General Clinical
Chemistry

Gamma Glutamyltranspeptidase and Long-Term Survival: Is It Just the Liver?

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Background: Increased gamma glutamyltranspeptidase (GGT) is associated with cardiovascular disease. To date, however, few studies with sufficient sample size and follow-up have investigated the association of GGT with all-cause mortality.

Methods: The relation of GGT to the risk of death was examined in a cohort of 283 438 first attendants (inpatients or outpatients) of the Vienna General Hospital with request for GGT analysis as part of a routine screening panel and was then monitored for up to 13 years. To evaluate GGT as a predictor, Cox proportional hazards models were calculated, which were adjusted for age and sex.

Results: In both men and women, GGT above the reference category (GGT $\geq$9 U/L in women, $\geq$14 U/L in men) was significantly ($P <0.001$) associated with all-cause, cancer, hepatobiliary, and vascular mortalities. Hazard ratios (HRs) for men and women were similar in all categories. Among patients who presented with GGT above the reference category for the first time, those younger than 30 years had higher all-cause mortality rates than did those older than 80 years (HR 1.5–3.3 vs HR 1–1.3 >80 years, respectively).

Conclusions: GGT is associated with mortality in both men and women, especially in patients younger than 30 years, and even high-normal GGT is a risk factor for all-cause mortality.

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The glycoprotein gamma glutamyltranspeptidase (GGT)[4] is located on membranes of cells with high secretory or absorptive activities, such as liver, kidney, pancreas, intestine, heart, brain, and prostate cells, but not in bone cells or erythrocytes *(1, 2)*. Serum GGT is increased in hepatobiliary diseases, with highest concentrations in cholestatic conditions *(1, 3)*.

Increased serum GGT has been reported in a wide variety of clinical conditions, including pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes, and alcoholism *(1, 4–6)*. Alterations in serum GGT concentrations are also found in patients who are taking medications such as phenytoin and barbiturates *(1)*, as well as in people with increased meat intake *(7)*. Serum GGT activity is affected by genetic and environmental factors, with heritability estimated at 0.52 *(8)*. The widespread availability and frequent use of liver chemistry tests have resulted in a dramatic increase in the number of abnormal GGT values that must be judged by physicians.

Although GGT is mainly seen as an indicator for hepatobiliary disease and alcohol consumption, several studies have shown its association with morbidity and mortality from other causes, especially cardiovascular disease (CVD) *(9)*. There have also been important advances in the definition of the associations of serum GGT with type 2 diabetes *(4, 10)* and with stroke *(11)*. Serum GGT concentrations are associated with increased risk of myocardial infarction and cardiac death *(9, 12–14)*. An independent prognostic role of GGT for all-cause mortality in males has also been reported *(15, 16)*.

In the present study we addressed the value of GGT as a marker for the identification of men and women with unfavorable prognoses for long-term survival. Early identification of high-risk patients would allow for optimiza-

[4] Nonstandard abbreviations: GGT, gamma glutamyltranspeptidase; CVD, cardiovascular disease; IQR, interquartile range; CI, confidence interval; HR, hazard ratio.

tion of therapeutic procedures in this subgroup during both the acute phase and at follow-up.

Materials and Methods

PATIENTS AND STUDY DESIGN

We included all attendants of the General Hospital of Vienna between June 1991 and September 2003 (n = 283 438). Inclusion criteria comprised first ever visit as outpatient or first ever hospitalization in the General Hospital of Vienna, and request for laboratory analyses of GGT for any reason at that time. GGT is analyzed on admittance to our hospital as part of a routine laboratory screening panel. Exclusion criteria were incomplete or missing data making clear patient identification impossible.

We evaluated the association of GGT with mortality. Because Austrian laws stipulate that all deaths have to be recorded in the central death registry, this approach allows for an almost complete follow-up of all patients. The few losses that occurred were due to spelling errors in names, which resulted in faulty record linkage, or disappeared persons, who are not recorded as deaths until 50 years after disappearance. We estimated that overall these losses were negligible for statistical analysis, because <1% of the study population was lost to follow-up. Because of the high frequency of autopsy in Austria (~35%) we estimate that diagnoses of disease leading to death are recorded correctly in >95% of patients.

LABORATORY ANALYSES

GGT was determined as a routine analysis for detection of liver damage. GGT concentrations were analyzed with an enzyme kinetic assay (Modular Hitachi 747 and Hitachi 917, Roche Diagnostics). Within-run and between-run imprecision (CV) was ~2.5%. Between-analyzer differences were <5%.

DETERMINATION OF OUTCOME VARIABLES

The main outcome variable was all-cause mortality defined as death occurring after determination of GGT before December 31, 2004. Noncancer mortality was defined as death occurring from causes other than neoplasia (defined as ICD9 groups 140–239 and ICD10 groups C00 to D48), and all-cause vascular mortality was considered to be present in case of ICD9 codes 390–459 and ICD10 groups I00 to I99. Mortality due to ischemic heart disease was defined as ICD9 diagnosis coded as 410–416 and ICD10 I20–I25, and death due to cerebrovascular disease was defined as ICD9 groups 430–438 and ICD10 groups I60–I69. Mortality due to hepatobiliary disease was defined as ICD9 diagnosis coded as 570–576 and ICD10 K70–K77, and death due to hepatoma was defined as ICD9 diagnosis coded as 155 and ICD10 as C22.

Observation time was calculated in years from the time point of GGT determination to death, or until the end of follow-up (December 31, 2004) in survivors. Age of patients was calculated at the time of GGT measurement.

GGT was classified separately for women and men according to Ruttmann et al. (9) as normal low (<9 U/L for women, <14 U/L for men), normal high (9 to 17, 14 to 27 U/L), moderately increased (18 to 26, 28 to 41 U/L), increased (27 to 35, 42 to 55 U/L), and highly increased (≥36, ≥56 U/L). The lowest category served as reference.

STATISTICAL ANALYSIS

The influence of GGT on all-cause mortality was assessed in a multivariate Cox regression model adjusted for sex and age as a continuous variable.

Baseline characteristics of the study patients, grouped according to reference values of GGT, are presented as percentages for dichotomous variables and medians and interquartile ranges (IQRs) for continuous variables, unless otherwise stated. Baseline characteristics were compared among categories with use of the χ^2 test for discrete variables and the Wilcoxon or Kruskal–Wallis rank-sum test for continuous variables, as appropriate. To evaluate the effect of different concentrations of GGT on mortality, relative risks and 95% confidence intervals (CIs) were calculated as hazard ratios (HR) derived from the Cox proportional-hazards regression model. Multivariable models were fitted with use of the demographic covariates age and sex. The assumptions underlying the proportional-hazards model (proportional hazards, lack of interaction, and linearity of continuous variables) were tested and found valid unless otherwise indicated.

To test for homogeneity between strata, we applied the log-rank and the generalized Wilcoxon rank sum tests. SPSS Version 12.0™ (SPSS Inc.) was used for all analyses.

ESTIMATE OF SAMPLE BIAS

To give an estimate of a possible sample bias, we compared the observed all-cause mortality in our study to the estimated mortality during our observation period in the general Austrian population. For this purpose, we calculated the individual probability of death within the hypothetical maximum observation period (date of analysis until the last day included in the record linkage analysis) considering individual age, sex and maximum observation time using the official Austrian mortality tables provided by Statistik Austria (http://www.statistik.at/fachbereich_03/Stt2000_2002.xls, 2005).

Mean expected and observed mortality and its respective 99% CIs for each GGT category were calculated and are shown in Fig. 1.

Results

PATIENTS

Between June 1991 and September 2003, a total of 283 438 community-dwelling patients attending the Vienna General Hospital underwent analyses of GGT. Clinical and laboratory data of patients are presented in Table 1. The median age of the patients was 50 years (range 0.01–103 years) with a moderate disbalance of males (128 777, 45.4%), reflecting the demographic distribution of a hos-
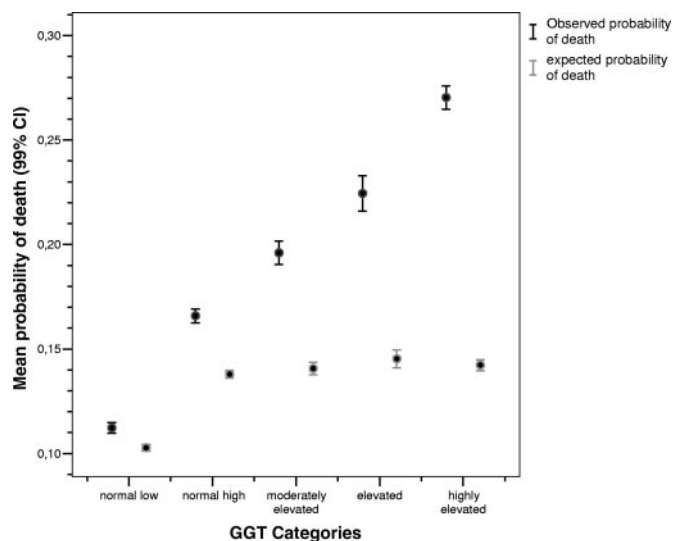
Fig. 1. Expected and observed mortality normalized to background mortality within the Austrian population in 283 438 patients.

Individuals with GGT within the reference category had no major increase in all-cause mortality, but patients with GGT values above the reference category had a worse outcome with increasing GGT concentrations. GGT was categorized as described in *Materials and Methods*.

pital-based patient cohort. Total time at risk was 2 089 332 person-years.

The vast majority of patients had laboratory values well within the normal reference interval, but in 91 936 patients (32.5%) GGT was higher (≥18 U/L in women and ≥28 U/L in men, moderately to highly increased; Table 1).

RELATIONSHIP OF GGT TO OVERALL SURVIVAL

The median follow-up time among the 283 438 patients was 7.6 years (IQR 3.8–11.1), yielding an observation period of 2 089 332 person-years. Kaplan–Meier estimates

of survival for all patients according to subgroups of GGT are shown in Fig. 2. Measurement of GGT provides strong predictive information about long-term survival in patients.

In a Cox regression analysis with GGT concentration as a categorical variable, the adjusted HRs for death of all patients (all-cause mortality) with GGT concentrations in the 2nd, 3rd, 4th, and 5th subgroups, compared with those in the 1st subgroup, were 1.2 (95% CI, 1.1 to 1.2; P <0.0001), 1.4 (95% CI, 1.3 to 1.4; P <0.0001), 1.6 (95% CI, 1.5 to 1.6; P <0.0001), and 2 (95% CI, 2 to 2.1; P <0.0001), respectively (Fig. 3; see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue5).

ASSOCIATIONS OF GGT CATEGORIES TO CANCER MORTALITY

A significant relation was found between GGT concentrations and cancer death in both sexes (P <0.001; see Table 1 in the online Data Supplement). Adjusted HRs rose from 1.3 to 2.3 according to GGT subgroups (normal high to highly increased; Fig. 3).

ASSOCIATIONS OF GGT WITH NONCANCER MORTALITY

In both men and women, GGT was significantly (P <0.001) associated with noncancer mortality (see Fig. 2 in the online Data Supplement). HRs increased from 1.1 to 1.9 for this mode of death according to GGT categories (normal high to highly increased; Fig. 3).

Within the general category of noncancer deaths, both mortality from all vascular causes and mortality specifically from ischemic heart disease were significantly (P <0.001) correlated with serum concentrations of GGT activity. Adjusted HRs increased from 1.3 and 1.2, respectively, to 1.6 according to GGT categories (normal high to highly increased; Fig. 3).

Table 1. Clinical and laboratory data of patients.

|	Males (128 777/45.4%)	Females (154 661/54.6%)	Total (283 438)
Median age at entry, years (IQR)	51 (35–64)	49 (33–66)	50 (34–65)
Median observation period, years (IQR)	7.3 (3.6–11.0)	7.8 (4.0–11.2)	7.6 (3.8–11.1)
Person-years at risk	922 387	1 166 945	2 089 332
Mortality (%)	25 852 (20.1%)	21 911 (14.2%)	47 763 (16.9%)
Noncancer death (%)	15 074 (11.7%)	12 446 (8.0%)	27 520 (9.7%)
Death due to cancer (including hepatoma) (%)	10 778 (8.4%)	9465 (6.2%)	20 243 (7.2%)
Death due to hepatobiliary disease (%)	1844 (1.4%)	962 (0.6%)	2806 (1.0%)
All cause vascular mortality (%)	9062 (7.0%)	8101 (5.2%)	17 163 (6.1%)
Death due to ischemic heart disease (%)	4714 (3.7%)	3295 (2.1%)	8009 (2.8%)
Cerebrovascular death (%)	1304 (1.0%)	1491 (1.0%)	2795 (1.0%)
GGT concentrations			
Normal low (%)	44 818 (34.8%)	60 417 (39.1%)	105 235 (37.1%)
Normal high (%)	41 636 (32.3%)	44 631 (28.9%)	86 267 (30.4%)
Moderately elevated (%)	15 531 (12.1%)	17 929 (11.6%)	33 460 (11.8%)
Elevated (%)	7501 (5.8%)	8596 (5.6%)	16 097 (5.7%)
Highly elevated (%)	19 291 (15.0%)	23 088 (14.9%)	42 379 (15.0%)
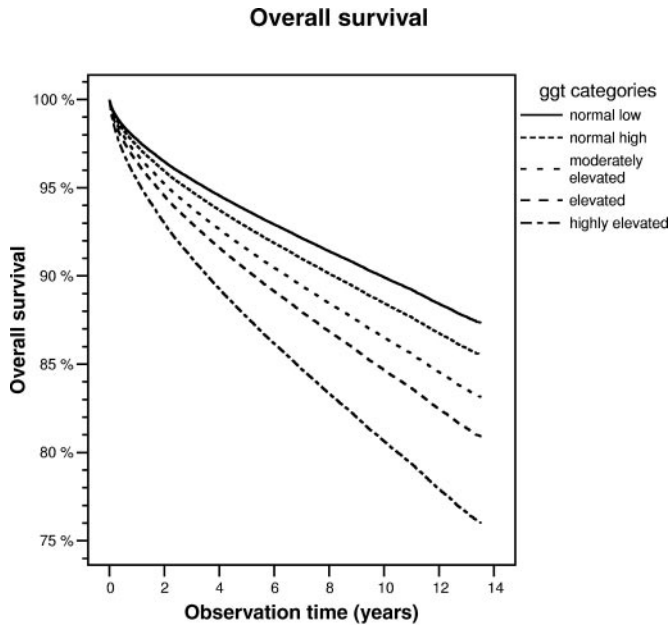
Overall survival

Fig. 2. Overall survival among patients according to subgroups of GGT in 283 438 patients.

GGT was categorized as described in *Materials and Methods*. Values for the respective subgroups were added up to present the entire population. Survival curves were calculated with a Cox proportional hazards model that was adjusted for sex and age.

As expected, GGT above the reference interval was a sensitive predictor of hepatobiliary-related death (cancer and noncancer causes; HR increased from 1.4 to 18.5 from normal high to highly increased GGT; Fig. 4).

EFFECT OF AGE AND SEX

Age and male sex were significant predictors of increased all-cause mortality, but HRs for different GGT categories did not significantly differ between men and women (see Table 1 in the online Data Supplement).

To evaluate the interaction of age and GGT we divided the patients into age groups of 10-year increments. Inter-
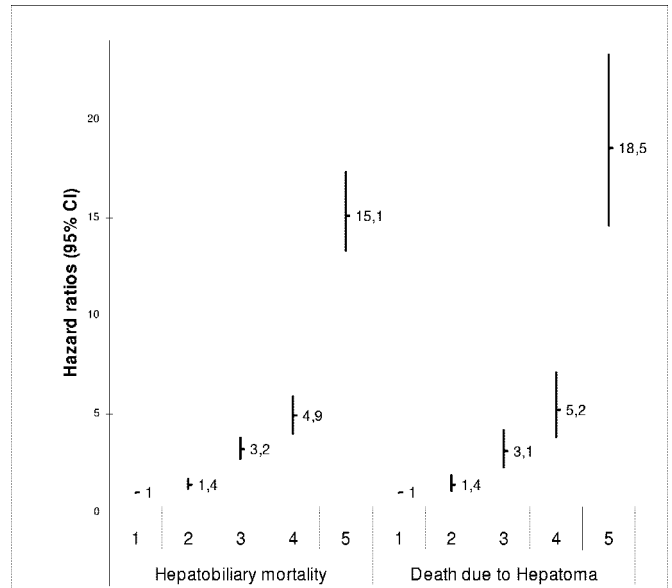

Fig. 4. Hepatobiliary and hepatoma mortality according to subgroups of GGT.

GGT was classified as described in *Materials and Methods*. The lowest category served as reference category.

estingly, individuals below the age of 30 years, who presented with GGT values above the reference category for the first time, had far worse outcome (HR 1.5–3.3 for all-cause mortality) than did older individuals (HR 1–1.3 for those >80 years for all-cause mortality; see Table 2 in the online Data Supplement).

Discussion

Recent studies have suggested an independent role for GGT in the pathogenesis and clinical evolution of CVDs brought on by atherosclerosis (5, 6). However, the long-term effects of increased GGT have not been studied sufficiently.

To the best of our knowledge, the present study is the largest retrospective investigation addressing specifically
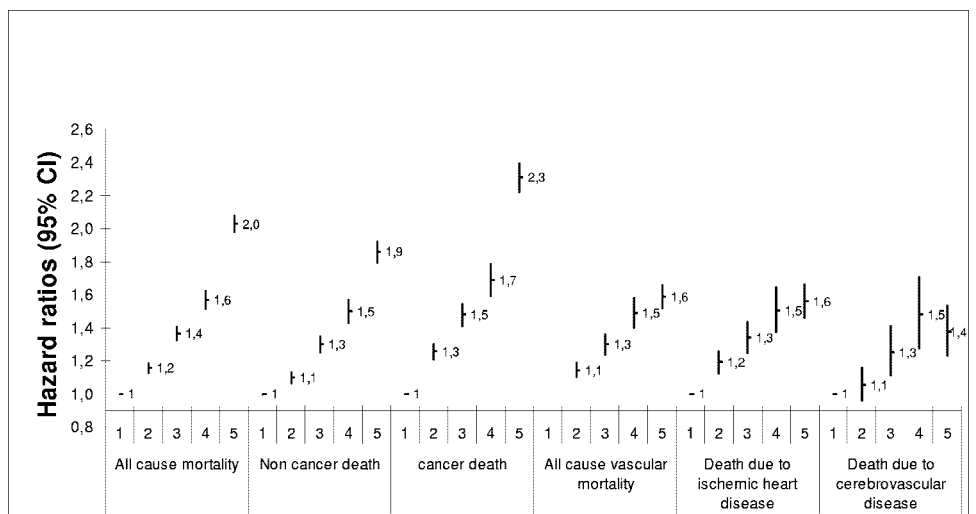

Fig. 3. Adjusted mortality among patients according to subgroups of GGT.

GGT was classified as described in *Materials and Methods*. The lowest category served as reference category.

the topic of GGT's prognostic value for several modes of death. Our large cohort study suggests that the measurement of GGT provides strong predictive information about long-term survival. Surprisingly, a similar observation was made for GGT values lower than the commonly accepted breakpoint for diagnosis of organ damage. GGT values only slightly higher than the reference category ($\geq$9 U/L in women and $\geq$14 U/L in men) were associated with increased mortality rates compared with the age-matched Austrian population derived from the official Austrian death registry database (Fig. 1). Mortality rates >25% were observed in the highest GGT category (Fig. 1).

We observed a stronger prognostic significance of GGT in younger persons (<30 years), who might especially benefit from risk stratification, underlining the recent findings of other investigators (9, 14). Although an effect of higher rates of hazardous drinking in younger persons cannot be excluded, the independent prognostic role of GGT from alcohol consumption, which can also exert a protective effect, has been shown in several studies (12, 17). In addition, in persons with coronary artery disease, a relative decrease of total serum GGT was observed in older persons compared with younger ones (18).

The results of this study did not show an effect of sex on the relationship of GGT to mortality, although male sex is an established risk factor for liver damage and CVD.

An overlap between GGT as a marker of current disease and GGT as a prospective risk factor is unlikely because, as shown in Fig. 2, the survival curves continually diverged across almost 14 years and did not show an initial drop followed by parallel lines.

Our results extend currently available knowledge about the value of GGT in a representative population at risk and widen the spectrum of its potential clinical usefulness as a prognostic tool for prediction of long-term mortality (9). In addition, it is tempting to speculate that a breakpoint value of $\geq$18 U/L in women and $\geq$28 U/L in men potentially fails to identify patients who are at increased risk of death.

POTENTIAL MECHANISMS OF INCREASED MORTALITY IN PATIENTS WITH MODERATELY INCREASED GGT

An increasing number of population studies (12, 13, 15, 16) have evaluated the relationship between serum GGT activity and mortality, since the observation of Conigrave et al. in 1993 (17) that indicated a prognostic value of GGT for mortality, irrespective of hepatic disease or alcohol consumption.

From the associations between increased serum GGT and features of the metabolic syndrome (9, 15)(16), especially type 2 diabetes (4, 10) and hypertension (4), one may expect an increased risk of stroke (11) and, as previously described, cardiovascular morbidity and mortality.

GGT participates in the metabolism of cellular glutathione, and serum GGT, within its reference interval, has

been proposed as a marker of oxidative stress (19). The presence of GGT enzyme activity has been demonstrated within coronary atherosclerotic plaques from endoarterectomy specimens (20). The oxidative stress mediated by GGT could thus play a relevant role in the evolution of atherosclerotic plaque and its instabilization. The evidence is growing in favor of a detrimental role of GGT, triggering a prooxidant action within the atherosclerotic plaque (5). A strong relation of serum GGT to CRP has been described, further pointing to the role of oxidative stress as a key component of many reactions associated with chronic inflammation (21) Serum GGT concentration has been thus proposed as a sensitive marker of epidemiologic transition portending a continuing rise in incidences of metabolic and CVDs in the coming years (22).

The expression of GGT is often significantly increased in tumors (1), and has been repeatedly suggested to have a role in tumor progression, invasion, and drug resistance.

THERAPEUTIC MEASURES FOR LOWERING GGT

In addition to known measures, such as avoidance of alcohol consumption and hepatotoxic drugs, a number of other variables, such as coffee consumption (23), weight loss (24), smoking cessation (25), and changes in nutrition (7), have been described to be beneficial in reduction of serum GGT. Both cutaneous and surgical revascularization are able to abolish the GGT prognostic value, confirming its link with the evolution of atherosclerotic plaque (12).

STRENGTHS AND LIMITATIONS OF THIS STUDY

We evaluated the association of GGT with all-cause mortality in a large hospital-based population (n = 283 438) over a long time period and using the central Austrian death registry, yielding an observation period of 2 089 332 person-years. The study design facilitated an almost complete follow-up of all patients, with negligible loss to follow-up of <1% of the study population.

In contrast to clinical diagnoses, which are subject to examiner bias and usually vary due to different diagnostic criteria, death is usually reliably recorded and misdiagnoses are less likely. We estimate that diagnoses leading to death were recorded correctly in ~95% of the cases, owing to the high autopsy frequency in Austria (35%), and the Austrian legal situation.

This study has several limitations. We are well aware that our hospital-based study population is not necessarily a representative sample of the healthy Austrian population and might be preselected for worse outcome. In an attempt to provide an estimate of selection bias within our sample population, we calculated the difference between the expected overall mortality in the Austrian population and the observed mortality in our study (Fig. 1). Within the reference category no major differences between expected and observed mortality were observed, indicating that overall mortality in this category was comparable to the Austrian population, whereas mortality rates in-

creased by up to 25% in patients with GGT values above the reference category.

Another concern might be the incidence of established liver disease in our population. However, this comprised only a relatively small number of patients in our cohort (2.1% in the lowest and 14.6% in the highest category) and thus does not change the overall message conveyed by our results. Thus, we did not observe evidence of a major selection bias.

The retrospective design is an evident limitation. Therefore, adjustment was possible only for age and sex in our analysis, and we could not adjust for other important confounders that have an influence on serum concentrations of GGT (4, 5, 7, 23). Thus, we cannot determine whether GGT is an independent risk factor, and the HRs might be overestimates compared with models allowing control for additional risk factors. GGT was, however, still associated with a significant increase in mortality from all causes and ischemic heart disease (15, 16), after adjustment for personal characteristics and biologic variables in several studies.

Another objection is the influence of preexisting disease, in particular diabetes and established CVD, on the association of GGT with mortality. With preexisting ischemic heart disease, the severity of the underlying myocardial damage is the determining factor (12, 16). Previous studies assessing mortality among the general population by use of GGT did predict CVD mortality but not cancer death (16). The association between cancer deaths and GGT might be attributable to the underlying illness itself. As noted above, the expression of GGT is often significantly increased in tumors (1). Overall, survival curves did not differ between cancer and noncancer deaths in this study (see Figs. 1 and 2 in the online Data Supplement). Another explanation might be the relation to lifestyle and socioeconomic variables not adjusted for in this study, although some of these, such as cigarette smoking, are a risk factor for both cancer and CVD.

In summary, this study investigated the relation of GGT to long-term mortality in a central European cohort of 283 438 individuals. The results provide evidence of strong associations between GGT and several modes of mortality in both sexes and in younger persons. GGT is a strong risk factor for all-cause mortality and thus allows for the identification of patients who are at increased risk of unfavorable outcome. The recent insights into the role of GGT not only have practical clinical applications in risk stratification but also may be useful in targeting of therapy.

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