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Gamma-glutamyltransferase: Determinants and Association with Mortality from Ischemic Heart Disease and All Causes

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The association of serum levels of gamma-glutamyltransferase (GGT) with cardiovascular disease risk factors, and with mortality from all causes, cardiovascular disease, and non-cardiovascular diseases, has been examined in a prospective study of 7,613 middle-aged British men followed for 11.5 years. GGT levels were strongly associated with all-cause mortality, largely due to a significant increase in deaths from ischemic heart disease and other non-cardiovascular disease causes, i.e., non-cancer deaths, in the top quintile of the GGT distribution. No association was seen with cancer mortality. However, GGT was significantly (positively) associated with alcohol intake, body mass index, smoking, preexisting ischemic heart disease, diabetes mellitus, antihypertensive medication, systolic and diastolic blood pressure, total and high density lipoprotein cholesterol, heart rate, and blood glucose, and negatively associated with physical activity and lung function (forced expiratory volume in 1 second (FEV_1)). After adjustment for these personal characteristics and biologic variables, elevated GGT (highest quintile ≥24 unit/liter vs. the rest) was still associated with a significant increase in mortality from all causes (relative risk (RR) = 1.22, 95% confidence interval (CI) 1.01–1.42; n = 818 deaths) and from ischemic heart disease (RR = 1.42, 95% CI 1.12–1.80; n = 332 deaths). The increase in other non-cardiovascular disease causes was of marginal significance (RR = 1.45, 95% CI 0.95–2.20; n = 127 deaths). When examined separately by the presence or absence of preexisting ischemic heart disease, the increased risk of ischemic heart disease mortality was more marked in those with evidence of ischemic heart disease at screening, particularly in those with previous myocardial infarction (RR = 1.67, 95% CI 1.03–2.69; n = 84 deaths). The increased risk of other non-cardiovascular disease deaths was only seen in men without preexisting ischemic heart disease, largely due to an excess of hepatic cirrhosis. In summary, many factors other than alcohol intake are associated with increased levels of GGT, in particular body mass index, diabetes mellitus, and serum total cholesterol. The finding of increased risk of ischemic heart disease mortality seen in men with preexisting ischemic heart disease is related to the severity of the underlying myocardial damage. The biologic significance of raised GGT in men with preexisting ischemic heart disease merits further study. *Am J Epidemiol* 1995;142:699–708.

gamma-glutamyltransferase; ischemic heart disease; mortality; risk factors

Gamma-glutamyltransferase (GGT) is a widely distributed enzyme associated with the uptake of amino acids (1) and is particularly common in the liver, small intestine, and kidney. It is considered to be a sensitive indicator of liver damage but is not specific (2) and is most commonly used as a marker of excessive alcohol consumption (3–6). Apart from alcohol, GGT is raised by increasing age, diabetes mellitus, obesity, and congestive heart failure (7, 8). GGT has also been used as a marker for acute myocardial infarction in which transient rises occur (9, 10). More recently, several population studies have shown strong associations between GGT and blood pressure and lipid metabolism (11, 12). This suggests that GGT may have predictive value in ischemic heart disease. Although some population studies have examined GGT in relation to stroke, hepatobiliary disease, and premature death, these studies have focused on GGT as a surrogate measure of alcohol intake (13–15). The predictive value of GGT in population studies for risk of ischemic heart disease, and for mortality in general, has received less attention. We have therefore examined the relation between GGT and cardiovascular disease risk factors and determined the influence of GGT on ischemic heart disease and all-cause mortality in a large prospective study of middle-aged British men.

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Abbreviations: CI, confidence interval; GGT, gamma-glutamyltransferase; FEV_1, forced expiratory volume in 1 second; HDL cholesterol, high density lipoprotein cholesterol; RR, relative risk; WHO, World Health Organization.

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MATERIALS AND METHODS

The British Regional Heart Study is a prospective study of cardiovascular disease in 7,735 men aged 40–59 years selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported previously (16). Research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, and medical history. Several physical measurements were made, and blood samples (non-fasting) were taken for measurement of biochemical and hematologic variables. Details of the measurement of serum lipid concentrations have been described (17). The men were classified according to their current smoking status: those who had never smoked, ex-cigarette smokers, and current smokers. Those who had only ever smoked pipe/cigars were classified as "never smoked." Ex-cigarette smokers who were currently pipe/cigar smokers were classified as ex-cigarette smokers. Alcohol consumption was recorded using questions on frequency, quantity, and type, similar to those used in the 1978 General Household Survey. Men were classified into five groups on the basis of their estimated weekly alcohol intake: none, occasional, light, moderate, and heavy drinkers (18). Heavy drinkers were defined as those who regularly consumed more than six drinks daily. The longest-held occupation of each man was recorded and then coded in accordance with the Registrar General's occupational classification. Body mass index (weight/height^2) was used as an index of relative weight. Forced expiratory volume in 1 second (FEV_1) was measured using Vitalograph spirometer model J49-B2 (Vitalograph Medical Instrumentation Ltd., Buckingham, England) with the subject seated. Two consecutive readings were made 15 seconds apart and the maximum of these two readings was used. The FEV_1 values are height-standardized to 1.73 m, the average height of the men in this study. The men were asked to indicate their usual pattern of physical activity, which included regular walking or cycling, recreational activity, and sporting activity. A physical activity score was derived for each man based on frequency and type of leisure activity (19). The men were grouped into six broad categories based on their total score: inactive, occasional, light, moderate, moderately vigorous, and vigorous. Active men were those whose physical activity was moderate or greater. Heart rate was determined at screening from a three lead orthogonal electrocardiogram (20).

Gamma-glutamyltransferase (GGT)

The men attended the examination center between 8:30 A.M. and 6:30 P.M. Blood samples (non-fasting) were taken into evacuated tubes for measurement of biochemical and hematologic variables. All samples reached the Department of Haematology, Queen Elizabeth Hospital, Birmingham by the following morning and estimations were completed by noon of that day. GGT was measured on serum with a Technicon SMA 12/60 Autoanalyzer (Technicon Instruments Corp., Tarrytown, New York). The distribution of GGT was skewed and log transformation was used. No estimate of GGT was available for 122 men, leaving 7,613 men for analysis.

Preexisting disease

The men were asked to recall a doctor's diagnosis of angina pectoris, myocardial infarction, diabetes mellitus, and a number of other disorders listed on the questionnaire. The World Health Organization (WHO) or Rose chest pain questionnaire was administered to all men at the initial examination (21), and a three-orthogonal lead electrocardiogram was recorded at rest with the subject recumbent and having been at rest at least half an hour prior to the recording.

Ischemic heart disease

The men were separated into three groups according to the evidence of ischemic heart disease or myocardial infarction present at screening:

Group 1. No evidence of ischemic heart disease on the WHO chest pain questionnaire or electrocardiogram and no recall of a doctor's diagnosis of ischemic heart disease.

Group 2. Men with evidence suggesting ischemic heart disease short of a definite myocardial infarction. This group contains those with electrocardiographic evidence of possible or definite myocardial ischemia or possible myocardial infarction, those with angina or a possible myocardial infarction on the WHO chest pain questionnaire, or with recall of a doctor's diagnosis of angina.

Group 3. Men with a previous definite myocardial infarction on electrocardiogram or who recalled a doctor's diagnosis of a myocardial infarction ("heart attack").

In the analyses, men with preexisting evidence of ischemic heart disease consist of men in Groups 2 and 3.

Follow-up

All men, whether or not they showed evidence of ischemic heart disease at initial examination, were

followed up for all-cause mortality and cardiovascular disease morbidity for 11.5 years (22). Information on death was collected through the established "tagging" procedures provided by the National Health Service registers in Southport (for England and Wales) and Edinburgh (for Scotland). Classification of deaths as being due to cardiovascular disease or non-cardiovascular disease causes was based on the *International Classification of Diseases*, Ninth Revision, codings on the death certificates.

Statistical methods

Direct standardization was used to obtain age-adjusted rates/1,000 per year using the study population as the standard. Cox's proportional hazards model (23) was used to obtain relative risks adjusted for age, social class, smoking, heavy drinking, physical activity, body mass index, diabetes, regular medication, preexisting ischemic heart disease, systolic blood pressure, serum total cholesterol, blood glucose, HDL cholesterol, and FEV_1. Age, body mass index, systolic blood pressure, serum total cholesterol, blood glucose, FEV_1, HDL cholesterol, and heart rate were fitted as continuous variables, physical activity as five dummy variables (for the six physical activity groups), smoking as four dummy variables (never, ex-smoker, light, moderate, and heavy smoker), social class as two dummy variables (manual, non-manual, and armed forces), alcohol as four dummy variables for the five alcohol categories, preexisting ischemic heart disease as two dummy variables for the three groups (Groups 1, 2, and 3), regular medication as two dummy variables for the three groups (none, antihypertensive drugs, other medication), diabetes mellitus as a dichotomous variable (yes/no), and elevated GGT as a dichotomous variable (top quintile vs. the rest). Subjects with missing values for covariates in the various adjustments using Cox's model were excluded from that particular analysis. The partial correlations adjusted for the personal characteristics were obtained using the procedure Proc Manova in SAS (24). The analysis of covariance was used to obtain adjusted mean GGT levels by the personal characteristics in table 2 and the adjusted mean levels of blood pressure, blood lipids, and heart rate by quintiles of GGT in figure 1.

RESULTS

The mean (geometric) level of GGT in the 7,613 men with available data on GGT was 15.6 unit/liter (range 3.0–524.0) with log standard deviation 1.77. During the follow-up period of 11.5 years, there were 876 deaths from all causes in the 7,613 men. Of these deaths, 449 deaths were attributed to cardiovascular disease causes (359 ischemic heart disease, 43 stroke, 47 other cardiovascular disease); 294 were attributed to cancer and 133 to other non-cardiovascular disease causes. Table 1 shows the relation between GGT and all-cause age-adjusted mortality rate/1,000/year by approximate quintiles of GGT. The all-cause mortality rate tended to increase with increasing GGT but was only substantially increased in the top quintile. The age-adjusted relative risk (RR) in the top quintile compared with the bottom quintile was 1.79 (95 percent confidence interval (CI) 1.43–2.23). The increased risk in total mortality was largely due to a significant increase in ischemic heart disease mortality and other non-cardiovascular disease mortality, i.e., non-cancer, non-cardiovascular disease death. There was little difference in mortality for these outcomes between the first four quintiles, but risk was significantly elevated in the top quintile (age-adjusted relative risk quintile 5: quintile 1, RR = 2.08, 95 percent CI 1.48–2.92, and RR = 1.77, 95 percent CI 1.05–2.97 for ischemic heart disease and other non-cardiovascular disease mortality, respectively). Cancer mortality was lowest in the bottom quintile, but there was little difference thereafter between the other four quintiles.

GGT and coronary disease risk factors

Personal characteristics and preexisting disease. Age showed little association with GGT ($r = 0.02$). Table 2 shows the geometric mean GGT level and the proportion of men in the top quintile of the GGT distribution by levels of personal characteristics and preexisting ischemic heart disease. Alcohol intake, body mass index, and cigarette smoking were significantly and positively associated with higher GGT levels. Men who had never smoked showed the lowest GGT levels, but there was little difference in mean GGT between current smokers and ex-smokers. Physical activity was significantly inversely associated with GGT. There was little difference in mean GGT levels between the two main social class groups, although the armed forces group had significantly higher GGT levels than non-manual and manual workers. Presence of ischemic heart disease, diabetes mellitus, or regular medication or use of antihypertensive treatment were significantly associated with higher mean GGT levels. These associations persisted even after adjustment for each of the other factors in table 2. Alcohol, body mass index, and diabetes remained strongly associated with higher levels of GGT. Smoking, physical activity, preexisting ischemic heart disease, use of antihypertensive drugs, and other regular treatment remained significantly associated with elevated GGT, but the differences were small.

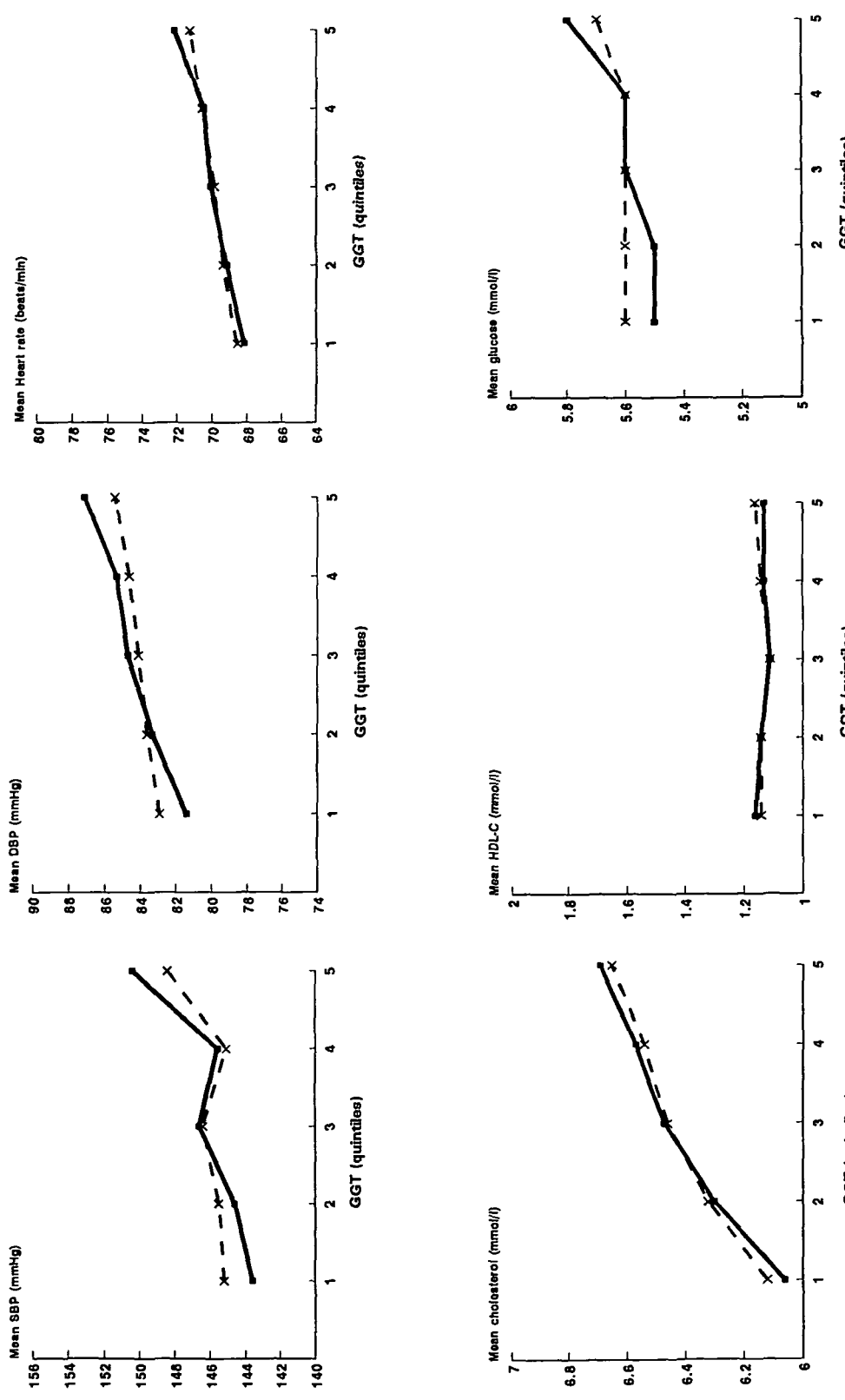

FIGURE 1. Mean systolic blood pressure, diastolic blood pressure, heart rate, serum total cholesterol, high density lipoprotein (HDL) cholesterol, and blood glucose by quintiles of gamma-glutamyltransferase (GGT) adjusted for age, alcohol intake, body mass index, smoking, physical activity, social class, preexisting ischemic heart disease, diabetes mellitus, and use of antihypertensive and other regular medication. Dashed line indicates adjustment in addition for forced expiratory volume in one second (FEV_1), systolic blood pressure, heart rate, cholesterol, HDL cholesterol, and blood glucose.

TABLE 1. Gamma-glutamyltransferase (GGT) and age-adjusted all-cause mortality rate/1,000/year: British Regional Heart Study, Great Britain, 1978–1980

GGT quintile (unit/liter)	Total mortality	Cardiovascular disease mortality		Non-cardiovascular disease mortality	
		IHD†	Other	Cancer	Other
≤9 (*n* = 1,350)	8.0 (119)‡	3.3 (48)	0.9 (13)	2.4 (37)	1.4 (21)
10–12 (*n* = 1,685)	9.2 (178)	3.2 (62)	0.9 (17)	3.7 (72)	1.4 (27)
13–16 (*n* = 1,633)	9.5 (183)	3.8 (73)	1.1 (21)	3.2 (62)	1.4 (27)
17–23 (*n* = 1,392)	9.8 (161)	4.0 (66)	1.0 (17)	3.7 (61)	1.0 (17)
≥24 (*n* = 1,553)	13.4 (235)	6.2 (110)	1.2 (22)	3.5 (62)	2.3 (41)
p values*	<0.0001	<0.0001	NS§	NS	<0.05

* Test for overall difference between groups.
† IHD, ischemic heart disease.
‡ Numbers in parentheses.
§ NS, not significant.

GGT and biologic variables. There was a significant positive correlation between GGT and systolic and diastolic blood pressure ($r = 0.14$ and $r = 0.17$; both $p < 0.0001$), total cholesterol ($r = 0.20$; $p < 0.0001$), lung function (FEV_1) ($r = -0.10$; $p < 0.0001$), and heart rate ($r = 0.13$; $p < 0.0001$). A small but significant correlation was seen between GGT and HDL cholesterol ($r = 0.04$; $p < 0.001$) and with blood glucose ($r = 0.07$). Adjustment for the personal characteristics and preexisting ischemic disease (in table 2) markedly reduced the association between GGT and systolic and diastolic blood pressure, but the associations remained significant (partial correlations $r = 0.06$ and $r = 0.08$ for systolic and diastolic blood pressure, respectively; both $p < 0.0001$). The associations between GGT, total cholesterol, heart rate, and lung function (FEV_1) were only slightly reduced and remained significant ($r = 0.16$, $r = 0.11$, and $r = -0.09$, respectively; $p < 0.0001$). The associations with HDL cholesterol and blood glucose, although small, remained significant ($r = 0.04$; $p < 0.01$).

GGT and blood lipids and blood pressure. To illustrate the relation between GGT and systolic and diastolic blood pressure, blood lipids, and heart rate, we have also presented the means of these factors by quintiles of GGT adjusted for the factors in table 2 (figure 1). Mean systolic blood pressure, diastolic blood pressure, heart rate, total serum cholesterol, and blood glucose tended to increase with increasing GGT levels. No consistent association was seen with HDL cholesterol. Further adjustment for FEV_1 and the other biologic variables reduced the association between GGT and systolic and diastolic blood pressure, although a weak but significant trend remained ($p < 0.0001$). Further adjustment made little difference to the GGT-total cholesterol and GGT-heart rate associations, but the association with blood glucose was diminished and nonsignificant.

Adjustment for confounding factors

Because the biologic factors (systolic blood pressure, total cholesterol, lung function, heart rate, and HDL cholesterol) may be mediating factors, we have examined the relation between GGT and all-cause mortality adjusting only for those personal characteristics in table 2. Adjustment for these factors reduced the increased risk seen, but a significant increase in risk still remained for mortality from all causes (RR = 1.32, 95 percent CI 1.11–1.55), ischemic heart disease (RR = 1.56, 95 percent CI 1.22–1.97), and other non-cardiovascular diseases (RR = 1.58, 95 percent CI 1.06–2.36) (table 3). Further adjustment for the biologic variables, e.g., systolic blood pressure, total serum cholesterol, HDL cholesterol, blood glucose, heart rate, and FEV_1 reduced the increased risk for all-cause mortality and ischemic heart disease mortality but they remained significant. The relation with other non-cardiovascular disease mortality was attenuated, although it remained marginally significant (RR = 1.45, 95 percent CI 0.95–2.20; $p = 0.08$).

Men with and without preexisting ischemic heart disease

The presence of ischemic heart disease is associated with changes in GGT levels (table 2). To assess whether elevated GGT was of similar predictive significance for ischemic heart disease mortality in men with and without evidence of ischemic heart disease, we have examined the relation between GGT and mortality from all causes, ischemic heart disease, and other non-cardiovascular diseases separately in men with no evidence of myocardial ischemia (Group 1), in men with evidence of ischemic heart disease short of a myocardial infarction (Group 2), and in men with

TABLE 2. Personal characteristics and mean (geometric) gamma-glutamyltransferase (GGT) and proportion of men in the top quintile of the distribution (≥24 unit/liter): British Regional Heart Study, Great Britain, 1978–1980

Characteristic	Geometric mean	*p* value*	% top quintile	Adjusted mean†	*p* value*
Alcohol consumption					
None (*n* = 461)	13.7		15	14.0	
Occasional (*n* = 1,814)	13.3	<0.0001	12	13.6	<0.0001
Light (*n* = 2,503)	14.4		16	14.7	
Moderate (*n* = 2,011)	17.5		26	17.5	
Heavy (*n* = 811)	22.4		42	22.2	
Body mass index (kg/m²)					
<22 (*n* = 957)	12.9		12	12.8	
22–23.9 (*n* = 1,527)	14.0		15	14.1	
24–25.9 (*n* = 2,039)	15.2	<0.0001	19	15.2	<0.0001
26–27.9 (*n* = 1,609)	16.4		23	16.3	
≥28 (*n* = 1,478)	18.9		31	18.2	
Smoking (cigarettes/day)					
Never smoker (*n* = 1,796)	14.3		19	14.5	
Ex-smoker (*n* = 2,669)	15.8		22	15.2	
1–19 (*n* = 1,171)	16.0	<0.0001	22	15.9	<0.0001
20 (*n* = 825)	15.6		20	15.2	
≥21 (*n* = 1,137)	16.8		24	15.7	
Physical activity					
None/occasional (*n* = 2,978)	16.6		24	16.4	
Light (*n* = 1,731)	15.5	<0.0001	19	15.6	<0.0001
Moderate (*n* = 1,194)	14.6		17	15.0	
Moderately vigorous or vigorous (*n* = 1,605)	14.6		17	14.9	
Social class					
Non-manual (*n* = 3,006)	15.3		20	16.1	
Manual (*n* = 4,386	15.6	0 .02	21	15.3	<0.0001
Armed forces (*n* = 221)	16.8		26	16.8	
Grade of preexisting IHD or MI‡					
1. No preexisting IHD (*n* = 5,694)	15.2		19	15.5	
2. Preexisting evidence of IHD, short of an MI (*n* = 1,497)	16.9	<0.0001	25	16.3	0.001
3. Preexisting definite MI (*n* = 422)	16.8		25	16.0	
Diabetes mellitus					
No (*n* = 7,497)	15.5		20	15.6	
Yes (*n* = 116)	19.3	<0.0001	34	19.1	0.002
Regular medication					
None (*n* = 5,424)	15.0		20	15.2	
Antihypertensive (*n* = 374)	17.5	<0.0001	26	16.3	<0.0001
Other (*n* = 1,815)	16.9		26	16.8	

* Test for difference in mean between groups.
† Adjusted for each of the other characteristics in the table.
‡ IHD, ischemic heart disease; MI, myocardial infarction.

definite myocardial infarction (Group 3). Elevated GGT was associated with a significant increase in risk of all-cause mortality only in men with no evidence of ischemic heart disease (table 4). The increased risk of mortality in men with no ischemic heart disease was largely due to a significant increase in risk of death from other non-cardiovascular diseases ($p < 0.01$). No association was seen with other non-cardiovascular diseases in men with preexisting ischemic heart disease (Groups 2 and 3). The number of deaths from other non-cardiovascular diseases was, however, small in these two groups. For ischemic heart disease mortality, the increased risk associated with raised GGT became more apparent with increasing severity of preexisting ischemic heart disease and was significant in men with preexisting definite myocardial infarction (RR = 1.67, 95 percent CI 1.03–2.69).

Other non-cardiovascular disease mortality

The number of specific deaths from other non-cardiovascular disease causes in men with no preexisting ischemic heart disease is examined in table 5. The significant increase in other non-cardiovascular disease causes in men with GGT >24 unit/liter with no evidence of preexisting ischemic heart disease was

TABLE 3. Relative risks (RR) (95% confidence intervals (CI)) for mortality from all causes, ischemic heart disease (IHD), and other non-cardiovascular disease (non-CVD) in men with elevated gamma-glutamyltransferase (GGT) compared with all other men: British Regional Heart Study, Great Britain, 1978–1980

Top quintile of GGT (≥24 unit/liter) vs. rest	Total mortality		IHD mortality		Other non-CVD mortality	
	RR	95% CI	RR	95% CI	RR	95% CI
Age-adjusted	1.52	1.33–1.77	1.85	1.48–2.30	1.87	1.31–2.69
Adjusted*	1.32	1.11–1.55	1.56	1.22–1.97	1.58	1.06–2.36
Adjusted†,‡	1.22	1.01–1.42	1.42	1.12–1.80	1.45	0.95–2.20

* Adjusted for age, social class, smoking, physical activity, alcohol intake, body mass index, diabetes mellitus, other regular medication, antihypertensive treatment, and preexisting IHD.
† Adjusted for above variables and in addition for systolic blood pressure, serum total cholesterol, blood glucose, forced expiratory volume in 1 second (FEV_1), heart rate, and high density lipoprotein (HDL) cholesterol.
‡ Analysis based on 7,080 men with available data on all covariates; 818 deaths from all causes, 332 IHD deaths, and 127 other non-CVD deaths.

largely due to an excess of hepatic cirrhosis and to a lesser extent to renal failure and endocrine/metabolic causes. Most of the liver cirrhosis deaths occurred within 5 years of follow-up. No excess was seen for respiratory causes or injury/poisoning.

Duration of follow-up

Because raised GGT may be a marker of subclinical disease, e.g., congestive heart failure, and because such subjects are likely to die earlier in the follow-up, we have examined the relation between GGT and ischemic heart disease and other non-cardiovascular diseases by preexisting ischemic heart disease, excluding men who died in the first 5 years of follow-up. The relation with ischemic heart disease mortality persisted and indeed was strengthened after such exclusion. The relative risks for the three preexisting ischemic heart disease groups were 1.32, 1.52, and 1.77, respectively. However, the association with other non-cardiovascular disease mortality in men with no preexisting ischemic heart disease was substantially reduced from a relative risk of 2.01 to 1.50.

DISCUSSION

In this study of middle-aged men British men, elevated gamma-glutamyltransferase (GGT) was associated with a significant increase in all-cause mortality largely due to an excess of deaths from ischemic heart disease mortality and non-cardiovascular disease causes other than cancer. The range of GGT in this study is consistent with that reported in the Tromsø Study (11). The increased mortality was seen only in the top quintile of the distribution in whom the majority would be considered to have a normal value (≤80 unit/liter) (25); only 106 men had levels >80 unit/liter. Few population studies have examined the relation between GGT and morbidity and all-cause mortality and of those studies that have examined the relation most have focused on GGT as an indicator of alcohol consumption (13–15).

TABLE 4. Adjusted* relative risks (RR) (95% confidence intervals (CI)) for mortality from all causes, ischemic heart disease, and other non-cardiovascular disease (non-CVD) in men with elevated gamma-glutamyltransferase (GGT) compared with all other men by grades of preexisting ischemic heart disease (IHD) or myocardial infarction (MI) at screening (analysis based on 7,082 men with data on all covariates): British Regional Heart Study, Great Britain, 1978–1980

Grade of preexisting IHD or MI	No. of men in top quintile of GGT (≥24 unit/liter)	All-cause mortality			IHD mortality			Other non-CVD mortality		
		No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI
1. No preexisting IHD (n = 5,309)	988	462	1.27	1.02–1.58	152	1.21	0.81–1.80	78	2.01	1.17–3.45
2. Preexisting evidence of IHD, short of an MI (n = 1,384)	336	225	1.10	0.81–1.49	96	1.32	0.84–2.10	31	1.11	0.50–1.47
3. Preexisting definite MI (n = 389)	95	130	1.16	0.76–1.74	84	1.67	1.03–2.69	18	0.31	0.06–1.49

* Adjusted for age, social class, smoking, physical activity, antihypertensive treatment, other regular medication, diabetes mellitus, body mass index, serum total cholesterol, systolic blood pressure, high density lipoprotein (HDL) cholesterol, blood glucose, heart rate, and forced expiratory volume in 1 second (FEV_1).

TABLE 5. Elevated gamma-glutamyltransferase (GGT) and number of cause-specific deaths from other non-cardiovascular disease causes in men with no preexisting ischemic heart disease (n = 5,309 men; n = 78 deaths; analysis based on 7,082 men with data on all covariates): British Regional Heart Study, Great Britain, 1978–1980

Cause of death*	GGT (unit/liter)	
	<24 (n = 4,321)	≥24 (n =988)
Respiratory disease (ICD codes 460–519)	27	5
Cirrhosis/liver disease (ICD codes 571–573)	1	5
Other digestive disease (ICD codes 520–579)	5	2
Renal disease (ICD codes 580–589)	3	3
Endocrine/metabolism disorders (ICD codes 241–279)	3	3
Injury/poisoning (ICD codes 800–999)	12	3
Other	4	2
Total	55	23

* ICD, *International Classification of Diseases*, 9th Revision.

The relation between reported alcohol intake and all-cause mortality has generally been found to be U-shaped (18, 26) and for ischemic heart disease mortality the relation is usually "inverse" (26, 27). This differs markedly from the relation seen between GGT and all-cause mortality and ischemic heart disease mortality in the present study where the relation is positive. The lack of a U-shaped relation with GGT is unlikely to be explained by the inclusion of former heavy drinkers, who may have an increased risk of mortality, falling into the top quintile of the GGT distribution. Our earlier paper on 25 biochemical/hematologic markers of alcohol intake (25) showed that nondrinkers, of whom 70 percent were ex-drinkers, had the lowest level of GGT. Indeed, only 15 percent of nondrinkers fell into the top quintile of the GGT distribution. Our findings of a strong positive association between GGT and all-cause mortality are similar to the findings observed in the Malmö Study (13). As in the Malmö Study, no association was seen between GGT and cancer mortality in this study, although previous work from Oklahoma (28) had demonstrated a relation between GGT and cancer incidence. This may relate to the type of cancers, because there were very few deaths from alcohol-related cancers in this study.

GGT and risk factors

Several studies have shown GGT to be influenced by factors other than alcohol, in particular body mass index (11, 12, 25). In this study, only 22 percent of men in the top quintile of the GGT distribution were heavy drinkers, i.e., >42 units/week. The strong linear association between GGT and alcohol intake has been reported previously from this study (5). Significant associations have now been observed between GGT and many of the cardiovascular disease risk factors, in particular body mass index, diabetes mellitus, and serum total cholesterol, and, to a lesser extent, preexisting ischemic heart disease, regular medication, physical activity, smoking, blood pressure, heart rate, and FEV_1. These associations were independent of alcohol intake, preexisting disease, regular medication, and other personal characteristics. The significant positive association between GGT and serum total cholesterol is consistent with findings from other recent studies (11, 12). No association was seen with HDL cholesterol. Although GGT was not associated with blood glucose, higher GGT levels were seen in diabetics, which appeared to be independent of body mass index and blood pressure, factors associated with risk of diabetes (29, 30). Although it is well established that alcohol intake is strongly associated with blood pressure (31), some studies have reported an association between GGT and blood pressure in nondrinkers, suggesting that the GGT-blood pressure relation is not mediated by alcohol (11, 32). A weak but significant association was observed between GGT and both systolic and diastolic blood pressure in this study, and this association appeared to be independent of alcohol intake in a multivariate analysis. However, when the relation was examined separately in nondrinkers/occasional drinkers, no association was seen between GGT and systolic blood pressure, but a weak association was still seen with diastolic blood pressure (data not shown).

The relation between GGT and ischemic heart disease mortality in this study appears to be independent of age, preexisting disease, ischemic heart disease, regular medication, personal characteristics, and the biologic variables in the multivariate analysis. This implies that the underlying mechanism relating GGT and ischemic heart disease mortality is either to some extent independent of the biologic factors measured or that the process of adjustment does not take into account the imprecision of the measured risk factors. Indeed, adjustment for these factors may lead to underestimation of the strength of the association with GGT. GGT is unlikely to be a proxy measure for alcohol intake or body mass index, because in this cohort of men both of these measures show a U-shaped relation with all-cause mortality (26, 33). The association with non-cardiovascular disease mortality was attenuated after these adjustments and was of marginal significance. Elevated heart rate is consid-

ered to be a nonspecific marker of ill-health and has been shown to be associated with other non-cardiovascular diseases (34). FEV_1 is an indicator of impaired lung function. These findings suggest that part of the excess risk of other non-cardiovascular disease mortality in men with elevated GGT is likely to reflect underlying chronic diseases resulting in raised GGT.

Preexisting ischemic heart disease

When the GGT-mortality relations were examined separately in those with and without preexisting ischemic heart disease, the predictive effect of GGT on mortality appeared to be influenced by the presence of preexisting heart disease at screening. In *men with no preexisting ischemic heart disease*, the increased mortality was largely due to an excess of other non-cardiovascular disease mortality, in particular liver cirrhosis, renal failure, and endocrine/metabolic causes, many of which are alcohol-related, and most of the liver disease deaths occurred within 5 years of follow-up. This is consistent with other studies that have found associations between elevated GGT and disorders caused by alcohol consumption (13, 15).

The increased risk of ischemic heart disease mortality associated with elevated GGT was more apparent in *men with preexisting ischemic heart disease*, particularly those with previous myocardial infarction. In men with no evidence of preexisting ischemic heart disease, GGT was associated with a 21 percent increase in ischemic heart disease mortality (nonsignificant). The strong association seen particularly in those with previous definite myocardial infarction (67 percent increase in ischemic heart disease mortality) suggests that the raised GGT and the increased mortality may be due to hepatic congestion due to cardiac failure (35) and that deaths would be concentrated early in the follow-up period. However, the relation between GGT and ischemic heart disease mortality was not affected by exclusion of those men who died early in the follow-up, suggesting that the relation between GGT and ischemic heart disease mortality may be due to other mechanisms.

Mechanisms

GGT is involved in glutathione metabolism (36). Glutathione is of major importance in oxidation/reduction reactions involving glutathione peroxidase and glutathione reductase. This system protects cells from oxidative attack by free radicals and peroxides. Intracellular substrates for the synthesis of glutathione are provided by amino acid transport mechanisms and by a glutathione salvaging function mediated by GGT (37). It is possible that elevated GGT levels are a marker for defects in amino acid transport and glutathione salvaging systems that might be expected to lead to an increased risk of cellular injury due to oxidants. If raised GGT indicates increased oxidative stress, an association between GGT and cancer might be predicted (37) but was not found. However, two recent randomized controlled trials of the effects of antioxidant vitamin supplements in the prevention of rectal (38) and lung cancer (39) found no benefits of treatment, which suggests that oxidants may not have a causal role in carcinogenesis.

Alternatively, men exposed to risk factors might be expected to mount protective antioxidant responses leading to induction of GGT to aid glutathione salvage and amino acid transport. Adjustment for oxidative stressors such as smoking and diabetes might be expected to reduce the strength of the GGT and ischemic heart disease relation. Although this effect was observed, there still remained an excess risk associated with elevated GGT. However, our analysis did not adjust for dietary and other factors that may be important in determining oxidation reactions. Knowledge of the relative importance of different exposures and their role in oxidative mechanisms is lacking (37). The degree of oxidative stress is likely to be important in determining physiologic responses and the type and severity of tissue damage (40).

Conclusion

The findings in this study suggest that higher levels of GGT in a population, i.e., the top quintile of the distribution, may need to be viewed with concern as to the factors responsible for such readings. The biologic significance of higher levels of GGT in the presence and absence of cardiovascular disease requires further work to understand the mechanisms between oxidant-induced cellular damage, the role of GGT in modifying the metabolism of glutathione, and the relation between GGT and cardiovascular disease risk factors. In particular, the impact on mortality and on GGT levels of antioxidant therapy in men with evidence of ischemic heart disease would help determine whether GGT is directly involved in pathologic mechanisms.

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