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Association between serum gamma-glutamyltransferase and cardiovascular mortality varies by age: the Minnesota Heart Survey

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Background Although serum γ-glutamyltransferase (GGT) predicted cardiovascular diseases (CVD) in prospective studies and may be useful in risk assessment, prediction in older adults was weaker in several studies.

Methods We performed a nested case–control study with 5–12-year follow-up in 137 CVD deaths and 249 controls (frequency-matched on age, sex, and examination year, age range 26–85 years).

Results An age interaction of serum GGT and CVD mortality (P value for interaction = 0.02) was observed. After adjusting for known CVD risk factors, compared with the lowest tertile, odds ratios (95% confidence intervals) in participants less than 70 years (half the participants) were: middle tertile: 2.17 (0.68–6.97), top tertile up to GGT less than 50 U/l: 3.54 (1.07–11.7), and GGT ≥ 50 U/l: 4.69 (1.16–18.9). In participants aged more than or equal to 70 years, GGT was not related to CVD. Well-known demographic and health behavior associations with serum GGT were observed only in controls among participants aged less than 70 years.

Conclusion Our findings suggest that serum GGT within its normal range can predict CVD mortality in those aged less than 70 years, but may have limited usefulness for risk assessment in older adults. *Eur J Cardiovasc Prev Rehabil* 00:000–000 © 2008 The European Society of Cardiology

Introduction

Several population-based studies have reported that serum γ-glutamyltransferase (GGT) predicts incident cardiovascular diseases (CVD) [1–6]. In a recent meta-analysis of fully adjusted results of 10 prospective studies, a change of 1 U/l of GGT was associated with a 20% increase in the risk of coronary heart disease (CHD) and a 54% increase in the risk of stroke [7]. Although the underlying mechanism is still unclear, predictability, technical simplicity, and inexpensive measurement have

led some researchers to propose serum GGT for risk assessment in clinical and epidemiological studies [8].

Several studies, however, have shown that the predictive ability of serum GGT varies by age: [1,2] predictability was stronger in the relatively younger age group, less than 60 years, than among older participants. As vascular outcomes more frequently occur among older persons, inability of serum GGT to predict vascular events in the elderly would substantially limit its use in risk assessment. Considering that epidemiological interactions sometimes fail to replicate across studies, confirmation of age-related differences would be helpful in deciding how and when to use serum GGT in screening.

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This nested case–control study was performed to explore whether the association between serum GGT and CVD mortality differed by age. Further, to help find an explanation for the expected interaction, we examined if associations of serum GGT with demographic and health behavior variables differed by age.

Methods

Minnesota Heart Survey and selection of cases and controls

Briefly, the Minnesota Heart Survey [9–11] is an ongoing population-based surveillance on risk factors for CHD, initiated in 1980, based on cluster sampling of residents of the Minneapolis St Paul, MN 7 county metropolitan area and aiming to characterize metropolitan area-wide time changes in CVD risk factor levels. Here we used data and stored blood samples from the surveys conducted in the years between 1990–1992 and 1995–1997, with mortality follow-up by matching with a registry of all Minnesota death certificates through 31 December 2002. We identified 173 CVD deaths (International Classification of Diseases ninth revision codes 390–459 or tenth revision codes I00–I99). Controls were frequency-matched on age within each sex and survey ($n = 343$). Therefore, all participants examined in 1990–92 were followed for 10–12 years and all those examined in 1995–1997 were followed for 5–7 years. Age range was 26–85 years. Excluding those with no stored serum left 137 CVD deaths and 249 controls (three of whom had died from non-CVD). Disproportionately more controls than cases were lost for absence of blood sample: we included 96 cases and 198 controls from the 1990–1992 survey compared with 41 cases and 51 controls from the 1995–1997 survey.

Measurement

Activity of serum GGT was assessed in nonfasting participants using an Ortho Clinical Diagnostics (Rochester, New York, USA) Vitros 950 analyzer which uses a thin film, kinetic reflectance spectrophotometry method which uses L-g-glutamyl-p-nitroanalide and glycylglycine as reagents and monitors release of p-nirtoanaline at 400 nm. Serum GGT values were similar across study periods: median and interquartile ranges were 22 U/l and 17–29 U/l for 1990–1992 and 22 U/l and 17–33 U/l for 1995–1997. Total cholesterol was assayed with an AutoAnalyzer II (Technicon Corporation) nonenzymatically between 1990 and 1992, and with an enzymatic method thereafter. Serum high-density lipoprotein (HDL) cholesterol was measured after precipitation of non-HDL cholesterol with heparin and Mn^{2+} (1990–1992) [12] or magnesium dextran sulfate (1995–2002) [13].

Height was measured in stocking feet with a wooden triangle and a rigid ruler attached to a wall. Weight was measured without coat and shoes with a balance beam scale, calibrated daily with a 22.7-kg weight. We computed body mass index (BMI) as weight (kg)/height squared (m^2). Systolic and fifth phase diastolic blood pressures were measured with a random zero sphygmomanometer (Hawksley, West Sussex, United Kingdom) throughout the study by trained technicians [14]. The average of two blood pressure measurements taken 1 min apart was presented.

Information on leisure-time physical activity, smoking, and the consumption of alcoholic beverages was obtained by interviewer-administered questionnaires. For leisure-time physical activity, questions were asked about the intensity, duration, and frequency of exercise sessions. A score (metabolic equivalent h/week) was derived.

Data analysis

The association between serum GGT and CVD mortality was assessed in tertiles, based on the GGT distribution in controls. To isolate those above the laboratory reference range, the highest tertile of serum GGT activity was split at 50 U/l. Odds ratios (OR) and 95% confidence intervals for the relation of serum GGT with cardiovascular mortality were obtained from logistic regression models. We computed P for trend in a model in which we coded the four categories 0,1,2,3 and treated that as a continuous variable. Use of median values of serum GGT to represent each category did not change the trend test. In multivariable analysis, we first included BMI, cigarette smoking, physical activity, and the intake of alcohol. This model was then extended with serum total and HDL cholesterol, systolic blood pressure, and (nonfasting) serum glucose. Additional adjustment for study period did not influence the findings (data not shown). We substituted median values computed from nonmissing control group data for missing alcohol consumption (participants), systolic blood pressure (one participant), HDL cholesterol (12 participants), and serum glucose (one participant); exclusion of these 16 individuals did not change any conclusions.

Effect modification by age was assessed by dichotomizing age at its median value of 70 years; there was insufficient sample to dichotomize at the age of 60 years, the cut-off value that was used in two other studies [1,2]. Analyses were conducted with SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

No significant differences in age, sex, BMI, physical activity, total and HDL cholesterol, blood pressure, smoking, diabetes, or use of aspirin or medication for lipid or blood pressure lowering were seen between the 386 participants in whom stored blood samples were available versus the 130 in whom there was no sample. Of the 137 cases, 70 (51%) had died of CHD, 28 (20%) of stroke, 26 (19%) of other atherosclerotic CVD, and 13

(9%) of nonatherosclerotic CVD. Ninety-five percentage of cases and 97% of controls were Caucasian (Table 1). Overall, cases were more likely to smoke, had higher average systolic blood pressure and antihypertensive treatment, nonfasting serum glucose and diabetes, serum GGT, and lower average serum HDL cholesterol. These differences were mutually independent, apart from the higher prevalent diabetes in the cases, which lost statistical significance in multiple regression, including adjustment for GGT (data not shown).

Across all ages, serum GGT activity of 50 U/l and higher was significantly positively related to CVD mortality when clinical variables were not adjusted, but no association was observed within its normal range in any model (Table 2). The relation between GGT and CVD mortality differed by age (*P* for interaction = 0.02). In those aged less than 70 years, serum GGT was positively associated with CVD mortality with a clear dose–response relation. After adjusting for known CVD risk factors, compared with the lowest tertile, OR (95% confidence

Table 1   Baseline (1990–1992 or 1995–1997) characteristics of the total study population by case–control status, the Minnesota Health Survey

Variable	Cases (*n* = 137)	Controls (249)	*P*[a]
Sex, *n* (%)[b]			
Men	78 (56.9)	140 (56.2)	0.87
Age (years)[b]			
Mean (SD)	69.3 (11.8)	67.8 (12.1)	0.27
Range	33–85	26–84	
BMI (kg/m²)			
Mean (SD)	28.0 (5.3)	27.3 (4.3)	0.16
Range	18–52	14–40	
≥ 25 kg/m², *n* (%)	99 (72.3)	179 (71.9)	0.97
Current smoker, *n* (%)	29 (21.2)	21 (8.4)	<0.001
Alcohol use, *n* (%)			
Yes	57 (41.6)	101 (40.6)	0.84
Number of alcoholic beverages per week in consumers, median (IQR)	7 (4–15)	6 (2–11)	0.10
Physical activity score (MET hours/week)	8.1 (12.5)	7.7 (10.7)	0.75
Blood pressure (mmHg)			
Systolic	136.5 (19.6)	129.9 (18.8)	0.001
Diastolic	75.7 (12.7)	74.6 (10.5)	0.34
Antihypertensive use, *n* (%)	57 (41.9)	63 (25.3)	<0.001
Hypertension, *n* (%)[c]	92 (68.2)	107 (43.2)	<0.001
Serum cholesterol (mg/dl)			
Total	220 (42)	217 (38)	0.55
HDL	42 (14)	45 (15)	0.04
Medication for high cholesterol, *n* (%)			
Hypercholesterolemia, *n* (%)[d]	57 (41.6)	84 (33.7)	0.12
Diabetes (self-reported), *n* (%)	28 (20.4)	19 (7.6)	<0.001
Aspirin use, *n* (%)	51 (37.0)	84 (33.7)	0.52
Serum GGT (U/l), median (IQR)	23 (18–40)	21 (17–28)	0.01
Serum glucose (nonfasting) (mg/dl)	130 (62)	109 (35)	0.0003

Shown are means (SDs) unless otherwise stated. [a]On the basis of two-sample *t*-test, Mann–Whitney *U* test, or χ^2 test. [b]Matching factor. [c]Defined as SBP >140 mm Hg, DBP >90 mm Hg, or the use of antihypertensive medication. [d]Defined as serum total cholesterol >200 mg/dl. DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; IQR, interquartile range; MET, metabolic equivalent; SBP, systolic blood pressure.

intervals) in participants aged less than 70 years were 2.17 for the middle tertile, 3.54 for the top tertile up to GGT activity less than 50 U/l, and 4.69 for levels more than or equal to 50 U/l. In contrast, among participants aged more than or equal to 70 years, serum GGT was not associated with CVD mortality, possibly excepting a nonsignificant increased risk in abnormal serum GGT activity more than or equal to 50 U/l. Excluding 13 cases of nonatherosclerotic CVD death did not change the results (data not shown). Results were consistent in separate analysis by study period. OR for age less than 70 years were 1.00, 1.38 (0.36–5.25), 3.09 (0.86–11.1), and 4.32 (0.91–20.4) (*P* for trend = 0.03) for 1990–1992 after adjusting for all covariates and 1.00, 17.6 (1.00–310.7), 14.0 (0.70–267.4), and 22.0 (0.98–494.3) (*P* for trend = 0.09) for 1995–1997 after adjusting for age and sex (the fully adjusted models in 1995–1997 were unstable because of small sample size). Serum GGT for ages more than or equal to 70 years was not associated with CVD mortality in either study period.

The association of serum GGT with most demographic and health behavior variables (Table 3) also varied by age, although the *P* value for age interaction was significant only for sex. For age less than 70 years, male sex, BMI, overweight (BMI ≥ 25 kg/m²), and alcohol drinking were significantly associated with serum GGT. Although both cigarette smoking and physical activity failed to reach statistical significance, serum GGT showed the expected positive trend with smoking and inverse trend with physical activity at ages less than 70 years, especially within normal range of serum GGT. For ages, however, more than or equal to 70 years, only BMI showed a marginal significance with serum GGT.

Discussion
In this nested case–control study, serum GGT was not associated with CVD morality across all participants, except the increasing tendency in the highest (abnormal) range. CVD mortality, however, was strongly associated with serum GGT within its range in participants aged less than 70 years, independent of conventional CVD risk factors. Our finding is consistent with two earlier prospective studies [1,2] in which GGT was more strongly positively related to CVD in participants aged less than 60 years versus participants aged less than or equal to 60 years. In another study, serum GGT was more strongly positively associated to all-cause mortality in younger than in older persons [15].

It may be important in the interpretation of epidemiological findings on serum GGT that the risk for clinical outcomes started to increase even across its low normal values. Here, the estimated relative risk for CVD mortality in those aged less than 70 years was already 2.17 for serum GGT 18–25 U/l compared with serum

Table 2   Odds ratios (ORs) and 95% confidence intervals (CIs) of CVD mortality by levels of serum GGT: the Minnesota Heart Survey

	Baseline serum GGT level (U/l)				
	<18	18 to <25	25 to ≤ 50	>50	P trend
All ages (years)					
Cases/controls	33/75	43/88	36/68	26/18	
Odds ratio (95% CI)					
Model 1[a]	1.00	1.09 (0.62–1.90)	1.25 (0.70–2.23)	3.59 (1.70–7.60)	<0.01
Model 2[b]	1.00	1.01 (0.57–1.80)	1.08 (0.59–1.98)	2.68 (1.22–5.88)	0.05
Model 3[c]	1.00	0.91 (0.50–1.65)	0.88 (0.47–1.66)	1.88 (0.82–4.33)	0.37
Age less than 70 years					
Cases/controls	7/38	14/40	20/34	16/12	
Odds ratio (95% CI)					
Model 1[a]	1.00	2.28 (0.79–6.56)	3.87 (1.37–10.9)	9.07 (2.80–29.4)	<0.01
Model 2[b]	1.00	2.10 (0.68–6.45)	3.64 (1.18–11.2)	6.70 (1.83–24.6)	<0.01
Model 3[c]	1.00	2.17 (0.68–6.97)	3.54 (1.07–11.7)	4.69 (1.16–18.9)	0.02
Age more than or equal to 70 years					
Cases/controls	26/37	28/48	16/34	10/6	
Odds ratio (95% CI)					
Model 1[a]	1.00	0.81 (0.40–1.64)	0.68 (0.31–1.49)	2.34 (0.75–7.30)	0.67
Model 2[b]	1.00	0.85 (0.42–1.75)	0.68 (0.31–1.51)	2.35 (0.72–7.66)	0.72
Model 3[c]	1.00	0.76 (0.35–1.62)	0.51 (0.22–1.20)	1.63 (0.45–5.82)	0.63

[a]Adjusted for matching factors age (continuous) and sex. [b]Adjusted for matching factors age (continuous) and sex, BMI (continuous), current cigarette smoking, alcohol use (continuous), physical activity (continuous). [c]Adjusted as in model 2 and serum total cholesterol (continuous), serum HDL cholesterol (continuous), systolic blood pressure (continuous), and nonfasting serum glucose (continuous). CVD, cardiovascular diseases; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein.

Table 3   Association of serum GGT with demographic or health behavior variables by age group in the control group: the Minnesota Heart Survey

	Baseline serum GGT level (U/l)				
	<18	18 to <25	25 to ≤ 50	>50	P trend
Age less than 70 years					
Number of participants	38	40	34	12	
Male (%)	50.0	82.5	91.2	91.7	<0.01
BMI (kg/m^2)	25.6	27.7	28.7	28.8	<0.01
Obesity (BMI ≥ 25 kg/m^2, %)	52.6	77.5	88.2	91.7	<0.01
Smoker (%)	13.2	10.0%	14.7%	25.0%	0.38
Drinker (%)	36.8	57.5	64.7	75.0	<0.01
Physical activity score (MET hours/week)	9.6	8.1	5.6	7.2	0.18
Age more than or equal to 70 years					
Number of participants	37	48	34	6	
Male (%)	43.2	35.4	26.5	66.7	0.63
BMI (kg/m^2)	26.6	26.4	27.9	30.4	0.05
Obesity (BMI ≥ 25 kg/m^2, %)	70.3	60.4	76.5	100.0	0.20
Smoker (%)	2.7	6.3	0	0	0.46
Drinker (%)	21.6	31.3	26.5	33.3	0.48
Physical activity score (MET h/week)	5.2	9.6	8.l	4.9	0.48

GGT, gamma-glutamyltransferase; MET, metabolic equivalent.

GGT less than 18 U/l. Other clinical outcomes [16–18] show similar increased risk across the normal range of GGT. Furthermore, many population-based studies [1–6] observed that serum GGT within its normal range was strongly associated with various demographic and health behavior variables. The positive associations we observed with elevated serum GGT level were male sex, BMI, smoking, alcohol consumption, and lack of exercise. Similar to the CVD outcome, these associations were predominantly among control participants aged less than 70 years. Although liver pathology is suspected when GGT is abnormal, the increase in risk within the normal range of GGT led us to speculate about physiological roles of GGT that may be involved in these associations.

We [19] have pointed out that serum GGT may predict vascular events and other clinical outcomes as a marker of oxidative stress related to glutathione (GSH) metabolism. Others [20] have noted that the role of GGT in nonalcoholic fatty liver disease may be relevant, though it seems likely that liver-related enzymes would be elevated in nonalcoholic fatty liver disease, and that this pathway would be less relevant to GGT in its normal range [21]. Finally, it could be relevant that serum GGT participates in a critical step in metabolizing GSH conjugates with xenobiotics.

Recently, we reported that serum or urinary concentrations of heavy metals such as lead or cadmium and serum concentrations of persistent organic pollutants such as dioxin or some pesticides had clear positive dose–response relations with serum GGT within its normal range [22–25], possibly reflecting the amount of xenobiotics conjugated with GSH. In fact, our hypotheses on serum GGT first as a marker of oxidative stress [19], then of xenobiotics, led us to focus on xenobiotic persistent organic pollutants to explain why various clinical outcomes are associated with serum GGT [21]. Of these physiologic roles, the concept of serum GGT as a marker of xenobiotics is the most consistent with absence of association of serum GGT with CVD mortality in those aged more than or equal to 70 years. Specifically, there is

progressive impairment of the ability of an organism to maintain homeostasis [26] and reduced hepatic ability to clear xenobiotics in older ages [27]. As serum GGT may increase proportional to the amount of GSH conjugates, rather than the amount of xenobiotics themselves, serum GGT levels in older ages may not reflect the extent of exposure to xenobiotics as well in older as younger ages.

Strengths of this study include its prospective, population-based design. Limitations are also present. First, we used CVD death, not incident CVD. Some nonfatal incident CVD cases may be included as controls. This type of bias, however, may attenuate the true association of serum GGT with CVD mortality. Second, our study was small and numbers of CVD deaths, especially for age less than 60 years, were few. The age cut-point used was higher than in earlier studies [1,2], which limits comparability across studies. Finally, there was a larger proportion of missing blood samples in the 1995–1997 controls than in the 1990–1992 controls, but bias was apparently minimal, given consistent findings within each survey.

In conclusion, our nested case–control study showed that serum GGT predicted CVD mortality only among persons aged less than 70 years. Serum GGT activity may be useful in risk assessment up to age 70 years, but its physiologic characteristics may limit its usefulness for the risk assessment in the elderly. Impaired hepatic ability to clear xenobiotics in old ages as an explanation of the lack of association between serum GGT and CVD mortality in the elderly is a speculation that should be studied by others.

Acknowledgements

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