno Ulmer, PhD; and the Vorarlberg Health Monitoring and Promotion Program Study Group

Background—There is evidence from recent studies that γ-glutamyltransferase (GGT) is likely to be associated with cardiovascular disease (CVD). However, few studies to date with sufficient sample size and follow-up investigated the association of GGT with CVD mortality.

Methods and Results—The relation of GGT to the risk of death from CVD was examined in a cohort of 163 944 Austrian adults that was monitored for up to 17 years. To evaluate GGT as an independent predictor, Cox proportional hazards models were calculated, which adjusted for established risk factors. In both men and women, high GGT was significantly ($P<0.001$) associated with total mortality from CVD, showing a clear dose-response relationship. Adjusted hazard ratios (95% CI) per log GGT increase were 1.66 (1.40 to 1.98) in men and 1.64 (1.36 to 1.97) in women. In men, subgroup analyses showed that high GGT was positively associated with incident fatal events of chronic forms of coronary heart disease ($P=0.009$), congestive heart failure ($P<0.001$), and hemorrhagic ($P=0.01$) and ischemic stroke ($P<0.001$). No significant associations were observed for acute myocardial infarction ($P=0.16$). In women, hazard ratios suggested associations in all subgroups; however, for hemorrhagic and ischemic stroke they were not statistically significant ($P=0.09$ and $P=0.07$, respectively). In addition, subgroup analyses stratified by age revealed a stronger relationship of GGT in younger participants. Hazard ratios for total CVD were 2.03 (1.53 to 2.69) in men and 2.60 (1.53 to 4.42) in women younger than 60 years.

Conclusions—This study demonstrates in a large, prospectively observed cohort that GGT is independently associated with cardiovascular mortality. **(*Circulation*. 2005;112:2130-2137.)**

Key Words: arteriosclerosis ■ cardiovascular diseases ■ prevention ■ risk factors ■ gamma-glutamyltransferase

In clinical practice, γ-glutamyltransferase (GGT) is a commonly used diagnostic test. Although GGT is mainly seen as an indicator for liver function and alcohol consumption, several studies showed that it is associated with morbidity and mortality from causes other than liver disease, including cardiovascular disease (CVD).[1] In regard to coronary heart disease, it was observed that serum GGT levels were associated with increased risk of myocardial infarction and cardiac death.[2–5] More recently, associations with stroke were reported.[6,7] However, such reports are rare, and consistent evidence is lacking because of the limited number of performed studies.

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Although there is no doubt about the use of GGT as a monitor of liver function, there are now indications of GGT having a direct involvement in atherosclerotic plaque formation.[8] GGT, present in serum and on the surface of most cell types, is the enzyme responsible for the extracellular catabolism of glutathione, the main antioxidant in mammalian cells, and its role in CVDs may be more complex than is currently thought.[9] The possible role of GGT in the atherosclerotic process suggests that its predictive value is at least partly independent of self-reported alcohol consumption. On the other hand, alcohol consumption has been recently confirmed to have a protective effect against myocardial infarction.[10]

The Vorarlberg Health Monitoring and Promotion Program (VHM&PP), located in western Austria, is one of the world's largest ongoing population-based risk factor surveillance programs.[11] Since 1985, approximately two thirds of the adult population in the region have been examined, and the database currently includes information from health examinations of 166 547 men and women. From the outset, mea-

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From the Department of Medical Statistics, Informatics, and Health Economics, Innsbruck Medical University, Innsbruck, Austria (E.R., H.U.); Gerontology Research Center, National Institute on Aging, Baltimore, Md (L.J.B.); Agency for Preventive and Social Medicine, Bregenz, Austria (H.C., G.D., H.U.); and Department of Epidemiology, University of Ulm, Ulm, Germany (K.R.).

Correspondence to Hanno Ulmer, PhD, Department of Medical Statistics, Informatics, and Health Economics, Innsbruck Medical University, Schoepfstrasse 41, A-6020 Innsbruck, Austria. E-mail hanno.ulmer@uibk.ac.at

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surements for cardiovascular risk factors, including GGT, have been routinely collected.

A few studies to date have investigated the association of GGT with CVD mortality. This report therefore presents a prospective investigation of the association of GGT and death from CVD in this large population that was monitored for up to 17 years.

Methods

Study Population

The VHM&PP is a risk factor surveillance program in Vorarlberg, the westernmost province of Austria. It is routinely performed by the Agency of Social and Preventive Medicine and addresses all adults (aged ≥19 years) of the entire province. Participation in the health examination is voluntary and is conducted by local physicians. The program includes a physical examination, a blood test, and a consultation with a physician. Costs are covered by the participant's (compulsory) health insurance. From the outset, approximately two thirds of the adult population of the province have participated in this risk factor surveillance program.[12] Participation is highest between the ages of 25 and 54 years, with a mean age of 42 years for both men and women. Detailed descriptions of the VHM&PP have been presented previously.[11–13] For this study, institutional review board approval was obtained by the Research Ethics Committee of Innsbruck Medical University.

Between 1985 and 2001, 166 547 adult Vorarlberg residents aged ≥19 years (54.5% women) were enrolled in the VHM&PP study cohort. Participants signed informed consents to have personal data such as height, weight, smoking, serum measurements, and sociodemographic factors, such as marital and work status, stored and processed. The cohort considered for the present analysis was restricted to 163 944 participants with complete data on GGT at enrollment. For this reason, 2603 participants (1.6%) were excluded from the present study.

Measurements

Serum GGT levels were measured at 37°C and recalculated to 25°C and were given as units per liter. Serum measurements of GGT, cholesterol, triglycerides, and glucose were performed by 2 central laboratories that underwent regular internal and external quality control procedures. Measurements were done on fasting blood samples. Because GGT values differ significantly by sex, the upper laboratory reference limit was set at 18 U/L for women and 28 U/L for men. In the present analysis, GGT was classified separately for women and men according to the usual practice as normal low (<9 U/L for women, <14 U/L for men), normal high (9 to 17, 14 to 27 U/L), moderately elevated (18 to 26, 28 to 41 U/L), elevated (27 to 35, 42 to 55 U/L), and highly elevated (≥36, ≥56 U/L). In addition, GGT was categorized into quintiles and compared with CVD mortality.

End Points

By the end of 2001, 6990 deaths were recorded, of which 3026 (43.3%) were cardiovascular-related deaths. Date and cause of death information was provided by the local health authority and was linked in the database with the use of a validated procedure. All deaths were identified from death certificates that were confirmed by authorized physicians only. Deaths from CVD were grouped into the following subgroups according to *ICD-9*: acute and subacute forms of coronary heart disease (*ICD-9* 410, 411), chronic forms of heart disease including occlusive coronary heart disease and its complications (*ICD-9* 414), congestive heart failure (*ICD-9* 428, 429), other cardiovascular disease (*ICD-9* 401 to 405, 440 to 443), hemorrhagic stroke (*ICD-9* 431), and ischemic stroke (*ICD-9* 433 to 438). In addition, information about cancer morbidity was available for all VHM&PP participants through the local cancer registry that is accredited by the International Agency for Research on Cancer.[14] However, data on morbidity from CVD were not available.

Statistical Analysis

To determine associations of GGT with established risk factors such as systolic blood pressure and cholesterol, partial correlation coefficients adjusted for age and sex were calculated. Because alcohol consumption has not been documented routinely in the VHM&PP, correlations between GGT and alcohol consumption were calculated from a subsample of participants who took part in one of the regularly scheduled health surveys.[15] GGT and triglycerides were logarithmically transformed to utilize parametric analytic techniques. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% CIs for high GGT categories relative to normal low GGT, adjusted for age, body mass index, systolic blood pressure, cholesterol, triglycerides, glucose, smoking, occupational status (blue collar, white collar, or self-employed), and year of examination. In addition, HRs were given for log unit changes of GGT. Significance testing was performed with a Wald χ^2 test on the GGT log unit changes. The Wald statistic was also used to assess the strength of the association of GGT with CVD mortality relative to other risk factors. Subgroup analyses were performed for different categories of CVD and for age groups with the same Cox models. The proportional hazards assumption was checked and found to be fulfilled for all models. Significance testing of age and sex as an effect modifier of the relation of GGT to CVD mortality was done through the assessment of interaction terms in the models.

To check the sensitivity of our analyses with regard to cancer morbidity and short-term mortality, we repeated all analyses excluding participants who had been diagnosed with a malignancy before enrollment or within 1 year after enrollment. In addition, all participants who died within 1 year of enrollment were excluded from this analysis.

To identify cutoff values for GGT to predict mortality from CVD, we performed receiver operating characteristic analyses. All analyses were performed separately for men and women. Probability values <0.05 were considered to indicate statistical significance.

Results

Characteristics of study participants are shown in Table 1. The study cohort consisted of 74 830 men and 89 114 women who were followed up for a median time of 11.1 and 12 years, respectively. Total time at risk was ≈1.7 million person-years. Mean age at study entry was 41.8 years for men and 42.0 years for women. Total mortality was 5% for men and 3.7% for women, and mortality from CVD was 2.1% and 1.6%, respectively. Prevalence of elevated GGT was 21.9% in men (GGT >28 U/L) and 15.6% in women (GGT >18 U/L).

Associations of GGT With Established Risk Factors and Alcohol Consumption

Table 2 shows that GGT was significantly correlated with established risk factors for CVD. The strongest age- and sex-adjusted correlation was observed between GGT and triglycerides ($r=0.30$). GGT was further positively correlated with uric acid ($r=0.29$), body mass index ($r=0.21$), cholesterol ($r=0.20$), blood pressure ($r=0.15$), glucose ($r=0.12$), and smoking ($r=0.08$) and negatively correlated with HDL cholesterol ($r=-0.14$), physical activity ($r=-0.11$), and education ($r=-0.10$).

Alcohol consumption has not been documented routinely in the VHM&PP; however, a randomly selected subsample of 731 participants[15] provided self-reported alcohol data. In these participants, a statistically significant correlation ($r=0.12$, $P=0.001$) of GGT with the average number of alcoholic units per week was observed.

TABLE 1. Characteristics of the Study Population, VHM&PP 1985–2001

	Men	Women
VHM&PP participants 1985–2001, n (%)	75 697 (45.5)	90 850 (54.5)
Eligible participants with valid GGT measurements, n (%)	74 830 (45.6)	89 114 (54.4)
Age at entry, mean±SD (range), y	41.8±14.7 (19–95)	42.0±15.9 (19–95)
Mortality, n (%)	3731 (5.0)	3259 (3.7)
Cardiovascular/cerebrovascular deaths	1571 (2.1)	1455 (1.6)
Cancer deaths	1210 (1.6)	1046 (1.2)
Liver disease deaths	109 (0.15)	57 (0.06)
Other deaths	840 (1.1)	701 (0.78)
Follow-up, mean±SD (median), y	10.1±5.0 (11.1)	10.8±4.9 (12.0)
Maximum follow-up, y	17	17
Person-years at risk	757 370	958 659

Associations of GGT With CVD Mortality

In both men (Table 3) and women (Table 4), raised GGT was significantly ($P<0.001$) associated with total mortality from CVD, showing a clear dose-response relationship. In men, adjusted HRs increased from 1.17 to 1.64 according to GGT classes (normal high, moderately elevated, elevated, highly elevated), and in women, adjusted HRs increased from 1.04 to 1.51. CVD death risk was increased by 1.66 (95% CI, 1.40 to 1.98) per log unit of GGT in men and by 1.64 (95% CI, 1.36 to 1.97) per log unit of GGT in women. The Figure shows the adjusted cumulative survival for participants at average covariate levels within the 17-year follow-up period.

In men, subgroup analyses showed that elevated GGT was positively associated with incident fatal events of chronic forms of coronary heart disease ($P=0.009$), congestive heart failure ($P<0.001$), and hemorrhagic ($P=0.01$) and ischemic stroke ($P<0.001$). No statistically significant associations were observed in acute (myocardial infarction *ICD-9* 410) and subacute forms of coronary heart disease ($P=0.16$) and other CVD ($P=0.16$).

TABLE 2. Clinical Correlates of GTT, VHM&PP 1985–2001

	Correlation Coefficient*	*P*
Triglycerides, mg/dL	0.30	<0.001
Uric acid, mg/dL	0.29	<0.001
Body mass index, kg/m^2	0.21	<0.001
Total cholesterol, mg/dL	0.20	<0.001
Systolic blood pressure, mm Hg	0.15	<0.001
Diastolic blood pressure, mm Hg	0.15	<0.001
HDL cholesterol, mg/dL†	−0.14	<0.001
Glucose, mg/dL	0.12	<0.001
Average No. of alcoholic units per week†	0.12	0.001
Physical activity†	−0.11	0.02
Education†	−0.10	0.005
Current smoking	0.08	<0.001

*Partial correlation coefficients, age and sex adjusted. GGT and triglycerides were logarithmically transformed.

†Calculations are based on a subsample of participants (n=731). Education and physical activity were measured with an ordinal scale with increasing categories indicating higher education or physical activity.

In women, HRs suggested associations in all subgroups; however, hemorrhagic and ischemic stroke were not statistically significant ($P=0.09$ and $P=0.07$, respectively). Acute and subacute forms of coronary heart disease ($P=0.04$), chronic forms of coronary heart disease ($P=0.002$), congestive heart failure ($P=0.02$), and other CVD ($P=0.04$) were significantly associated with log increases of GGT.

Comparisons between the fifth and the first quintile of GGT revealed HRs of 1.57 (95% CI, 1.30 to 1.91) and 1.68 (95% CI, 1.26 to 2.25) for total mortality from CVD in men and women, respectively. In addition, subgroup analyses stratified by age revealed stronger associations of GGT in younger participants. When 2 age groups were considered (aged <60 or ≥60 years at enrollment), HRs (95% CI) for log GGT increases and mortality from total CVD were 2.03 (1.53 to 2.69) in younger men and 2.60 (1.53 to 4.42) in younger women versus 1.42 (1.14 to 1.77) in men and 1.52 (1.24 to 1.85) in women aged ≥60 years. In addition, risk for acute/subacute coronary heart disease in younger men was significantly raised per log unit of GGT (HR=1.59 [1.01 to 2.50]; $P=0.04$). In younger women, HRs were even higher at 3.13 (1.62 to 2.79; $P=0.01$). The age of participants proved to be a significant effect modifier for the relation of GGT to total CVD mortality in both men ($P=0.036$) and women ($P<0.001$). There was no significant effect modifying by sex ($P=0.476$).

All associations that were statistically significant in the main analysis remained unchanged in terms of statistical significance when reanalyzed, excluding cancer patients and deaths within the first year. However, the insignificant association for ischemic stroke in women became significant (HR=1.54, $P=0.03$). Sensitivity analyses that examined whether temporal changes, as well as changes in assays and machines, are likely to explain the effects of GGT did not significantly change the estimated HRs (data not shown).

Strength of the Association and Cutoff Values

When the risk factors were ordered according to the strength of their relationship to CVD mortality in the regression models, GGT was ranked third after systolic blood pressure and smoking and before cholesterol. However, in acute and subacute forms of coronary heart disease, cholesterol showed the strongest association, and GGT was less important.

TABLE 3. Mortality From CVD According to GGT Among Men, VHM&PP 1985–2001

	GGT						
	<14 U/L (Normal Low)	14–27 U/L (Normal High)	28–41 U/L (Moderately Elevated)	42–55 U/L (Elevated)	≥56 U/L Highly Elevated	Total per Log Increase*	*P* for Log Increase
No. of men	29 320	29 121	8085	3334	4970	74 830	
All cardiovascular/cerebrovascular							
Fatal events, n (%)	389 (1.3)	678 (2.3)	231 (2.9)	94 (2.8)	179 (3.6)	1571 (2.1)	
HR (95% CI)†	1.00	1.17 (1.02–1.33)	1.28 (1.08–1.53)	1.39 (1.09–1.78)	1.64 (1.35–2.0)	1.66 (1.40–1.98)	*P*<0.001
Subgroups							
Acute and subacute forms of coronary heart disease (*ICD-9* 410, 411)							
Fatal events, n (%)	119 (0.4)	206 (0.7)	63 (0.8)	33 (1)	52 (1)	473 (0.6)	
HR (95% CI)†	1.00	1.00 (0.79–1.27)	0.91 (0.65–1.26)	1.15 (0.75–1.74)	1.22 (0.86–1.74)	1.27 (0.92–1.75)	*P*=0.16
Chronic forms of coronary heart disease (*ICD-9* 414)							
Fatal events, n (%)	124 (0.4)	201 (0.7)	66 (0.8)	26 (0.8)	56 (1.1)	473 (0.6)	
HR (95% CI)†	1.00	1.11 (0.87–1.41)	1.14 (0.83–1.58)	1.16 (0.73–1.85)	1.60 (1.12–2.26)	1.53 (1.11–2.11)	*P*=0.009
Congestive heart failure (*ICD-9* 428, 429)							
Fatal events, n (%)	34 (0.1)	75 (0.3)	24 (0.3)	10 (0.3)	19 (0.4)	162 (0.2)	
HR (95% CI)†	1.00	1.58 (1.04–2.41)	1.68 (0.96–2.95)	2.31 (1.12–4.76)	2.62 (1.45–4.76)	2.69 (1.64–4.43)	*P*<0.001
Other CVD (*ICD-9* 401–405, 440–443)							
Fatal events, n (%)	35 (0.1)	55 (0.2)	22 (0.3)	7 (0.2)	16 (0.3)	135 (0.2)	
HR (95% CI)†	1.00	1.12 (0.71–1.78)	1.64 (0.92–2.92)	1.39 (0.60–3.23)	1.46 (0.73–2.95)	1.53 (0.84–2.98)	*P*=0.16
Hemorrhagic stroke (*ICD-9* 431)							
Fatal events, n (%)	15 (0.1)	27 (0.1)	12 (0.1)	6 (0.2)	10 (0.2)	70 (0.1)	
HR (95% CI)†	1.00	1.58 (0.81–3.11)	2.26 (0.98–5.21)	3.24 (1.20–8.77)	2.77 (1.11–6.93)	2.64 (1.25–5.55)	*P*=0.01
Ischemic stroke (*ICD-9* 433–438)							
Fatal events, n (%)	62 (0.2)	114 (0.4)	44 (0.5)	12 (0.4)	26 (0.5)	258 (0.3)	
HR (95% CI)†	1.00	1.42 (1.02–1.97)	2.10 (1.39–3.17)	1.63 (0.85–3.15)	2.05 (1.23–3.40)	2.17 (1.43–3.29)	*P*<0.001

*GGT was logarithmically transformed, excluding at most 0.8% missing values within body and blood measurements and 4.9% within work status.

†HRs (95% CIs) from Cox proportional hazards model adjusted for age, body mass index, systolic blood pressure, cholesterol, triglycerides, glucose, smoking, work status, and year of examination.

Table 5 shows the sensitivities and specificities for selected threshold values of GGT predicting mortality from total CVD. The receiver operating characteristic analyses suggested GGT cutoff values of 15.5 U/L for men and 10.5 U/L for women with corresponding sensitivities of 66% and 74%. Area under the curve was significantly greater in women, indicating a closer relationship of GGT to CVD.

Discussion

The results of this study demonstrate a strong dose-response relationship of serum GGT to CVD mortality. The association with high GGT was consistent over all subgroups of disease with the exception of acute/subacute forms of coronary heart disease in men. However, this latter association was significant in men aged <60 years. Additionally, GGT was significantly associated with established risk factors such as triglycerides, body mass index, and cholesterol. Adjustment for these variables in multiple risk factor regression analyses confirmed GGT as an independent predictive factor for CVD mortality.

The monotonic increasing trend of mortality with high GGT levels is unlikely to simply reflect the effects of alcohol consumption[16] because most studies have shown a U- or J-shaped relationship of alcohol drinking to cardiovascular[17,18] and all-cause mortality.[19] There is evidence supporting a mild to moderate independent beneficial effect of alcohol consumption on CVD risk.[17] It has been shown that GGT is more influenced by drinking intensity than drinking frequency.[20] Thus, alcohol-related elevation of GGT mainly reflects excessive alcohol consumption or binge drinking and may therefore not have a U-shaped relationship to CVD. In this study a subsample of the participants indicated that there was a weak correlation between GGT and self-reported alcohol consumption, even though there was a nonsignificant protective association with moderately elevated GGT, particularly in men dying from myocardial infarction.

Numerous epidemiological studies[17] have investigated the relationship of alcohol consumption to heart disease and stroke. Because of its multiple pathways of both positive and negative influences, there is still no conclusive evidence about its biological mechanism. It has been shown that alcohol affects lipid metabolism,[21] as well as hemostatic[22] and oxidative factors. Mainly because of caloric intake,

TABLE 4. Mortality From CVD According to GGT Among Women, VHM&PP 1985–2001

	GGT						
	< 9 U/L (Normal Low)	9–17 U/L (Normal High)	18–26 U/L (Moderately Elevated)	27–35 U/L (Elevated)	≥36 U/L (Highly Elevated)	Total per Log Increase*	*P* for Log Increase
No. of women	34 731	40 505	7496	2557	3825	89 114	
All cardiovascular/cerebrovascular							
Fatal events, n (%)	203 (0.6)	718 (1.8)	261 (3.5)	110 (4.3)	163 (4.3)	1455 (1.6)	
HR (95% CI)†	1.00	1.04 (0.88–1.22)	1.35 (1.11–1.64)	1.46 (1.14–1.88)	1.51 (1.21–1.89)	1.64 (1.36–1.97)	*P*<0.001
Subgroups							
Acute and subacute forms of coronary heart disease (*ICD-9* 410, 411)							
Fatal events, n (%)	39 (0.1)	162 (0.4)	60 (0.8)	24 (0.9)	38 (1.0)	323 (0.4)	
HR (95% CI)†	1.00	1.17 (0.81–1.67)	1.48 (0.97–2.26)	1.47 (0.85–2.54)	1.71 (1.08–2.74)	1.52 (1.03–2.26)	*P*=0.04
Chronic forms of coronary heart disease (*ICD-9* 414)							
Fatal events, n (%)	50 (0.1)	208 (0.5)	62 (0.8)	29 (1.1)	49 (1.3)	398 (0.4)	
HR (95% CI)†	1.00	1.20 (0.87–1.66)	1.33 (0.90–1.97)	1.56 (0.96–2.56)	1.87 (1.23–2.83)	1.71 (1.21–2.40)	*P*=0.002
Congestive heart failure (*ICD-9* 428, 429)							
Fatal events, n (%)	30 (0.1)	101 (0.3)	38 (0.5)	18 (0.7)	17 (0.5)	204 (0.2)	
HR (95% CI)†	1.00	0.97 (0.63–1.47)	1.32 (0.79–2.21)	2.13 (1.17–3.86)	1.22 (0.65–2.26)	1.76 (1.09–2.82)	*P*=0.02
Other CVD (*ICD-9* 401–405, 440–443)							
Fatal events, n (%)	20 (0.1)	56 (0.1)	13 (0.2)	10 (0.4)	18 (0.5)	117 (0.1)	
HR (95% CI)†	1.00	0.91 (0.53–1.56)	0.66 (0.31–1.42)	1.36 (0.58–3.18)	1.75 (0.87–3.50)	1.93 (1.03–3.6)	*P*=0.04
Hemorrhagic stroke (*ICD-9* 431)							
Fatal events, n (%)	5 (0.0)	23 (0.1)	13 (0.2)	6 (0.2)	5 (0.1)	52 (0.1)	
HR (95% CI)†	1.00	1.85 (0.69–4.95)	3.88 (1.33–11.37)	5.25 (1.56–17.7)	1.75 (0.41–7.52)	2.21 (0.88–5.53)	*P*=0.09
Ischemic stroke (*ICD-9* 433–438)							
Fatal events, n (%)	59 (0.2)	168 (0.4)	75 (1.0)	23 (0.9)	36 (0.9)	361 (0.4)	
HR (95% CI)†	1.00	0.88 (0.65–1.20)	1.45 (1.01–2.09)	1.06 (0.62–1.84)	1.08 (0.67–1.74)	1.43 (0.97–2.12)	*P*=0.07

*GGT was logarithmically transformed, excluding at most 0.7% missing values within body and blood measurements and 4% within work status.

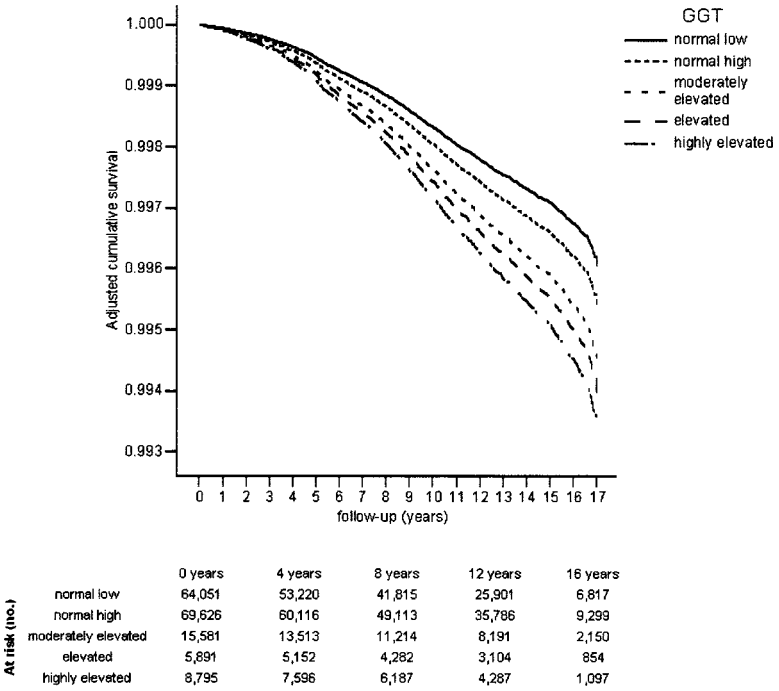
†HRs (95% CIs) from Cox proportional hazards model adjusted for age, body mass index, systolic blood pressure, cholesterol, triglycerides, glucose, smoking, work status, and year of examination.

alcohol consumption has been shown to be associated with obesity and elevated blood pressure.[23] In the case of GGT, whether through alcohol consumption or not, the influence is likely to be either directly metabolic or oxidative in the development of atherosclerotic plaque formation.

There is evidence that GGT is a potential biochemical marker for the preclinical development of atherosclerosis. GGT was found to play a role in the pathogenesis of atherosclerosis because it was detected in atheromatous plaques of carotid and coronary arteries triggering the oxidation of LDLs.[8,24] GGT is a heterodimeric, membrane-associated component of the γ-glutamyl cycle responsible for the recycling of the scavenger glutathione.[1] The link between serum GGT activity and plaque formation is based on the pro-oxidant action of glutathione catabolites in the extracellular space.[25] Through the hydrolysis of the γ-glutamyl bond, GGT is the enzyme responsible for the extracellular catabolism of glutathione. This reaction releases the cysteine-glycine dipeptide that is used by cells as a source of cysteine for the synthesis of intracellular GSH. Outside the cell, however, before being taken up, this dipeptide reduces Fe^{3+} to its bivalent form and releases a free thyil radical. This released radical oxidizes LDL. In this way, GGT acts as a pro-oxidant in the extracellular space.[8,24]

Recent studies have demonstrated that GGT is expressed not only in the liver and kidney but also in the cerebrovascular endothelium, the pericytes, and most other cell types.[26] Therefore, GGT activity can be used as a biochemical marker for the blood-brain barrier.[27] This might explain the predictive value of GGT in fatal cerebrovascular events, because GGT is released by impaired cerebral endothelial cells in the formation of atherosclerotic plaques.

Nikkari and colleagues[28] demonstrated that high carbohydrate-deficient transferrin and low GGT levels were associated with a favorable blood lipid profile in 5675 Finnish subjects, and they suggested that elevated GGT may have adverse affects on lipoprotein metabolism, including hypercholesterolemia and hypertriglyceridemia as vascular risk factors. GGT was also found to be associated with the risk of metabolic syndrome and type 2 diabetes.[29,30] However, after adjustment for dyslipidemia, blood pressure, and glucose, the results of this study indicate that high GGT by itself



Adjusted cumulative survival from CVD mortality according to categories of GGT among 163 944 women and men (mean age, 42 years) in the VHM&PP estimated at the average values of covariates. GGT was classified separately for women and men as normal low (<9 U/L for women, <14 U/L for men), normal high (9 to 17, 14 to 27 U/L), moderately elevated (18 to 26, 28 to 41 U/L), elevated (27 to 35, 42 to 55 U/L), and highly elevated (>36, >56 U/L). Survival curves were calculated with a Cox proportional hazards model that was adjusted for sex, age, body mass index, systolic blood pressure, cholesterol, triglycerides, glucose, smoking, work status, and year of examination. Numbers at bottom of graph indicate participants available for analysis at given time points.

is of predictive value for the early development of atherosclerosis-related CVDs and cerebrovascular diseases. This is further supported by the observation that GGT was more predictive in younger participants. The association of high GGT with death from CVD remained stable in analyses excluding participants who were diagnosed with malignancies or who died within 1 year after enrollment. This indicates a relationship of GGT to CVD that is independent of the expected reexpression of GGT in patients with malignant lesions.[31]

In the VHM&PP population, which is predominantly white, prevalence of high GGT was 21.9% in men and 15.6% in women. Because comparable studies do not reveal GGT prevalence figures, we are not able to compare our prevalence with that of other cohorts or countries. However, 2 recent studies assessed ethnic differences with regard to elevated GGT, alcohol consumption, and liver disease.[32,33] Both studies demonstrated a higher alcohol-related hepatic vulnerability in African and Hispanic Americans together with higher GGT levels in all categories of drinking status, after adjustment for potential confounders, compared with the white population. A very recent study from the northwest region of Russia revealed GGT levels in both sexes that were more than twice as high as those found in comparable studies.[34] This study offers further evidence that elevated GGT is significantly associated with increased risk for CVD.

Strengths and Potential Study Limitations

Major strengths of this study are the prospective design, the length of follow-up, and the standardized protocol. Addition-

TABLE 5. Sensitivity and Specificity for Selected Thresholds of GGT Predicting Fatal CVD, VHM&PP 1985–2001

	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)*
Men (n=74 830)			0.60 (0.59–0.62)
Threshold 14 U/L	0.75 (0.73–0.77)	0.39 (0.39–0.40)	
Threshold 28 U/L	0.32 (0.30–0.34)	0.78 (0.78–0.79)	
Threshold 42 U/L	0.17 (0.16–0.19)	0.85 (0.85–0.85)	
Threshold 56 U/L	0.11 (0.10–0.13)	0.93 (0.93–0.94)	
Threshold 15.5 U/L†	0.66 (0.64–0.69)	0.49 (0.49–0.49)	
Women (n=89 114)			0.71 (0.69–0.72)
Threshold 9 U/L	0.86 (0.84–0.88)	0.39 (0.39–0.40)	
Threshold 18 U/L	0.37 (0.34–0.39)	0.85 (0.85–0.85)	
Threshold 27 U/L	0.19 (0.17–0.21)	0.93 (0.93–0.93)	
Threshold 36 U/L	0.11 (0.10–0.13)	0.96 (0.96–0.96)	
Threshold 10.5 U/L†	0.74 (0.72–0.76)	0.58 (0.58–0.58)	

*Area under the curve (AUC) derived from receiver operating characteristic analyses.
†Threshold maximizing the sum of sensitivity and specificity.

ally, examinations were only performed by experienced physicians on a large number of study subjects, representing more than two thirds of the adult population in most age groups. Even though information on all major risk factors was collected, this study was unable to account for additional factors that might confound the relationship between GGT and CVD, including lipid subfractions or apolipoproteins, C-reactive protein, homocysteine, alcohol consumption, physical activity, diet, and genetic and psychosocial factors. A further limitation of this study is the inability to examine the effect of medication (eg, statins, antihypertensive drugs) use on the relationship of GGT with CVD. In regard to statins in this study, there is little, if any, effect of statin use on the relationship of GGT with CVD mortality because 75% of the study participants were examined before the implementation of statin therapy in Austria in 1995.

Alcohol consumption was only measured in a subsample of the participants. Therefore, we were unable to examine for confounding or effect modification by alcohol use. However, including self-reported alcohol consumption as a covariate is of questionable value because its reliability and validity have often been debated.[35] In addition, despite the size of the cohort, fatal events in subgroups (eg, hemorrhagic stroke) were relatively infrequent. Finally, morbidity data from CVD were not generally available.

In summary, this study investigated the relation of GGT to CVD mortality in a central European population-based cohort of >160 000 men and women. The results provide strong evidence of positive associations between high GGT and mortality from CVD in both men and women. Both the strength of the association and the consistent dose-response relationship support the hypothesis that high GGT is an independent risk factor for CVD.

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References

1. Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum γ-glutamyltransferase in cardiovascular diseases. *Clin Chem Lab Med*. 2004;42:1085–1091.
2. Betro MG, Oon RC, Edwards JB. Gamma-glutamyl transpeptidase and other liver function tests in myocardial infarction and heart failure. *Am J Clin Pathol*. 1973;60:679–683.
3. Hood B, Kjellstrom T, Ruter G, Kristenson H. Serum cholesterol, serum triglyceride, alcohol, myocardial infarction and death: necessary to pay attention to serum GT in assessment of risks of myocardial. *Lakartidningen*. 1990;87:3295–3298.
4. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart diseases and all cause. *Am J Epidemiol*. 1995;142:699–708.
5. Emdin M, Passino C, Michelassi C, Titta F, L'Abbate A, Donato L, Pompella A, Paolicchi A. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. *Eur Heart J*. 2001;22:1802–1807.
6. Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self reported alcohol drinking, and the risk of stroke. *Stroke*. 2000;31:1851–1855.
7. Bots ML, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, Sivenius J, Trichopoulou A, Tuomilehto J, Koudstaal PJ, Grobbee DE. γ-Glutamyltransferase and risk of stroke: the EUROSTROKE project. *J Epidemiol Community Health*. 2002;56(suppl 1):2529.
8. Paolicchi A, Emdin M, Ghliozeni E, Ciancia E, Passino C, Popoff G, Pompella A. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. *Circulation*. 2004;109:1440.
9. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci*. 2001;38:263–355.
10. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
11. Ulmer H, Kelleher C, Diem G, Concin H. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme. *Eur Heart J*. 2003;24:1004–1013.
12. Ulmer H, Kelleher C, Diem G, Concin H. Why Eve is not Adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. *J Womens Health*. 2004;13:41–53.
13. Ulmer H, Kelleher C, Diem G, Concin H, Ruttmann E. Estimation of seasonal variations in risk factor profiles and mortality from coronary heart disease. *Wien Klin Wochenschr*. 2004;116:662–668.
14. Parkin DM, Whelan SL, Ferlay J, eds. *Cancer Incidence in Five Continents: Volume VIII*. Lyon, France: IARC Scientific Publications; 2003.
15. Ulmer H, Diem G, Bischof HP, Ruttmann E, Concin H. Recent trends and sociodemographic distribution of cardiovascular risk factors: results from two population surveys in the Austrian WHO CINDI demonstration area. *Wien Klin Wochenschr*. 2001;113:573–579.
16. Emdin M, Passino C, Donato L, Paolicchi A, Pompella A. Serum gamma-glutamyltransferase as a risk factor of ischemic stroke might be independent of alcohol consumption. *Stroke*. 2002;33:1163–1164.
17. Hill DA. In vino veritas: alcohol and heart disease. *Am J Med Sci*. 2005;329:124–135.
18. Leppala JM, Paunio M, Virtamo J, Fogelholm R, Albanes D, Taylor PR, Heinonen OP. Alcohol consumption and stroke incidence in male smokers. *Circulation*. 1999;100:1209–1214.
19. Gronbaek M, Johansen D, Becker U, Hein HO, Schnohr P, Jensen G, Vestbo J, Sorensen TI. Changes in alcohol intake and mortality: a longitudinal population-based study. *Epidemiology*. 2004;15:222–228.
20. Albert CM, Manson JE, Cook NR, Ajani UA, Gaziano JM, Hennekens CH. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation*. 1999;100:944–950.
21. De Oliveira E Silva ER, Foster D, McGee Harper M, Seidman CE, Smith JD, Breslow JL, Brinton EA. Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. *Circulation*. 2000;102:2347–2352.
22. Mukamal KJ, Jadhav PP, D'Agostino RB, Massaro JM, Mittleman MA, Lipinska I, Sutherland PA, Matheney T, Levy D, Wilson PW, Ellison RC, Silbershatz H, Muller JE, Tofler GH. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. *Circulation*. 2001;104:1367–1373.
23. Langer RD, Criqui MH, Reed DM. Lipoproteins and blood pressure as biological pathways for effect of moderate alcohol consumption on coronary heart disease. *Circulation*. 1992;85:910–915.
24. Paolicchi A, Minotti G, Tonarelli P, Tongiani R, De Cesare D, Mezzetti A, Dominici S, Comporti M, Pompella A. Gamma-glutamyl-transpeptidase-dependent iron reduction and LDL oxidation: a potential mechanism in atherosclerosis. *J Invest Med*. 1999;47:151–160.
25. Emdin M, Passino C, Pompella A, Paolicchi A. Serum gamma-glutamyl transpeptidase: a prognostic marker in cardiovascular diseases. *Biofactors*. 2003;17:199–205.
26. Frey A, Meckelein B, Weiler-Güttler H, Möckel B, Flach R, Gassen HG. Pericytes of the brain microvasculature express γ-glutamyl transpeptidase. *Eur J Biochem*. 1991;202:421–429.
27. Goldstein GW, Wolinsky JS, Csejtey J, Diamond I. Isolation of metabolically active capillaries from rat brain. *J Neurochem*. 1975;25:715–717.

28. Nikkari ST, Koivu TA, Kalela A, Strid N, Sundvall J, Poikolainen K, Jousilahti P, Alho H, Sillanaukee P. Association of carbohydrate-deficient transferrin (CDT) and gamma-glutamyl-transferase (GGT) with serum lipid profile in the Finnish population. *Atherosclerosis*. 2001;154: 485–492.
29. Nakanishi N, Suzuki K, Tatara K. Serum γ-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. *Diabetes Care*. 2004;27:1427–1432.
30. Lee DH, Steffen LM, Jacobs DR. Association between serum γ-glutamyltransferase and dietary factors: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Clin Nutr*. 2004; 79:600–605.
31. Maellaro E, Dominici S, Del Bello B, Valentini MA, Pieri L, Perego P, Supino R, Zunino F, Lorenzini E, Paolicchi A, Comporti M, Pompella A. Membrane γ-glutamyl transpeptidase activity of melanoma cells: effects on cellular H_2O_2 production, cell surface protein thiol oxidation and NF-κB activation status. *J Cell Sci*. 2000;113:2671–2678.
32. Stranges S, Freudenheim JL, Muti P, Farinaro E, Russell M, Nochajski TH, Trevisan M. Greater hepatic vulnerability after alcohol intake in African Americans compared with Caucasians: a population-based study. *J Natl Med Assoc*. 2004;96:1185–1192.
33. Stewart SH. Racial and ethnic differences in alcohol-associated aspartate aminotransferase and gamma-glutamyltransferase elevation. *Arch Intern Med*. 2002;162:2236–2239.
34. Nilssen O, Averina M, Brenn T, Brox J, Kalinin A, Archipovski V. Alcohol consumption and its relation to risk factors for cardiovascular disease in the north-west of Russia: the Arkhangelsk study. *Int J Epidemiol*. 2005 April 15 [Epub ahead of print].
35. Sommers MS, Dyehouse JM, Howe SR, Wekselman K, Fleming M. "Nurse, I only had a couple of beers": validity of self-reported drinking before serious vehicular injury. *Am J Crit Care*. 2002;11:106–114.