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CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Elevated Serum Alanine Aminotransferase and γ-Glutamyltransferase and Mortality in the United States Population

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Background & Aims: **Elevated serum alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) activities are markers of liver injury, but may also be associated with other diseases and death. In a prospective, national, population-based sample, we examined whether elevated ALT and GGT were associated with increased risk of all-cause and disease-specific mortality.** ***Methods:*** **Death certificate–based 12-year mortality was analyzed among 14,950 adult participants in the third US National Health and Nutrition Examination Survey, 1988–1994, who were negative for markers of viral hepatitis B and C. Abnormal ALT was defined as >30 U/L in men or >19 U/L in women, and abnormal GGT as >51 U/L in men or >33 U/L in women.** ***Results:*** **Cumulative mortality was 13.9% from all causes, including 4.2% from cardiovascular disease, 4.2% from neoplasms, 0.44% from diabetes, and 0.13% from liver disease. In multivariate-adjusted analyses, elevated ALT was not associated with all-cause mortality (hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.88–1.6). ALT elevation was associated with deaths from liver disease (HR, 8.2; 95% CI, 2.1–31.9), but not from cardiovascular disease (HR, 0.90; 95% CI, 0.56–1.4), neoplasms (HR, 1.0; 95% CI, 0.65–1.5), or diabetes (HR, 2.4; 95% CI, 0.65–9.1). All-cause mortality increased with elevated GGT (HR, 1.5; 95% CI, 1.2–1.8), as did mortality from liver disease (HR, 13.0; 95% CI, 2.4–71.5), neoplasms (HR, 1.5; 95% CI, 1.01–2.2), and diabetes (HR, 3.3; 95% CI, 1.4–7.6), but not from cardiovascular disease (HR, 1.3; 95% CI, 0.80–2.0).** ***Conclusions:*** **In the US population, elevated GGT was associated with mortality from all causes, liver disease, cancer, and diabetes, while ALT was associated only with liver disease mortality.**

The most commonly used marker for chronic liver disease is elevated alanine aminotransferase (ALT) activity. Although produced by other organs, it is found predominantly in hepatocytes and is considered a specific marker for liver injury. Few studies have investigated the relationship of abnormal ALT with mortality. Higher ALT was associated with mortality from all causes in some studies,[1–3] but not others.[4,5] Data on mortality from specific causes are even more limited.[1] To our knowledge, the relationship of ALT with mortality outcomes has not been established in the general US population. Elevated γ-glutamyltransferase (GGT) results from fatty liver disease, both alcoholic and nonalcoholic, cholestatic liver disease, and induction by drugs such as phenytoin. Although detection and diagnosis of liver disease is its primary clinical use, GGT is a nearly ubiquitous epithelial enzyme that is responsible for catabolism of extracellular glutathione. In addition to liver disease, GGT has been associated with high all-cause mortality, cardiovascular disease (CVD) incidence and death, diabetes, and cancer incidence and death.[4,6–20]

Using death certificate data from the third National Health and Nutrition Examination Study (NHANES III), a prospective, population-based sample, we examined whether elevated ALT and GGT were associated with increased mortality overall and from specific causes. The multitude of other variables collected in NHANES III allowed evaluation of potential confounders for mortality.

Methods

NHANES III was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Con-

Abbreviations used in this paper: ALT, alanine aminotransferase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; HR, hazard ratio; ICD, International Classification of Diseases; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey.

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trol and Prevention (CDC).[21] It consisted of interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample of the civilian, noninstitutionalized population aged 2 months and older, with oversampling of the elderly, non-Hispanic blacks, and Mexican Americans. The study was approved by the CDC Institutional Review Board, and all participants provided written consent to participate. Of 23,258 sampled persons aged 20 years and older, 16,573 (71%) attended an examination at a mobile examination center. For the primary analyses, we excluded participants with hepatitis B (positive serum hepatitis B surface antigen) or hepatitis C (positive serum hepatitis C antibody) (n = 453). We excluded persons with missing data on hepatitis B or hepatitis C (n = 1047), serum ALT (n = 112), or mortality status (n = 11). The sample for analysis of ALT, therefore, consisted of 14,950 participants. An additional 3320 participants were surveyed before GGT was added to the protocol and, therefore, were excluded from analyses of GGT, resulting in an analysis sample of 11,630. A serum sample was collected and shipped weekly at −20°C. Serum ALT and GGT concentrations were assayed by using a Hitachi 737 Analyzer (Boehringer–Mannheim Diagnostics, Indianapolis, IN) at the White Sands Research Center, Alamogordo, New Mexico.[22] Abnormal liver enzymes were defined based on recommended cutoffs as a serum concentration of >30 U/L for men and >19 U/L for women for ALT,[23] and of >51 U/L for men and >33 U/L for women for GGT.[22]

Participants were passively followed up for mortality through December 31, 2000, using a probabilistic match that linked NHANES III participants with National Death Index records to ascertain vital status and cause of death This matching methodology is well established and has been described in detail.[24] The accuracy of the NHANES III–National Death Index matching methodology was high in a validation study that applied it to the NHANES I Epidemiologic Follow-up Study (96.1% of decedents and 99.4% of living participants were classified correctly).[25] Persons not matched to a death record were considered to be alive through the end of follow-up and were administratively censored on December 31, 2000. Mortality outcomes were based on death certificate underlying cause of death coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) for deaths occurring between 1988 and 1998, and according to the *International Classification of Diseases, Tenth Revision* (ICD-10) for deaths occurring between 1999 and 2000.[24] Outcomes consisted of all-cause mortality and the following cause-specific mortality: CVD (ICD-9 codes: 410–414, 428, 429.2, 433–435, 437.0–437.1, 440, and 444; ICD-10 codes: G45, I20–I25, I50, I63, I65–I66, I67.2, I67.8, I69.3, I70, and I74), diabetes (ICD-9 code: 250; ICD-10 codes: E10–E14), liver disease (ICD-9 codes: 70.2–70.9, 275.0–275.1, and 570–573; ICD-10 codes: B16–B19, E83.0–E83.1, and K70–K77), neoplasms (ICD-9 codes: 140–239; ICD-10 codes: C00–D48), and all other mortality. Deaths with liver cancer coded as underlying cause of death (n = 13) were included with neoplasms.

Data were collected at baseline, as previously described, on factors known or thought to be related to elevated liver enzymes or mortality and included as covariates in multivariate analyses: age (years), sex, ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), education (years: <12, 12, >12), cigarette smoking (never, former, <1 pack/day, ≥1 pack/day), alcohol drinking (never, former, <1 drink/day, 1–2 drinks/day, or >2 drinks/day), doctor-diagnosed diabetes, physical activity, caffeinated beverage consumption, body mass index (BMI; weight [kg]/height [m^2]), waist and hip circumferences, blood pressure, hemoglobin A_{1C}, serum total and high-density lipoprotein (HDL) cholesterol concentrations, and serum transferrin saturation.[22,26–32] C-reactive protein was assayed using a Behring Nephalometric Analyzer (Behring Diagnostics Inc, Somerville, NJ) and categorized as 0–0.3 and >0.3.[22]

Statistical Analysis

Separate analyses were conducted for ALT and GGT. Baseline characteristics were compared by liver enzyme status using a *t* test for continuous variables or a χ^2 test for categorical variables. Cumulative mortality during follow-up among persons with and without liver enzyme elevation was calculated using Kaplan–Meier analysis. Hazard rate ratio (HR) estimates (relative risk) for mortality outcomes were calculated by Cox proportional hazard regression analysis (SUDAAN, PROC SURVIVAL, SUDAAN User's Manual, Release 8.0, 2001; Research Triangle Institute, Research Triangle Park, NC) to control for effects of potential risk factors while taking into consideration varying lengths of follow-up. Time at risk was from the date of the NHANES III examination to the date of death or to December 31, 2000. For analyses of cause-specific mortality, participants who died of other causes were censored at the date of death. All factors met the proportional hazard assumption of a relatively constant risk ratio through examination of -log (-log) plots of survival versus time by categories.[33] Multivariate analyses excluded persons with missing values for any risk factor included in the model. A *P* value of <.05 was considered to indicate statistical significance. All analyses utilized sample weights that accounted for unequal selection probabilities and nonresponse. All variance calculations accounted for the design effects of the survey using Taylor series linearization.[34]

Results

ALT

The prevalence (±SE) of elevated ALT was 13.5% (±0.77%). Compared with participants with normal ALT, those with ALT elevation were younger and more likely to be Mexican American, obese, diabetic, lighter smokers,

Table 1. Baseline Characteristics of Participants by Liver Enzyme Activity Status

Characteristic	ALT			GGT		
	Normal (n = 12,794)	Elevated[a] (n = 2156)	*P* value[b]	Normal (n = 9632)	Elevated[c] (n = 1998)	*P* value[b]
ALT (*U/L*)	13.8 ± 0.18	38.9 ± 0.62	<.001	155 ± 0.34	29.4 ± 1.2	<.001
GGT (*U/L*)	23.8 ± 0.37	57.0 ± 2.4	<.001	20.1 ± 0.16	83.7 ± 2.4	<.001
Age (*y*)	45.3 ± 0.50	42.1 ± 0.60	<.001	44.2 ± 0.57	48.3 ± 0.61	<.001
Education (*y*)	12.4 ± 0.09	12.3 ± 0.17	.60	12.6 ± 0.12	11.8 ± 0.19	<.001
BMI (kg/m^2)	26.1 ± 0.10	29.4 ± 0.25	<.001	26.3 ± 0.12	29.0 ± 0.25	<.001
Waist-to-hip ratio	90.6 ± 0.17	93.1 ± 0.31	<.001	90.2 ± 0.20	94.5 ± 0.28	<.001
Serum total cholesterol (*mg/dL*)	204 ± 0.8	211 ± 1.6	<.001	202 ± 0.8	219 ± 1.6	<.001
Serum HDL cholesterol (*mg/dL*)	51.2 ± 0.36	47.3 ± 0.48	<.001	50.6 ± 0.40	49.9 ± 0.65	.29
Systolic blood pressure (*mm Hg*)	122 ± 0.4	124 ± 0.6	.054	122 ± 0.5	128 ± 0.7	<.001
Diastolic blood pressure (*mm Hg*)	73.7 ± 0.17	76.7 ± 0.39	<.001	73.8 ± 0.23	77.3 ± 0.39	<.001
Caffeine (*mg/day*)[d]	230 ± 5.8	208 ± 9.0	.041	231 ± 6.6	196 ± 7.4	<.001
Physical activity intensity (*METs*)[e]	112 ± 3.3	101 ± 4.6	.011	113 ± 3.8	90.8 ± 4.5	<.001
Transferrin saturation (%)	26.1 ± 0.23	26.9 ± 0.41	.037	25.9 ± 0.26	26.7 ± 0.40	.062
Women (%)	52.2 ± 0.54	55.7 ± 1.6	.073	52.4 ± 0.67	54.5 ± 1.8	.33
Race-ethnicity (%)			<.001			<.001
Non-Hispanic white	77.9 ± 1.2	74.6 ± 2.1		78.2 ± 1.8	65.8 ± 2.9	
Non-Hispanic black	10.5 ± 0.62	7.4 ± 0.70		9.4 ± 0.85	18.2 ± 1.9	
Mexican American	4.4 ± 0.35	9.6 ± 1.0		4.4 ± 0.57	6.7 ± 0.98	
Abnormal glucose status (%)[f]	6.5 ± 0.34	13.1 ± 1.1	<.001	5.5 ± 0.29	16.6 ± 1.4	<.001
Cigarette smoking (%)			<.001			.15
Never	45.9 ± 0.90	49.9 ± 1.2		47.8 ± 1.0	44.1 ± 2.0	
Former	26.0 ± 0.66	27.4 ± 1.8		25.4 ± 0.79	28.9 ± 2.2	
<1 pack per day	11.9 ± 0.55	12.8 ± 1.3		11.6 ± 0.67	13.9 ± 1.4	
≥1 pack per day	16.1 ± 0.77	9.9 ± 1.0		15.2 ± 0.94	13.0 ± 1.2	
Alcohol drinking (%)			.065			<.001
Never	13.0 ± 0.81	14.1 ± 1.5		13.6 ± 0.98	13.7 ± 1.4	
Former	32.4 ± 1.1	33.5 ± 1.8		32.9 ± 1.1	32.2 ± 1.9	
<1 drink per day	40.4 ± 1.3	35.9 ± 1.4		40.6 ± 1.3	33.0 ± 2.2	
1–2 drinks per day	8.4 ± 0.55	8.9 ± 1.5		7.8 ± 0.52	11.1 ± 1.4	
>2 drinks per day	5.7 ± 0.37	7.7 ± 1.1		5.1 ± 0.41	10.1 ± 1.3	
C-reactive protein >0.3 mg/dL (%)	24.8 ± 1.0	34.2 ± 1.6	<.001	25.7 ± 1.0	46.9 ± 2.2	<.001

NOTE. Values are mean ± SE.

ALT, alanine aminotransferase; BMI, body mass index; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; METs, ratio of work metabolic rate to resting metabolic rate.

[a]ALT >30 U/L in men or >19 U/L in women.

[b]From *t* test for continuous variables or χ^2 test for categorical variables.

[c]GGT >51 U/L in men or >33 U/L in women.

[d]Sum of caffeine from regular coffee (137 mg/cup), regular tea (47 mg/cup), and regular or diet colas and sodas (46 mg/bottle or can).[30]

[e]Sum of the products of activity frequency in the previous month and an intensity rating[29] for 9 common activities.

[f]Doctor-diagnosed diabetes or hemoglobin A_{1C} ≥6.4% (95th percentile).

and less physically active, and to have a central fat distribution; higher total cholesterol, diastolic blood pressure, serum transferrin saturation, and prevalence of elevated C-reactive protein; and a lower HDL cholesterol and caffeine intake, but did not differ significantly with respect to sex, systolic blood pressure, alcohol intake, or education (Table 1).

The median follow-up among the 14,950 participants was 8.8 years (range, 0.02–12.1 years). The cumulative mortality from all causes was 13.9% (2189 deaths) at 12 years of follow-up. The cause-specific cumulative mortality (underlying cause) was 4.2% (665 deaths) from CVD, 4.2% (499 deaths) from cancer, 0.44% (69 deaths) from diabetes, 0.13% (34 deaths) from liver disease, and 5.5% (922 deaths) from all other causes.

Because persons with elevated ALT were younger (Table 1), they had lower unadjusted cumulative mortality rates for all outcomes except diabetes and liver disease (Table 2). However, after age-adjustment, an elevated ALT was not associated with a significantly higher risk of all-cause mortality (Table 2), and this was unchanged after adjusting for multiple factors (Table 2). For CVD mortality, the HR for persons with an elevated ALT was not increased in either age-adjusted (HR, 0.88; 95% confidence interval [CI], 0.57–1.4) or multivariate-adjusted analysis (HR, 0.90; 95% CI, 0.56–1.4). A negative result was likewise found for neoplasms. For diabetes, the cumulative mortality was higher among participants with an elevated ALT (Table 2). After adjusting for age, ALT elevation was associated with more than 3 times the risk

Table 2. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 14,950)			Multivariate-adjusted (n = 13,361)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	2005	14.4	1.0			1.0		
Elevated ALT[d]	184	10.1	1.2	0.92–1.5	.19	1.2	0.88–1.6	.24
CVD								
Normal ALT	624	4.6	1.0			1.0		
Elevated ALT	41	1.9	0.88	0.57–1.4	.56	0.90	0.56–1.4	.67
Liver disease								
Normal ALT	18	0.073	1.0			1.0		
Elevated ALT	16	0.47	11.2	3.1–40.5	<.001	8.2	2.1–319	.003
Neoplasms								
Normal ALT	460	4.5	1.0			1.0		
Elevated ALT	39	2.7	0.99	0.66–1.5	.97	1.0	0.65–1.5	1.0
Diabetes								
Normal ALT	58	0.35	1.0			1.0		
Elevated ALT	11	1.1	3.3	1.3–8.4	.012	2.4	0.65–9.1	.18
Other								
Normal ALT	845	5.7	1.0			1.0		
Elevated ALT	77	4.3	1.2	0.85–1.8	.24	1.3	0.79–2.1	.29

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.
[a]Estimated using Kaplan–Meier analysis.
[b]Estimated using Cox proportional hazard regression analysis.
[c]Adjusted for age, sex, race-ethnicity, BMI, waist-to-hip ratio, glucose status, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in models for liver disease and diabetes, education was excluded from the model for liver disease, and glucose status was excluded from the model for diabetes.
[d]ALT >30 U/L in men or >19 U/L in women.

of diabetes mortality ($P = .012$) (Table 2). ALT activity was strongly associated with diabetes at baseline. In a model adjusting for multiple factors, but not baseline glucose status, an increased risk remained but no longer reached statistical significance (HR, 2.4; 95% CI, 0.65–9.1) (Table 2). Glucose status could not be included in the multivariate-adjusted model because of the relatively small number of diabetes deaths and the strong association of diabetes mortality with abnormal glucose status. However, in a model adjusting for only baseline glucose status, ALT activity was unrelated to diabetes mortality (HR, 0.99; 95% CI, 0.44–2.2; $P = .99$).

For liver disease, the cumulative mortality was higher among participants with an elevated ALT (Table 2). After adjusting for age, ALT elevation was associated with 11 times the risk of liver disease mortality ($P < .001$). The risk remained increased more than 8-fold with adjustment for additional factors ($P = .003$). If liver disease mortality was defined based on any of the multiple causes recorded on the death certificate, rather than underlying cause alone, there were 66 deaths. The cumulative mortality was higher among persons with ALT elevation (0.85%) compared with those without (0.25%). In age-adjusted analysis, persons with elevated ALT had 5 times the risk of liver disease mortality (HR, 5.3; 95% CI, 1.9–15.3; $P = .002$), which decreased only slightly in multivariate-adjusted analysis (HR, 4.8; 95% CI, 1.7–13.6; $P = .004$).

We conducted sensitivity analyses to evaluate the robustness of our findings. (supplementary Tables 1–13, see supplementary Tables 1–13 online at www.gastrojournal.org.) Because higher alcohol intake is associated with ALT elevation, we excluded 2454 persons who consumed one or more drinks per day. The association of elevated ALT with liver disease mortality was strengthened, while the lack of an association with other mortality outcomes remained unchanged. Secondly, because ALT distributions differ between men and women, we conducted sex-specific analyses. With the exception of an increased risk of diabetes mortality among women but not men in age-adjusted analyses, the results were consistent for men and women separately and jointly. Thirdly, because there is no universally agreed upon definition of abnormal ALT, we ran our analyses using the higher ALT cutoffs of the NHANES III reference laboratory, >40 U/L for men and >31 U/L for women, as well as with ALT coded as a continuous and log-transformed variable (because of its skewed distribution). With the higher ALT cut-points, the results were similar except that elevated ALT was not associated with greater diabetes mortality in age-adjusted analysis. However, the number of diabetes deaths among persons with elevated ALT was small. The results were

also similar for log ALT, except for inverse relationships with all-cause and CVD mortality. Fourthly, the 552 participants excluded from the main analysis with viral hepatitis B or C were added back. There was little effect on the results with the exception of an association of elevated ALT with increased all-cause mortality in age-adjusted, but not multivariate-adjusted analysis. Lastly, to address the possible effect of diurnal variation of ALT activity, we adjusted for time of blood draw (AM or PM), and the results were unchanged.

GGT

The prevalence (±SE) of elevated GGT was 13.2% (±0.61%). The relationships of GGT with some participant characteristics differed from those of ALT. Compared with participants with normal GGT, those with elevated GGT were older and more likely to be non-Hispanic black, and had fewer years of education and higher systolic blood pressure, but did not differ with regard to HDL level, transferrin saturation, and cigarette smoking. GGT was more strongly associated with caffeine (negatively) and alcohol consumption (positively) than was ALT (Table 1).

Compared with ALT, elevated GGT was more likely to be related to mortality. For both all-cause mortality and each specific cause, the cumulative mortality was higher among participants with elevated GGT (Table 3). The risk of all-cause mortality was 60% higher among persons with elevated GGT in age-adjusted analysis, and adjusting for multiple factors had little effect on this relationship. For CVD mortality, the HR for persons with elevated GGT was increased in age-adjusted analysis (HR, 1.5; 95% CI, 1.05–2.0); however, the risk was diminished in multivariate-adjusted analysis and no longer reached statistical significance (HR, 1.3; 95% CI, 0.80–2.0). Elevated GGT was associated with a 50% higher risk of cancer mortality in both age-adjusted and multivariate-adjusted analyses. For diabetes mortality, GGT elevation was associated with almost 5 times the risk in age-adjusted analysis and more than 3 times the risk after adjusting for multiple factors, but not baseline glucose status. Similarly to ALT, GGT activity was strongly associated with diabetes at baseline, and glucose status could not be included in the multivariate-adjusted model because of the small number of diabetes deaths and the strong association of diabetes mortality with abnormal glucose status.

For liver disease mortality, GGT elevation was associated with 19 times the risk ($P < .001$) in age-adjusted analysis (Table 3). The risk remained increased 13-fold with adjustment for additional factors ($P = .004$). If liver

Table 3. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000

Mortality outcome GGT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 11,630)			Multivariate-adjusted (n = 10,514)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal GGT	1260	10.6	1.0			1.0		
Elevated GGT[d]	306	16.3	1.6	1.3–1.8	<.001	1.5	1.2–1.8	<.001
CVD								
Normal GGT	397	3.6	1.0			1.0		
Elevated GGT	82	5.3	1.5	1.05–2.0	.026	1.3	0.80–2.0	.30
Liver disease								
Normal GGT	5	0.053	1.0			1.0		
Elevated GGT	13	0.58	19.4	3.7–101.4	<.001	13.0	2.4–71.5	.004
Neoplasms								
Normal GGT	288	2.8	1.0			1.0		
Elevated GGT	68	3.8	1.5	1.00–2.2	.052	1.5	1.01–2.2	.047
Diabetes								
Normal GGT	31	0.20	1.0			1.0		
Elevated GGT	16	1.3	4.9	2.1–11.1	<.001	3.3	1.4–7.6	.006
Other								
Normal GGT	539	4.3	1.0			1.0		
Elevated GGT	127	6.3	1.4	1.1–2.0	.022	1.5	0.99–2.2	.055

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, BMI, waist-to-hip ratio, glucose status, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of liver disease and diabetes deaths, Mexican American and other race-ethnicity were combined in models for these outcomes, glucose status was excluded from the model for diabetes, and covariates included in the model for liver disease were age, sex, race-ethnicity, waist-to-hip ratio, glucose status, smoking, alcohol, caffeine, C-reactive protein, and transferrin saturation.

[d]GGT >51 U/L in men or >33 U/L in women.

disease mortality was defined based on underlying or other causes of death, rather than underlying cause alone, there were 39 deaths. The cumulative mortality was higher among persons with GGT elevation (1.4%) compared with those without (0.15%). In age-adjusted analysis, persons with elevated GGT had greater than 11 times the risk of liver disease mortality (HR, 11.5; 95% CI, 4.0–32.8; $P < .001$), which was essentially unchanged in multivariate-adjusted analysis (HR, 11.4; 95% CI, 4.0–33.1; $P < .001$).

The same sensitivity analyses were conducted as for ALT. (supplementary Tables 1–13, see supplementary Tables 1–13 online at www.gastrojournal.org.) After excluding 1821 heavier drinkers, the association with liver disease mortality was strengthened, while other relationships were unchanged. In sex-specific analyses, there were insufficient deaths to evaluate diabetes in men or liver disease in women; HRs for other outcomes were in the same direction for both sexes as in the combined analyses, but no longer reached statistical significance. With log-transformed GGT, the results were similar to the main analysis except that there was no association with cancer. When 419 participants with viral hepatitis B or C were added back, the relationship with liver disease was somewhat attenuated but remained positively associated. With adjustment for time of blood draw (AM or PM), the results were unchanged.

Discussion

For ALT, the key finding of this study was the lack of an association with overall or CVD mortality in a large, national, population-based, prospective study. This was a consistent finding in both age-adjusted and multivariate-adjusted analyses. Few studies have performed similar analyses, and their results have been inconsistent and not comparable to those of the current study. A large Korean study found a strong association of all-cause mortality with ALT in men, but not women. It did not exclude persons with chronic viral hepatitis, and digestive disease and cancer mortality constituted a much higher proportion of deaths than in western countries.[1] A similar study from Japan found an association with overall mortality only at low BMI, and there were no exclusions for viral hepatitis.[2] A report that found a higher standardized mortality ratio for raised ALT in Olmsted County, Minnesota, did not exclude persons with known causes of liver disease or control for other mortality risk factors. A notably stronger mortality risk was found at lower levels of ALT for women than for men.[3] In contrast, a study of German male construction workers found a strong association of GGT and aspartate aminotransferase, but not ALT activity, with overall mortality.[4] A Dutch population-based study found a nonstatistically significant increased all-cause mortality risk for participants with the highest third of ALT activity that was attenuated after adjustment for CVD risk factors.[5] Data on the relationship between ALT elevation and CVD mortality are sparse. The Korean study found an association among men but not women.[1] The Dutch study found a higher incidence of fatal and nonfatal coronary heart disease, but not total CVD, among participants in the highest tertile of ALT after controlling for CVD risk factors.[5] An unexpected finding was an inverse relationship with all-cause and CVD mortality when ALT was coded as a continuous log-transformed variable. Because of the transformation, this supplemental analysis examined changes in ALT activity mainly within the normal range. The biological significance of these associations is unclear; however, they are outside the primary aim of the study, which was to evaluate whether mortality was increased with an elevated ALT.

The other important finding regarding ALT was its strong association with liver disease mortality, even after excluding participants with chronic viral hepatitis. The relatively small number of liver disease deaths resulted in a wide CI, and the magnitude of the association cannot be determined with certainty. However, the positive direction substantiates a recent American Association for the Study of Liver Disease policy document that supports measuring ALT in the general population as a screening test for liver disease.[35] Given that the increased liver disease mortality was based on a single ALT measurement, this is an especially significant result. It should be noted that the current study was able to detect an association of ALT and mortality from liver disease, but not from CVD, despite fewer than a tenth of the number of deaths from liver disease as from CVD.

Cancer mortality risk was not increased in either age- or multivariate-adjusted analysis. A higher ALT predicted cancer mortality among male Korean workers[1] and in an elderly Italian population.[36] The risk of diabetes mortality was increased among persons with an elevated ALT in age-adjusted analysis, but in multivariate analysis no longer reached statistical significance. Because both ALT activity and diabetes mortality were strongly associated with abnormal baseline glucose status, these results are difficult to interpret. Among prospective studies of ALT elevation and incident diabetes, an association was found in some[37–42] but not in others.[43–45] The risk of mortality from all other causes in the current study was slightly and nonstatistically significantly increased in age- and multivariate-adjusted analysis.

GGT is regarded as less specific for liver injury than ALT, and is used less for detection and monitoring of liver disease. However, as a prognostic indicator, it may be as discriminating as ALT for liver disease and more discriminating for other diseases. The increased all-cause mortality found in this study with elevated GGT is supported by a number of studies of disease association and mortality.[8,13,46] It is not entirely clear why elevated GGT would be associated with increased mortality. A relationship to oxidative stress is the hypothesis with the most

support.[47–49] Because GGT elevation is associated with heavy alcohol consumption, increased mortality could be a function of heavy drinking. In fact, there was a strong association of elevated GGT with alcohol consumption in the current study (Table 1). However, both with control for alcohol consumption and with restriction to light and nondrinkers, GGT remained associated with all-cause and cause-specific mortality.

There is considerable evidence for increased CVD incidence and mortality with elevated GGT.[7,12,14] This association may be independent of such standard risk factors as hypertension and commonly measured blood lipid levels. Active GGT has been experimentally demonstrated in atherosclerotic plaques and may play a role in the development of reactive oxygen species.[50] In multivariate analysis that controlled for numerous CVD risk factors, we did not find a statistically significant relationship of elevated GGT to CVD mortality, although the HR of 1.3 did indicate an increased risk.

Numerous studies have demonstrated an association of GGT activity with diabetes in both cross-sectional and longitudinal studies.[6,9,10,15,51–53] The strong association of GGT and insulin resistance may be the main reason for this association. There is less evidence for an association of GGT with cancer incidence and mortality. An Austrian population-based study found a clear dose-response relationship of GGT with cancer incidence.[18,19] Both men and women had an increased risk of malignant neoplasms of the digestive organs and respiratory system/intrathoracic organs. A hospital-based cohort study, also from Austria, found an association of GGT with increased cancer mortality.[8] In addition to the aforementioned relationship of GGT to oxidative stress as a potential explanation for the association with cancer, expression of GGT in cancer cells has been associated with chemotherapeutic drug resistance.[54]

Finally, the current study confirmed the well-known relationship of GGT to liver injury by demonstrating a mortality risk at least as great as for elevated ALT, even with adjustment for several known liver disease risk factors. GGT has been strongly associated with both alcoholic and nonalcoholic fatty liver disease.[55–59] There is surprisingly less evidence for elevated GGT and liver disease outcomes, including mortality.[8,60] We found a high relative risk of liver disease mortality with elevated GGT that was not strongly influenced by BMI and alcohol consumption. Although this result suggests that GGT could be considered a prognostic marker for liver disease, the increased risk was based on relatively few deaths and requires confirmation.

As previously reported, limitations of using NHANES to study liver injury are that liver biopsies cannot be conducted on the general population and ultrasound imaging was not performed, so single serum liver enzyme levels must be relied on as markers for liver injury.[26–28] In addition, there was a possible loss of ALT activity after the brief storage and the shipping that were used in NHANES III. However, the stability of serum ALT was concluded by a review to be adequate for shipping and storage if low temperatures were maintained.[61] Degradation of ALT activity could have diminished an association of ALT with mortality. Given the strong association of elevated ALT with mortality from liver disease, we believe that any effect would have been small. Because most ALT elevations were modest, we were unable to examine the relationship of higher abnormal levels with mortality. Another limitation of the current study is the lack of validation of cause of death. Although ascertainment of vital status using the National Death Index is very high, assigning cause of death based on death certificate diagnoses may lead to misclassification. Such inaccuracies might have resulted in misclassification of some participants, but they should not have led to biased results. The fact that all-cause mortality and certain cause-specific mortality were increased for high GGT argues against a strong effect for misclassification for common causes of death. Finally, the number of mortality outcomes, especially for liver disease and diabetes, was limited by the 12-year duration of follow-up. These limitations are balanced by the benefits of a large, national, population-based sample, particularly the avoidance of ascertainment bias that occurs in clinical studies of selected patients and the ability to generalize the results to the US population. In conclusion, in the US population, elevated GGT was associated with mortality from all causes, liver disease, cancer, and diabetes, while ALT was associated only with liver disease mortality.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.10.052.

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Supplementary Table 1. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Among Persons Drinking <1 Drink per Day

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 12,496)			Multivariate-adjusted (n = 11,644)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	1743	14.8	1.0			1.0		
Elevated ALT[d]	143	10.1	1.1	0.86–1.4	.44	1.1	0.82–1.5	.45
CVD								
Normal ALT	542	4.3	1.0			1.0		
Elevated ALT	34	1.7	0.81	0.50–1.3	.37	0.76	0.42–1.4	.36
Liver disease								
Normal ALT	12	0.054	1.0			1.0		
Elevated ALT	9	0.41	19.4	4.7–79.8	<.001	12.9	4.7–35.5	<.001
Neoplasms								
Normal ALT	391	4.8	1.0			1.0		
Elevated ALT	29	2.3	0.85	0.49–1.5	.56	0.90	0.50–1.6	.71
Diabetes								
Normal ALT	53	0.40	1.0			1.0		
Elevated ALT	9	1.4	3.4	1.2–9.1	.018	2.5	0.67–9.6	.17
Other								
Normal ALT	745	6.1	1.0			1.0		
Elevated ALT	62	4.6	1.2	0.84–1.8	.29	1.3	0.74–2.3	.36

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for liver disease, education was excluded from the model for liver disease, and glucose status was excluded from the model for diabetes.

[d]ALA >30 U/L in men or >19 U/L in women.

Supplementary Table 2. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Among Men

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 6953)			Multivariate-adjusted (n = 6174)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	1144	14.5	1.0			1.0		
Elevated ALT[d]	61	7.0	1.1	0.69–1.7	.69	1.1	0.62–1.9	.80
CVD								
Normal ALT	368	5.8	1.0			1.0		
Elevated ALT	11	0.93	0.47	0.20–1.1	.074	0.38	0.12–1.2	.092
Liver disease								
Normal ALT	14	0.099	1.0			1.0		
Elevated ALT	8	0.71	12.7	2.0–82.3	.009	8.8	2.0–38.7	.005
Neoplasms								
Normal ALT	278	3.9	1.0			1.0		
Elevated ALT	13	1.9	1.0	0.53–2.0	.96	1.3	0.66–2.6	.44
Diabetes								
Normal ALT	[e]	0.23	1.0			1.0		
Elevated ALT		0.041	0.98	0.24–3.9	.98	0.47	0.05–4.1	.49
Other								
Normal ALT	459	5.2	1.0			1.0		
Elevated ALT	27	3.5	1.3	0.61–2.8	.48	1.1	0.38–3.3	.83

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for liver disease, and glucose status was excluded from the model for diabetes.

[d]ALT >30 U/L in men.

[e]Cell contains <5 observations.

Supplementary Table 3. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Among Women

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 7997)			Multivariate-adjusted (n = 7187)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	861	14.5	1.0			1.0		
Elevated ALT[d]	123	12.5	1.4	0.96–2.0	.081	1.2	0.82–1.8	.32
CVD								
Normal ALT	256	3.4	1.0			1.0		
Elevated ALT	30	2.7	1.5	0.81–2.7	.20	1.2	0.64–2.2	.57
Liver disease								
Normal ALT	[e]	0.050	1.0			10		
Elevated ALT		0.27	16.5	2.6–104.3	.004	8.7	1.03–74.0	.047
Neoplasms								
Normal ALT	182	5.1	1.0			1.0		
Elevated ALT	26	3.3	1.1	0.56–2.0	.85	0.90	0.43–1.9	.78
Diabetes								
Normal ALT	33	0.46	1.0			1.0		
Elevated ALT	9	2.0	3.3	1.2–9.4	.027	2.3	0.61–8.6	.21
Other								
Normal ALT	386	6.2	1.0			1.0		
Elevated ALT	50	4.9	1.3	0.88–2.0	.18	1.3	0.81–2.2	.24

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in models for liver disease and diabetes, alcohol drinking was excluded from the model for liver disease, and glucose status and alcohol drinking were excluded from the model for diabetes.

[d]ALT >19 U/L in women.

[e]Cell contains <5 observations.

Supplementary Table 4. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Using Higher ALT Cut-Points

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 14,950)			Multivariate-adjusted (n = 13,361)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	2119	14.2	1.0			1.0		
Elevated ALT[d]	70	7.2	1.4	0.90–2.1	.13	1.4	0.88–2.2	.15
CVD								
Normal ALT	654	4.4	1.0			1.0		
Elevated ALT	11	1.7	1.1	0.44–2.8	.82	1.2	0.41–3.2	.78
Liver disease								
Normal ALT	24	0.11	1.0			1.0		
Elevated ALT	10	0.44	6.8	1.4–32.6	.017	4.6	1.03–21.0	.046
Neoplasms								
Normal ALT	481	4.3	1.0			1.0		
Elevated ALT	18	2.6	1.6	0.85–2.9	.15	1.8	0.91–3.5	.092
Diabetes								
Normal ALT	[e]	0.45	1.0			1.0		
Elevated ALT		0.27	1.6	0.28–9.2	.58	1.6	0.23–11.3	.62
Other								
Normal ALT	894	5.7	1.0			1.0		
Elevated ALT	28	2.3	1.2	0.58–2.6	.59	1.3	0.54–3.1	.55

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for liver disease, and glucose status was excluded from the model for diabetes.

[d]ALT >40 U/L in men or >31 U/L in women.

[e]Cell contains <5 observations.

Supplementary Table 5. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Including Persons With Hepatitis B or C

Mortality outcome ALT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 15,502)			Multivariate-adjusted (n = 13,746)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal ALT	2076	14.5	1.0			1.0		
Elevated ALT[d]	234	11.4	1.3	1.04–1.6	.024	1.2	0.91–1.6	.18
CVD								
Normal ALT	640	4.6	1.0			1.0		
Elevated ALT	48	2.8	1.0	0.67–1.5	.98	1.0	0.65–1.5	.98
Liver disease								
Normal ALT	22	0.099	1.0			1.0		
Elevated ALT	21	0.70	10.3	3.9–27.4	<.001	8.0	3.2–20.1	<.001
Neoplasms								
Normal ALT	473	4.5	1.0			1.0		
Elevated ALT	51	2.8	1.05	0.72–1.5	.81	1.0	0.66–1.5	.98
Diabetes								
Normal ALT	63	0.37	1.0			1.0		
Elevated ALT	16	1.2	3.9	1.8–8.6	.001	2.3	0.68–8.0	.17
Other								
Normal ALT	878	5.8	1.0			1.0		
Elevated ALT	98	4.4	1.3	0.92–1.9	.12	1.3	0.80–2.0	.30

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for diabetes, and glucose status was excluded.

[d]ALT >30 U/L in men or >19 U/L in women.

Supplementary Table 6. Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum ALT Status in the United States, 1988–2000, Adjusting for Time of Blood Draw

	Adjusted for time of blood draw (n = 14,950)			Adjusted for time of blood draw and age (n = 14,950)			Adjusted for time of blood draw and all other covariates (n = 13,361)		
Mortality outcome	HR[a]	95% CI	*P* value	HR[a]	95% CI	*P* value	HR[a,b]	95% CI	*P* value
All-cause									
Normal ALT	1.0			1.0			1.0		
↑ ALT[c]	0.74	0.60–0.93	.010	1.2	0.92–1.5	.19	1.2	0.88–1.6	.24
CVD									
Normal ALT	1.0			1.0			1.0		
↑ ALT	0.52	0.35–0.77	.002	0.88	0.57–1.4	.57	0.90	0.56–1.5	.67
Diabetes									
Normal ALT	1.0			1.0			1.0		
↑ ALT	2.0	0.88–4.7	.096	3.3	1.3–8.4	.012	2.5	0.70–9.2	.15
Noncancer liver disease									
Normal ALT	1.0			1.0			1.0		
↑ ALT	8.9	2.7–29.3	<.001	11.2	3.1–40.5	<.001	8.5	2.4–29.6	.001
Cancer									
Normal ALT	1.0			1.0			1.0		
↑ ALT	0.68	0.46–1.01	.057	0.99	0.66–1.5	.97	1.0	0.66–1.5	.99
Other									
Normal ALT	1.0			1.0			1.0		
↑ ALT	0.79	0.53–1.2	.23	1.2	0.85–1.8	.25	1.3	0.79–2.1	.29

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a]Estimated using Cox proportional hazard regression analysis.

[b]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, education, and time of blood draw. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in models for liver disease and diabetes, and glucose status was excluded from the model for diabetes.

[c]ALT >30 U/L in men or >19 U/L in women.

Supplementary Table 7. Unadjusted, Age-Adjusted, and Multivariate-Adjusted HRs and 95% CIs for Death (Underlying Cause) in the United States, 1988–2000, With Serum ALT Coded as Continuous (Log ALT)

	Unadjusted (n = 14,950)			Age-adjusted (n = 14,950)			Multivariate-adjusted (n = 13,361)		
Mortality outcome	HR[a]	95% CI	*P* value	HR[a]	95% CI	*P* value	HR[a,b]	95% CI	*P* value
All-cause	0.53	0.46–0.60	<.001	0.88	0.77–1.00	.047	0.83	0.72–0.96	.015
CVD	0.45	0.36–0.57	<.001	0.81	0.63–1.03	.081	0.68	0.51–0.90	.008
Diabetes	0.77	0.46–1.3	.31	1.4	0.78–2.5	.25	2.1	1.1–4.3	.032
Noncancer liver disease	4.2	2.4–7.2	<.001	5.6	2.9–10.8	<.001	3.8	2.0–6.9	<.001
Cancer	0.54	0.42–0.69	<.001	0.81	0.62–1.1	.13	0.77	0.55–1.1	.13
Other	0.53	0.42–0.66	<.001	0.88	0.71–1.1	.25	0.94	0.74–1.2	.57

ALT, alanine aminotransferase; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

[a]Estimated using Cox proportional hazard regression analysis.

[b]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for liver disease, and glucose status was excluded from the model for diabetes.

Supplementary Table 8. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, Among Persons Drinking <1 Drink per Day

Mortality outcome GGT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 9809)			Multivariate-adjusted (n = 9192)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal GGT	1114	10.3	1.0			1.0		
Elevated GGT[d]	241	17.0	1.5	1.2–1.8	<.001	1.4	1.1–1.8	.004
CVD								
Normal GGT	357	3.1	1.0			1.0		
Elevated GGT	62	4.2	1.3	0.86–1.9	.21	1.1	0.72–1.8	.56
Liver disease								
Normal GGT	[e]	0.044	1.0			1.0		
Elevated GGT		0.58	46.1	10.2–208.6	<.001	28.5	9.0–90.4	<.001
Neoplasms								
Normal GGT	242	2.8	1.0			1.0		
Elevated GGT	55	4.2	1.6	0.97–2.5	.068	1.6	1.03–2.6	.038
Diabetes								
Normal GGT	28	0.23	1.0			1.0		
Elevated GGT	15	1.8	5.2	2.2–12.4	<.001	2.9	1.4–6.0	.006
Other								
Normal GGT	483	4.5	1.0			1.0		
Elevated GGT	101	7.3	1.4	1.0–1.9	.050	1.3	0.87–2.1	.18

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of liver disease and diabetes deaths, Mexican American and other race-ethnicity were combined in models for these outcomes, glucose status was excluded from the model for diabetes, and covariates included in the model for liver disease were age, sex, race-ethnicity, waist-to-hip ratio, smoking, caffeine, C-reactive protein, and transferrin saturation.

[d]GGT >51 U/L in men or >33 U/L in women.

[e]Cell contains <5 observations.

Supplementary Table 9. Cumulative Probability (Unadjusted) Over 12 Years and Age- And Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, Among Men

Mortality outcome GGT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 5374)			Multivariate-adjusted (n = 4826)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal GGT	737	12.6	1.0			1.0		
Elevated GGT[d]	139	14.1	1.4	1.1–1.9	.010	1.3	0.89–1.9	.18
CVD								
Normal GGT	235	4.9	1.0			1.0		
Elevated GGT	36	5.0	1.1	0.74–1.7	.57	0.83	0.52–1.3	.41
Liver disease								
Normal GGT	5	0.11	1.0			1.0		
Elevated GGT	8	0.85	15.3	2.2–104.0	.006	9.0	2.1–38.6	.004
Neoplasms								
Normal GGT	188	3.5	1.0			1.0		
Elevated GGT	32	3.0	1.2	0.75–2.1	.39	1.3	0.82–2.2	.24
Diabetes								
Normal GGT	[e]	0.10	1.0			1.0		
Elevated GGT		0.033	0.43	0.08–2.3	.32	0.06	0.01–0.57	.016
Other								
Normal GGT	293	4.5	1.0			1.0		
Elevated GGT	61	6.0	1.6	1.01–2.6	.046	1.6	0.80–3.2	.18

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in models for diabetes and liver disease; covariates included in the model for diabetes were age, race-ethnicity, body mass index, waist-to-hip ratio, high-density lipoprotein cholesterol, systolic blood pressure, smoking (never, former, current), alcohol, physical activity, C-reactive protein, and education (<12 years, ≥12 years); and covariates in the model for liver disease were age, race-ethnicity, waist-to-hip ratio, caffeine, transferrin saturation, glucose status, smoking, alcohol drinking (never, former, current), and C-reactive protein.

[d]GGT >51 U/L in men.

[e]Cell contains <5 observations.

Supplementary Table 10. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, Among Women

Mortality outcome GGT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 6256)			Multivariate-adjusted (n = 5688)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal GGT	523	8.7	1.0			1.0		
Elevated GGT[d]	167	18.0	1.8	1.4–2.4	<.001	1.6	1.2–2.3	.006
CVD								
Normal GGT	162	2.5	1.0			1.0		
Elevated GGT	46	5.5	2.1	1.2–3.5	.008	1.7	0.75–3.7	.21
Liver disease								
Normal GGT	[e]	0						
Elevated GGT		0.36	—	—	—	—	—	—
Neoplasms								
Normal GGT	100	2.1	1.0			1.0		
Elevated GGT	36	4.5	1.9	1.1–3.3	.032	1.8	0.95–3.5	.072
Diabetes								
Normal GGT	15	0.29	1.0			1.0		
Elevated GGT	14	2.4	6.2	2.4–16.2	<.001	2.4	0.94–6.2	.067
Other								
Normal GGT	246	4.0	1.0			1.0		
Elevated GGT	66	6.6	1.4	0.86–2.2	.17	1.4	0.79–2.4	.25

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, the multivariate model for liver disease would not converge, and in the model for diabetes, Mexican American and other race-ethnicity were combined, glucose status and alcohol drinking were excluded, and covariates included in the model were age, race-ethnicity, body mass index, waist-to-hip ratio, high-density lipoprotein cholesterol, systolic blood pressure, smoking, physical activity, C-reactive protein, and education.

[d]GGT >33 U/L in women.

[e]Cell contains <5 observations.

Supplementary Table 11. Cumulative Probability (Unadjusted) Over 12 Years and Age- and Multivariate-Adjusted Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, Including Persons With Hepatitis B or C

Mortality outcome GGT status	No. of deaths	Unadjusted cumulative mortality (%)[a]	Age-adjusted (n = 12,049)			Multivariate-adjusted (n = 10,883)		
			Hazard ratio[b]	95% CI	*P* value	Hazard ratio[b,c]	95% CI	*P* value
All-cause								
Normal GGT	1,304	10.6	1.0			1.0		
Elevated GGT[d]	347	16.4	1.6	1.4–1.9	<.001	1.5	1.3–1.8	<.001
CVD								
Normal GGT	405	3.6	1.0			1.0		
Elevated GGT	87	5.1	1.5	1.1–2.1	.018	1.3	0.82–2.0	.26
Liver disease								
Normal GGT	9	0.12	1.0			1.0		
Elevated GGT	18	0.69	6.3	1.9–20.9	.003	6.2	2.9–13.6	<.001
Neoplasms								
Normal GGT	296	2.8	1.0			1.0		
Elevated GGT	77	3.8	1.5	1.01–2.1	.044	1.5	1.02–2.1	.041
Diabetes								
Normal GGT	34	0.21	1.0			1.0		
Elevated GGT	21	1.6	7.1	3.4–15.0	<.001	6.0	2.3–15.5	<.001
Other								
Normal GGT	560	4.3	1.0			1.0		
Elevated GGT	144	6.3	1.4	1.1–1.9	.012	1.5	1.03–2.2	.033

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase.

[a]Estimated using Kaplan–Meier analysis.

[b]Estimated using Cox proportional hazard regression analysis.

[c]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, and education. Because of smaller numbers of deaths, Mexican American and other race-ethnicity were combined in the model for diabetes, and glucose status was excluded.

[d]GGT >51 U/L in men or >33 U/L in women.

Supplementary Table 12. Hazard Ratios and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, Adjusting for Time of Blood Draw

Mortality outcome	Adjusted for time of blood draw (n = 11,630)			Adjusted for time of blood draw and age (n = 11,630)			Adjusted for time of blood draw and all other covariates (n = 10,514)		
	HR[a]	95% CI	*P* value	HR[a]	95% CI	*P* value	HR[a,b]	95% CI	*P* value
All-cause									
Normal GGT	1.0			1.0			1.0		
↑ GGT[c]	1.7	1.4–2.0	<.001	1.6	1.3–1.8	<.001	1.5	1.2–1.8	<.001
CVD									
Normal GGT	1.0			1.0			1.0		
↑ GGT	1.6	1.1–2.2	.007	1.5	1.05–2.0	.026	1.3	0.80–2.0	.31
Liver disease									
Normal GGT	1.0			1.0			1.0		
↑ GGT	21.2	4.0–113.2	<.001	19.4	3.7–101.2	<.001	12.3	2.2–67.0	.005
Neoplasms									
Normal GGT	1.0			1.0			1.0		
↑ GGT	1.6	1.1–2.4	.018	1.5	1.00–2.2	.052	1.5	1.00–2.2	.050
Diabetes									
Normal GGT	1.0			1.0			1.0		
↑ GGT	5.2	2.3–11.6	<.001	4.9	2.2–11.1	<.001	3.2	1.4–7.6	.008
Other									
Normal GGT	1.0			1.0			1.0		
↑ GGT	1.6	1.1–2.2	.007	1.4	1.1–2.0	.022	1.5	0.99–2.2	.055

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase; HR, hazard ratio.

[a]Estimated using Cox proportional hazard regression analysis.

[b]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, education, and time of blood draw. Because of smaller numbers of liver disease and diabetes deaths, Mexican American and other race-ethnicity were combined in models for these outcomes, glucose status was excluded from the model for diabetes, and covariates included in the model for liver disease were age, sex, race-ethnicity, waist-to-hip ratio, glucose status, smoking, alcohol, caffeine, C-reactive protein, and transferrin saturation.

[c]GGT >51 U/L in men or >33 U/L in women.

Supplementary Table 13. Unadjusted, Age-Adjusted, and Multivariate-Adjusted HRs and 95% CIs for Death (Underlying Cause) by Serum GGT Status in the United States, 1988–2000, With Serum GGT Coded as Continuous (Log GGT)

Mortality outcome	Unadjusted (n = 11,630)			Age-adjusted (n = 11,630)			Multivariate-adjusted (n = 10,514)		
	HR[a]	95% CI	*P* value	HR[a]	95% CI	*P* value	HR[a,b]	95% CI	*P* value
All-cause	1.5	1.4–1.6	<.001	1.4	1.3–1.6	<.001	1.3	1.1–1.5	<.001
CVD	1.4	1.2–1.7	<.001	1.4	1.2–1.7	<.001	1.2	0.87–1.5	.33
Liver disease	6.4	4.4–9.4	<.001	6.3	4.3–9.3	<.001	5.1	3.7–6.9	<.001
Neoplasms	1.4	1.1–1.7	.003	1.3	1.1–1.7	.010	1.2	0.93–1.5	.16
Diabetes	2.3	1.6–3.5	<.001	2.4	1.6–3.6	<.00	2.2	1.3–3.5	.003
Other	1.4	1.2–1.7	<.001	1.4	1.2–1.6	<.001	1.3	1.05–1.7	.020

CI, confidence interval; CVD, cardiovascular disease; GGT, γ-glutamyltransferase; HR, hazard ratio.

[a]Estimated using Cox proportional hazard regression analysis.

[b]Adjusted for age, sex, race-ethnicity, body mass index, waist-to-hip ratio, glucose status, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, smoking, alcohol, caffeine, physical activity, C-reactive protein, transferrin saturation, education, and time of blood draw. Because of smaller numbers of liver disease and diabetes deaths, Mexican American and other race-ethnicity were combined in models for these outcomes, glucose status was excluded from the model for diabetes, and covariates included in the model for liver disease were age, sex, race-ethnicity, waist-to-hip ratio, glucose status, smoking, alcohol, caffeine, C-reactive protein, and transferrin saturation.