Association of gamma-glutamyltransferase levels with total mortality, liver-related and cardiovascular outcomes: A prospective cohort study in the UK Biobank

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Summary

Background Gamma-glutamyltransferase (GGT) levels in the blood can be a sensitive marker of liver injury but the extent to which they give insight into risk across multiple outcomes in a clinically useful way remains uncertain.

Methods Using data from 293,667 UK Biobank participants, the relationship of GGT concentrations to self-reported alcohol intake and adiposity markers were investigated. We next investigated whether GGT predicted liver-related, cardiovascular (CV) or all-cause mortality, and potentially improved CV risk prediction.

Findings Higher alcohol intake and greater waist circumference (WC) were associated with higher GGT; the association was stronger for alcohol with evidence of a synergistic effect of WC. Higher GGT concentrations were associated with multiple outcomes. Compared to a GGT of 14.5 U/L (lowest decile), values of 48 U/L for women and 60 U/L for men (common upper limits of 'normal') had hazard ratios (HRs) for liver-related mortality of 1.83 (95% CI 1.60–2.11) and 3.25 (95% CI 2.38–4.42) respectively, for CV mortality of 1.21 (95% CI 1.14–1.28) and 1.43 (95% CI 1.27–1.60) and for all-cause mortality of 1.15 (95% CI 1.12–1.18) and 1.31 (95% CI 1.24–1.38). Adding GGT to a risk algorithm for CV mortality reclassified an additional 1.24% (95% CI 0.14–2.34) of participants across a binary 5% 10-year risk threshold.

Interpretation Our study suggests that a modest elevation in GGT levels should trigger a discussion with the individual to review diet and lifestyle including alcohol intake and consideration of formal liver disease and CV risk assessment if not previously done.

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Keywords: Gamma-glutamyltransferase; Cohort studies; Liver disease; Alcohol; Cardiovascular disease

Introduction

Gamma-glutamyltransferase (GGT) is used in clinical practice as a biochemical indicator of liver injury although it lacks specificity to aetiology.[1–4] Numerous studies have shown that higher GGT concentrations associate with higher risk of liver disease, cardiovascular disease (CV) and all-cause mortality.[5,6] Clinical guidelines recommend assessment for liver disease aetiology and fibrosis stage in patients with abnormal liver

Abbreviations: BMI, body mass index; CV, cardiovascular disease; HCC, hepatocellular carcinoma; HR, hazard ratio; IHD, ischaemic heart disease; NRI, net reclassification improvement; OR, odds ratio; SCORE, Systematic COronary Risk Evaluation; WC, waist circumference

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Research in context

Evidence before this study

We have searched on PubMed and Google Scholar on original papers studying the association between gamma-glutamyltransferase (GGT) and cardiovascular and liver-related clinical outcomes. Preliminary evidence has suggested a positive association of serum GGT concentration with cardiovascular (CV) outcomes. However the studies have been limited by their small sample size, study design, and/or limited range of outcomes.

Added value of this study

In our analysis, higher GGT concentrations were associated with multiple outcomes. Compared to a GGT of 14.5 U/L, values of 48 U/L for women and 60 U/L for men (common upper limits of normal) had hazard ratios (HRs) for liver-related mortality of 1.83 (95% CI 1.60−2.11) and 3.25 (95% CI 2.38−4.42), for CV mortality of 1.21 (95% CI 1.14−1.28) and 1.43 (95% CI 1.27−1.60) and for all-cause mortality of 1.15 (95% CI 1.12−1.18) and 1.31 (95% CI 1.24−1.38). Adding GGT to a risk algorithm for CV mortality reclassified an additional 1.24% of participants across a binary 5% 10-year risk threshold.

Implications of all evidence available

Our results suggest that a modest elevations in GGT might indicate a health risk and should therefore trigger an analysis of diet and lifestyle including alcohol intake and consideration of formal liver and CV risk assessment.

enzymes including GGT.[7] However the utility of GGT as an indicator of CV risk remains unclear. A mendelian randomisation study reported a modest association between GGT and risk of developing ischaemic heart disease (IHD) (OR=1.08) and similarly between low alcohol consumption and coronary heart disease (OR=0.90).[8]

Several retrospective studies have shown a positive association between GGT and traditional CV risk factors including increased alcohol intake, body mass index (BMI), smoking, IHD, diabetes, hypertension, and dyslipidaemia.[9] Increased CV risk may also, in part, relate to the known association between GGT and non-alcoholic fatty liver disease (NAFLD),[10] although the independence of the association between NAFLD and CVD remains contentious.[11]

Prospective studies show a positive association between GGT and incident myocardial infarction (MI),[12,13] heart failure (HF),[14] and cardiovascular mortality.[15] However, no study has examined the association between GGT and incident (including both fatal and nonfatal) CV outcomes after adjusting for confounding factors including other tests of liver function: alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). Previous analyses have examined the potential additional value of GGT for predicting CV events,[16,17] but lacked sufficient power to be robust.

Accordingly, we investigated factors associated with serum GGT concentrations in >250,000 participants in UK Biobank and, over a median follow-up of 11.8 years, the relationship of GGT with liver-related and CV events and all-cause mortality. Furthermore, we assessed whether the addition of GGT improved prediction of fatal CV,[18] and to what extent alcohol intake or adiposity levels explained elevations in GGT levels. These questions are important in view of rising levels of alcohol-related mortality in the UK[19] and elsewhere, and obesity levels during the COVID-19 pandemic.[20]

Methods

Study design and participants

This is a prospective cohort study with follow-up based on data linkage to hospital records and death certificates. Between 2007 and 2010, UK Biobank recruited 502,493 participants (aged 37−73 years) from the general population. Participants of the UK Biobank were generally less deprived and had a healthier lifestyle (e.g. higher physical activity level) than the UK population.[21] UK Biobank received ethical approval from the North-West Multi-centre Research Ethics Committee (reference 11/NW/0382) and all participants provided written informed content.

Participants attended one of 22 assessment centres across England, Scotland, and Wales where they completed a self-administered, touch-screen questionnaire and face-to-face interview, and trained staff took a series of measurements outlined below. Ethnicity, education level, sleep duration, smoking status, and alcohol intake were self-reported. Townsend area deprivation index was derived from postcode of residence using aggregated data on unemployment, car and home ownership, and household overcrowding.[22] Hours of physical activity were self-reported using the validated International Physical Activity Questionnaire.[23] Height was measured to the nearest centimetre, using a Seca 202 stadiometer, body weight to the nearest 0.1 kg, using a Tania BC-418 body composition analyser, and waist circumference (WC) and hip circumference to the nearest 1 mm using a standard scale. BMI was calculated as weight/height^2 and the World Health Organization's criteria were used to classify BMI into: underweight (<18.5), normal weight (18.5 to <25), overweight (25 to <30), and with obesity (≥30). Prevalent diabetes at baseline was reported in a nurse-led interview. Biochemistry measures were performed at a dedicated central laboratory between 2014 and 2017. Liver markers used in this study (GGT, ALT, AST, ALP) were analysed using enzymatic rate method with Beckman Coulter AU5800. All of these tests were externally verified with 97% (for

AST) to 100% (for GGT, ALT, and ALP) good or acceptable distribution. Details of these measurements and assay performances can be found in the UK Biobank online showcase and protocol.[24]

Outcome ascertainment

Clinical endpoints were ascertained through data linkage with national electronic administrative health records. Date and cause of death was obtained from death certificates held within the National Health Service Information Centre (England and Wales) and the National Health Service Central Register Scotland (Scotland). Date and cause of hospital admissions were obtained through record linkage to Health Episode Statistics (England and Wales) and Scottish Morbidity Records (Scotland). Detailed information about the linkage procedures can be found at http://content.digital.nhs.uk/services. At the time of analysis, mortality data were available up to 30 June 2020 and hospital admission data were available up to 31 May 2020 for participants in England and 31 March 2017 for those in Scotland and Wales. We defined liver-related disease with ICD-10 [international classification of diseases, 10th revision] codes K70–77), hepatocellular carcinoma (HCC) with ICD-10 codes C22.0; CV as IHD (I20–21 and I25), myocardial infarction (I21), heart failure (I50), and stroke (I60–64). In this study, we defined fatal events as those from death certificates, and all incident events as both fatal and nonfatal (from hospital records), whichever occurred earlier.

Statistical analysis

Nonlinear associations between GGT and health outcomes were explored using penalized cubic splines fitted in Cox proportional hazard models.[25] The estimated hazard ratio curves were zeroed at the 10th centile of the sample (14.5 U/L) while the detectable range of GGT is 5 U/L. Likelihood ratio tests were used to examine the overall statistical significance and nonlinearity. All results are reported as hazard ratios (HRs) together with 95% confidence intervals (CI). In the association analysis, participants who reported having prior chronic illnesses (n_{total}=76,629; $n_{liver\ disease}$=832), those who were receiving statin treatment (n = 46,261) and those who had never drunk alcohol (n = 21,566) were excluded to minimize reverse causation. In the prediction analysis, only participants who reported having any CV prior to baseline assessment were excluded (n = 31,299). A sensitivity analysis was conducted to examine whether the associations were consistent when these participants were included. A two-year landmark analysis was also conducted, excluding participants with events occurring in the first two years of follow-up. This could further minimise reverse causation.

Five adjustment models were used with an increasing number of covariates. Model 1 included: age, sex, ethnicity, and deprivation index; model 2 additionally included: physical activity level, dietary intake, and smoking; model 3: BMI categories, waist circumference, systolic blood pressure, prevalent diabetes, and total cholesterol; model 4: self-reported units of alcohol intake per week, and model 5: ALT, ALP, and AST. These models were fitted to explore whether, and to which extent, those factors could be confounders. The correlation coefficients between covariates were checked to ensure none had strong correlation (r>0.5) to minimise multicollinearity. In addition, we also estimated the population attributable fractions for each of the outcomes. These fractions indicate the proportion of events that were potentially attributable to elevated GGT, assuming causality.

Subgroup analyses were conducted for primary outcomes: all-cause mortality, fatal and all incident liver-related events, and fatal and all incident CV events. These factors were chosen a priori because they might modify the association between GGT and health outcomes. The nonlinear HRs and CI were presented by sex, alcohol intake (≤14 and >14 units/week), and BMI (normal and overweight/obese) categories. If the associations were found to be different by sex, sex-specific analysis for all outcomes would be presented. Proportional hazard assumptions were verified by tests based on Schoenfeld residuals.

We also conducted analysis to assess whether GGT provides incremental predictive performance to the Systematic COronary Risk Evaluation (SCORE) amongst 438,122 participants without prior CV.[26] This analysis included participants with other chronic illnesses and/or taking statin as risk prediction is still relevant to this group of patients. SCORE predicts fatal atherosclerotic CV events using sex, age, smoking, systolic blood pressure, total and high-density lipoprotein (HDL) cholesterol. In this analysis, as reverse causation is less of a concern, only participants with prior CV and missing data of CV were excluded. However, to illustrate external validity of the prediction performance, we randomly split the data into derivation (60%) and validation (40%) subsets. The derivation subset was used to derive the prediction models (both SCORE and SCORE + GGT), which was applied to the validation subset to estimate the prediction performance metrics. Both the Harrell's C-index and net reclassification improvement (NRI) were computed. C-statistic estimates the overall concordance between predicted and observed values, while NRI assesses the proportion of appropriate reclassification between models.[27] In NRI, event was defined as 10-year risk of CV mortality >5% as this is the suggested threshold to initiate statin therapy by the European Society of Cardiology.[28]

The nonlinear cross-sectional associations of alcohol intake, BMI, waist circumference (WC), and waist-hip ratio (WHR) were analysed using generalised additive model, adjusting for covariates in Model 5. Because of collinearity between WC and WHR, only the former was adjusted in the analyses of alcohol intake and BMI. Interaction between alcohol intake and obesity indicator was also examined. Analyses were conducted using R version 4.0.2 with packages *survival, gam, compareC,* and *nricens*.

Role of the funding source
The funders have no role in this study. FKH, PW, JPP, and NS have access to the dataset and decided to submit for publication.

Results

Amongst 502,493 participants in UK Biobank, 293,667 participants (median age [interquartile range (IQR)] 56^{48-62} years; 55.2% female) were included in the association analyses (Figure 1). Participants with higher GGT concentration were generally older, less likely to be white, more likely to be a smoker and obese, consumed more alcohol, processed and red meat and less fruit/vegetables, and undertook less physical activity. They also had higher concentrations of total cholesterol, ALP, ALT, and AST and lower concentrations of HDL cholesterol (Table 1).

GGT was associated strongly with alcohol intake even after adjusting for BMI, WC, and other covariates (Supplement Figure S1). BMI was not associated with GGT after adjusting for alcohol and WC. WC was associated with GGT linearly in men across the whole range but was only so in women when WC >100 cm. Replacing WC with waist-hip ratio resulted in similar findings. Assuming linearity, each SD increase in alcohol intake was associated with 4.5 and 5.5 U/L increase in GGT in women and men respectively (Figure 2), whilst each SD increase in WC was associated with a 1.5 and 1.3 increase in GGT in women and men respectively. There were also significant additive interactions between alcohol and WC (interaction terms 0.83 [95% CI 0.64–1.01] for female; 1.57 [95% CI 1.41–1.72] for male).

Over a median (interquartile range) follow-up of 11.8 (11.0–12.5) years, 4798 participants developed liver disease of whom 343 died. An incident CV event occurred in 23,414 participants, of whom 2442 died. There were 12,098 (4.1%) deaths from all-causes. The overall number of events and by GGT quintiles are shown in Supplementary Table S1.

After adjusting for all potential confounders, high GGT concentration was associated with all-cause, non-CV, liver-related, CV, MI and HF mortality (Figure 3). Compared with participants with 14.5 U/L of GGT (10th centile), those with 48 (HR 1.15, 95% CI 1.12–1.18) and 60 U/L (HR 1.31, 95% CI 1.24–1.38) were at higher risk for all-cause mortality. The corresponding HRs were 1.83 (95% CI 1.60–2.11) and 3.25 (95% CI 2.38–4.42) for liver-related mortality, and 1.21 (95% CI 1.14–1.28) and 1.43 (95% CI 1.27–1.60) for CV mortality. Associations with MI mortality appeared weaker.

GGT had a much weaker, yet significant, association with all incident events in the range of 14.5 to 50 U/L (Figure 4). The risk increment was more gradual above 50 U/L, except for liver-related, HCC and HF incidence which still exhibited a relatively linear increasing trend throughout the range of GGT. Compared with participants with 14.5 U/L of GGT (10th centile), those with 48 (HR 1.68, 95% CI 1.37–2.06) and 60 U/L (HR 2.92, 95% CI 1.87–4.56) were at higher risk for HCC incidence. Of all the associations, only liver-related incidence and ($p_{nonlinear}$ = 0.002) and mortality ($p_{nonlinear}$ = 0.03), HCC incidence ($p_{nonlinear}$ = 0.005), cardiovascular incidence ($p_{nonlinear}$ < 0.0001), and MI incidence ($p_{nonlinear}$ = 0.001) and mortality ($p_{nonlinear}$ = 0.009) were significantly non-linear. The HRs assuming linear relationships are shown in Supplement Table S2. When participants with chronic illnesses and/or receiving statin treatment were included in the analysis, the results were similar but with HRs slightly attenuated (Supplement Table S3). The two-year landmark analysis also showed very consistent results (Supplement Table S4).

Assuming causality, more fatal than all incident events were attributed to elevated GGT: 13.03% for all-cause mortality, 38.37% for liver-related mortality, 13.54% for CV mortality, 21.87% for heart failure mortality, and 38.27% for HCC incidence (Supplement Table S5).

The associations of GGT with outcomes by adjustment models are shown in Supplement Figs. S2 and S3. For mortality outcomes, the addition of each group of covariates attenuated the associations slightly but the association pattern was largely similar. However, the strength of association for incident outcomes was substantially attenuated after adjustment, particularly after adjusting for BMI, waist circumference, systolic blood pressure, prevalent diabetes, and total cholesterol, suggesting these might be stronger confounders for incident than mortality outcomes.

The associations of GGT with outcomes were generally similar by sex and alcohol intake (Supplement Figs. S4 and S5). As such, no sex-specific analyses were conducted. Stronger associations with all-cause ($P_{interaction}$=0.01) and non-CV mortality ($P_{interaction}$=0.04), and liver-related disease incidence ($P_{interaction}$<0.0001) were observed amongst participants of normal weight.

The incremental prediction performance of including GGT into SCORE is shown in Table 2. The addition of GGT to the SCORE mortality risk algorithm resulted in a modest but meaningful increment in the C-index of 0.0104 (95% CI 0.0074–0.0134) for CV mortality,

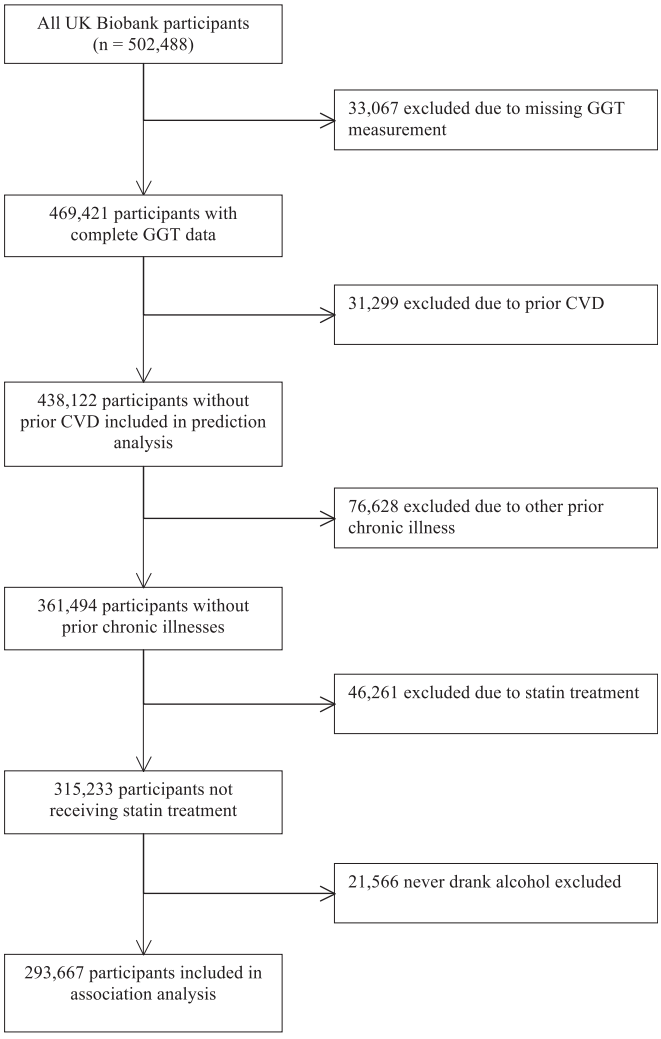

Figure 1. Flowchart of participants inclusion.

0.0032 (95% CI 0.0004–0.0060) for IHD mortality, 0.0065 for MI mortality (95% CI 0.0019–0.0111), 0.0111 (95% CI 0.0017–0.0205) for heart failure mortality, and 0.0059 (95% CI 0.0009–0.0109) for stroke mortality. After including GGT, the C-indices ranged from 0.7743 (stroke mortality) to 0.8039 (IHD mortality).

GGT also improved the classification of high risk (≥5% 10-year risk) in SCORE by 1.24% (95% CI 0.14%–2.34%) for CV mortality, even though the NRI for other CV mortality outcomes were minimal and non-significant (Table 2). Meanwhile, it might also reduce the proportion of true negative (−0.13%; 95% CI −0.23% to −0.02%) in CV mortality even though the magnitude was very small compared with the improvement in classifying high risk individuals (−0.13% versus 1.24%).

Discussion

The current study suggests independent and positive associations between GGT and all-cause, liver-related, and CV-related mortality, as well as hepatocellular carcinoma incidence. The association with greater outcome risks began well within the "normal" range and was more pronounced for liver-related diseases, followed by fatal CV and HF, than for all incident (i.e. combined fatal and nonfatal) CV events. Furthermore, the addition of GGT to the SCORE risk algorithm modestly improved 10-year prediction of fatal CV events with more than 1% correctly up classified into a higher risk category, a finding that highlights the potential of GGT as a simple risk predictor in clinical practice.[29]

GGT is often reported as a component of a 'liver panel' of biochemical tests and so the GGT may not have been specifically requested nor the focus of the clinical

	Overall	Sex-specific GGT quintile group (U/L)				
		Q1 Female: <15.1 Male: <21.9	Q2 Female: 15.1-<18.9 Male: 21.9-<28.7	Q3 Female: 18.9-<24.2 Male: 28.7-<37.9	Q4 Female: 24.2-<35.5 Male: 37.9-<55.8	Q5 Female: ≥35.5 Male: ≥55.8
Median (IQR) age in years	56 (48–62)	53 (46–61)	56.0 (48–62)	57 (49–62)	57 (50–62)	56 (50–62)
Men	131,550 (44.8)	28,567 (44.1)	27,600 (44.4)	26,437 (44.5)	25,280 (45.4)	23,666 (45.9)
Ethnicity						
White	280,595 (95.8)	62,495 (96.8)	59,752 (96.3)	56,787 (95.8)	52,806 (95.0)	48,755 (94.9)
Mixed	1776 (0.6)	381 (0.6)	348 (0.6)	368 (0.6)	348 (0.6)	331 (0.6)
South Asian	3259 (1.1)	650 (1.0)	706 (1.1)	632 (1.1)	661 (1.2)	610 (1.2)
Black	4218 (1.4)	403 (0.6)	630 (1.0)	923 (1.6)	1142 (2.1)	1120 (2.2)
Chinese	855 (0.3)	232 (0.4)	195 (0.3)	149 (0.3)	149 (0.3)	130 (0.3)
Others	2081 (0.7)	394 (0.6)	397 (0.6)	432 (0.7)	451 (0.8)	407 (0.8)
Median (IQR) deprivation Index	−2.33 (−3.74, 0.11)	−2.34 (−3.75, 0.03)	−2.40 (−3.78, −0.09)	−2.37 (−3.77, 0.05)	−2.31 (−3.72, 0.16)	−2.17 (−3.66, 0.46)
Smoking status						
Never	167,912 (57.3)	40,522 (62.7)	36,787 (59.3)	33,490 (56.5)	30,107 (54.2)	27,006 (52.6)
Previous	95,974 (32.8)	19,040 (29.5)	19,659 (31.7)	19,650 (33.2)	19,319 (34.8)	18,306 (35.7)
Current	28,901 (9.9)	5035 (7.8)	5610 (9.0)	6104 (10.3)	6120 (11.0)	6032 (11.7)
Median (IQR) physical activity in MET-min/week	1884 (890–3732)	2034 (1012–3912)	1968 (942–3795)	1878 (876–3732)	1795.5 (824–3607.5)	1653 (732–3440)
Weekly dietary intake						
Median (IQR) units of alcohol	12.0 (5.4–24.0)	9.6 (4.2–18.0)	11.7 (4.7–21.0)	12.0 (6.0–24.0)	13.80 (6.0–27.0)	15.75 (6.0–33.0)
Median (IQR) portions of red meat	2.0 (1.5–2.5)	1.5 (1.5–2.5)	1.50 (1.5–2.5)	2.0 (1.5–2.5)	2.0 (1.5–2.5)	2.0 (1.5–3.0)
Processed meat intake						
Never	25,645 (8.7)	7552 (11.7)	6015 (9.7)	4912 (8.3)	4005 (7.2)	3161 (6.1)
Less than once a week	90,557 (30.9)	20,377 (31.5)	19,846 (31.9)	18,672 (31.4)	16,704 (30.0)	14,958 (29.1)
Once a week	86,513 (29.5)	18,484 (28.6)	18,129 (29.2)	17,635 (29.7)	16,764 (30.1)	15,501 (30.1)
2–4 times a week	79,183 (27.0)	16,017 (24.8)	15,888 (25.6)	15,934 (26.8)	15,850 (28.5)	15,494 (30.1)
5–6 times a week	9113 (3.1)	1810 (2.8)	1777 (2.9)	1818 (3.1)	1848 (3.3)	1860 (3.6)
Once or more daily	2242 (0.8)	419 (0.6)	473 (0.8)	413 (0.7)	471 (0.8)	466 (0.9)
Median (IQR) portions of fruits/vegetables	3.71 (2.67–5.12)	4.0 (2.67–5.33)	3.83 (2.67–5.33)	3.71 (2.67–5.12)	3.67 (2.38–5.04)	3.48 (2.33–5.0)
Oily fish intake						
Never	30,157 (10.3)	7231 (11.2)	6208 (10.0)	5860 (9.9)	5709 (10.3)	5149 (10.1)
Less than once a week	100,870 (34.5)	22,534 (34.9)	21,256 (34.3)	20,224 (34.2)	19,047 (34.4)	17,809 (34.8)
Once a week	111,733 (38.2)	24,180 (37.5)	23,980 (38.7)	22,735 (38.4)	21,212 (38.3)	19,626 (38.3)
2–4 times a week	47,047 (16.1)	10,017 (15.5)	9979 (16.1)	9857 (16.7)	9022 (16.3)	8172 (16.0)
5–6 times a week	1902 (0.7)	405 (0.6)	418 (0.7)	388 (0.7)	349 (0.6)	342 (0.7)
Once or more daily	574 (0.2)	108 (0.2)	124 (0.2)	117 (0.2)	106 (0.2)	119 (0.2)

Table 1 (Continued)

	Overall	Sex-specific GGT quintile group (U/L)				
		Q1 Female: <15.1 Male: <21.9	Q2 Female: 15.1-<18.9 Male: 21.9-<28.7	Q3 Female: 18.9-<24.2 Male: 28.7-<37.9	Q4 Female: 24.2-<35.5 Male: 37.9-<55.8	Q5 Female: ≥35.5 Male: ≥55.8
BMI categories						
Underweight	1429 (0.5)	417 (0.6)	316 (0.5)	268 (0.5)	241 (0.4)	187 (0.4)
Normal	106,583 (36.4)	34,247 (53.0)	26,282 (42.3)	19,862 (33.5)	14,698 (26.4)	11,494 (22.4)
Overweight	125,289 (42.8)	24,660 (38.2)	26,669 (43.0)	26,683 (45.0)	24,786 (44.6)	22,491 (43.8)
Obese	59,685 (20.4)	5289 (8.2)	8812 (14.2)	12,514 (21.1)	15,884 (28.6)	17,186 (33.5)
Median (IQR) waist circumference in cm	88 (79–97)	83 (76–91)	86 (77–94)	89 (80–97)	91.50 (82–100)	93 (84–102)
Median (IQR) systolic blood pressure in mmHg	135.5 (124.0–148.5)	129.5 (119.0–142.0)	133.5 (122.5–146.5)	136.5 (125.0–149.0)	138.5 (127.3–151.5)	140.0 (129.0–153.5)
Systolic BP >140 mmHg						
Prevalent diabetes at baseline	3050 (1.0)	384 (0.6)	492 (0.8)	573 (1.0)	709 (1.3)	892 (1.7)
Median (IQR) total cholesterol in mmol/L	5.84 (5.17–6.56)	5.48 (4.88–6.14)	5.76 (5.11–6.44)	5.90 (5.25–6.60)	6.01 (5.34–6.72)	6.16 (5.46–6.90)
Median (IQR) HDL cholesterol in mmol/L	1.44 (1.21–1.71)	1.48 (1.26–1.74)	1.46 (1.23–1.74)	1.43 (1.20–1.71)	1.40 (1.17–1.68)	1.41 (1.19–1.69)
Median (IQR) GGT in U/L	25.0 (17.9–38.5)	14.4 (12.7–17.9)	18.6 (16.8–25.0)	23.8 (21.1–32.6)	34.5 (28.3–44.5)	65.9 (49.8–91.7)
Median (IQR) ALP in U/L	78.8 (66.0–93.7)	72.0 (60.4–85.3)	76.0 (64.2–90.0)	79.0 (66.7–92.9)	81.7 (69.0–96.4)	88.5 (74.4–105.6)
Median (IQR) ALT in U/L	19.50 (15.0–26.46)	15.47 (12.54–19.27)	17.40 (14.04–22.01)	19.51 (15.51–25.25)	22.47 (17.50–29.73)	28.96 (21.68–40.29)
Median (IQR) AST in U/L	24.0 (20.7–28.2)	22.0 (19.2–25.4)	22.9 (20.1–26.4)	23.9 (20.8–27.5)	25.1 (21.7–29.3)	28.2 (24.0–34.5)

***Table 1*: Participant characteristics across sex specific GGT quintiles.**
All data given as in n (%), unless stated otherwise.

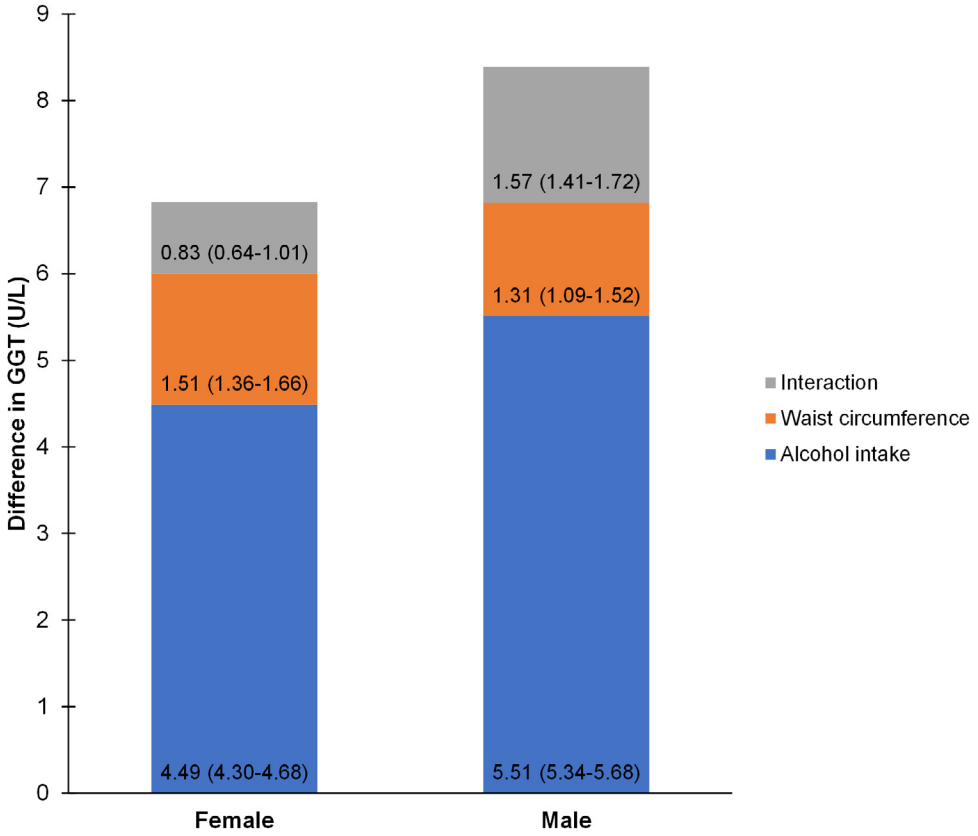

Figure 2. Difference in GGT per 1-SD increase in alcohol intake, waist circumference, and interaction.

Numbers shown are coefficients and 95% CIs in linear regression analysis. One SD increase correspond to 27.9 and 36.8 U/L increase of GGT in female and male respectively. Adjusted for each other and for age, sex, ethnicity, deprivation index, physical activity, dietary intake, smoking, BMI categories, waist circumference, systolic blood pressure, units of weekly alcohol intake, prevalent diabetes, total cholesterol, and other liver function tests.

encounter. Given these findings, we suggest physicians should consider elevations in GGT levels in their patients and take the opportunity to (re)emphasize advice on relevant lifestyle factors for liver and CV disease, such as alcohol intake (as many people underestimate their alcohol intake) and central obesity, as we shown in the cross-sectional analysis. Clinicians should follow existing guidance for assessment of liver disease aetiology and fibrosis stage[7] and formal cardiovascular risk stratification should also be considered and effective interventions implemented, as needed.[30] In this way, elevated GGT levels signal risk for multiple outcomes, and add to prediction for fatal CV events, a potential counselling point for patients. These points are particularly important in the face of recent rising alcohol-related deaths in the UK and rising obesity prevalence during the COVID-19 pandemic.[19,20]

Strengths of the current study include being by far the largest single study to assess the associations of GGT with all-cause and CV mortality, including individual CV outcomes, in the general population. We applied comprehensive adjustment for traditional cardiometabolic risk factors and excluded individuals with baseline CV including heart failure, chronic liver disease, and associated comorbidities to minimize reverse causality. Stratified analyses also ensured relationship between sexes and across self-reported alcohol intake, were similar. Finally, through calculating the C-indices and NRI for the addition of GGT to the SCORE algorithm, we have shown that GGT may be a useful marker in clinical practice to predict the risk of *fatal CV disease*. Limitations include potential residual confounding, particularly with regards to participants' self-reported alcohol intake. That note, GGT may also be an 'objective' indication of excess alcohol intake for some people who are in denial, to legitimise alcohol advice, with other supportive evidence sometimes coming from higher-than-expected AST, HDL-cholesterol or mean corpuscular volume levels.[31] The UK Biobank is not entirely representative of the whole UK population, with evidence of a healthy volunteer selection bias. However, estimates of effect size are still widely generalizable.[32] The length of follow-up was 2 years longer in

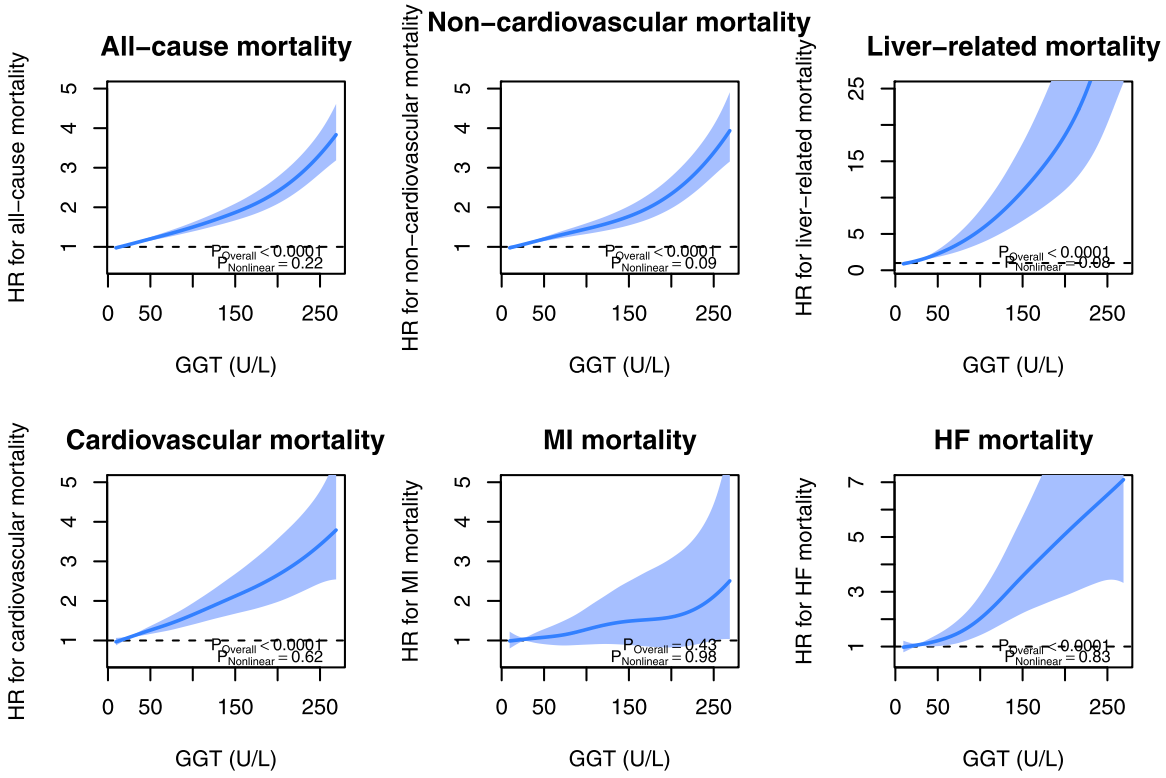

Figure 3. Association of GGT with all-cause, non-cardiovascular, liver-related, CV, MI, and HF mortality.

Shaded areas are 95% CIs. Adjusted for age, sex, ethnicity, deprivation index, physical activity, dietary intake, smoking, BMI categories, waist circumference, systolic blood pressure, units of weekly alcohol intake, prevalent diabetes, total cholesterol, and other liver function tests.

England than in Scotland and Wales, which could lead to selection bias if there were differential death rates for those two years that is also associated with GGT.

The present study builds on findings from previous studies which have demonstrated the association between GGT and all-cause and CV-related mortality,[33–35] by considering a wide range of covariates (including other liver markers), the use of nonlinear analysis techniques, and the evaluation of prediction performance using split-data. Analysis of 7613 middle-aged British men from the British Regional Heart Study showed those in the highest GGT quintile (>24 U/L) were at a 22% higher risk of death from any cause and a 42% higher risk of death from IHD, even after adjustment for known CV risk factors.[13] However, this study was limited to men and did not adjust for AST, ALT, or ALP, liver markers associated with NAFLD, nor was it able to examine differential associations with fatal versus nonfatal outcomes or with incident HF or HF mortality.

We found the association of GGT to be stronger for fatal than incident CV, as well as for fatal versus incident liver disease. This is consistent with previous findings. For example, in a study of 262 patients with prior MI, GGT was associated with 2.87 times higher risk of mortality but 2.17 times higher risk of a composite of mortality or MI.[17] Such findings could be related to a putative pathogenic role of GGT in the progression of atherosclerotic plaques[36] or its potential role in low-density lipoprotein (LDL) oxidation and subsequent plaque formation.[37,38]

GGT is a sensitive but non-specific marker of liver disease[39] including HCC development (at least in hepatitis B-infected individuals)[40] and may reflect more aggressive disease biology.[39] The extent to which elevations in GGT represent early events in liver diseases should be further explored in studies with biomarkers of liver disease stage and function such as bilirubin, albumin, and platelet counts.

GGT is a risk factor for fatal CV event independent of current SCORE predictors but previous studies did not explicitly estimate the improvement in predictive performance, such as with C index and NRI.[41] Another study found no significant improvement in prediction of a first CVD event with the addition of GGT.[42] However, our study shows that GGT concentrations *had a stronger association with fatal*, as opposed to non-fatal, events. The improvement in C-index (ΔC=0.0104) we noted with the addition of GGT for fatal CVD is only

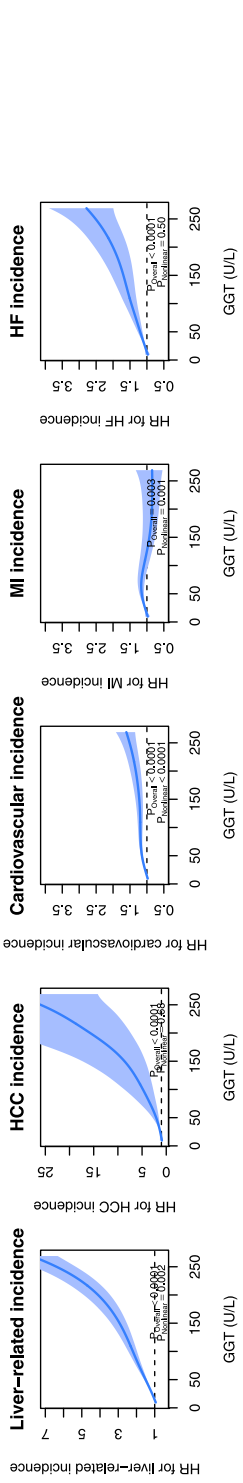

Figure 4. Association of GGT and incident outcomes.
Shaded areas are 95% CIs. Adjusted for age, sex, ethnicity, deprivation index, physical activity, dietary intake, smoking, BMI categories, waist circumference, systolic blood pressure, units of weekly alcohol intake, prevalent diabetes, total cholesterol, and other liver function tests.

modest in absolute terms but could be clinically relevant. Indeed, the noted C-index improvement was greater than the gains seen with other parameters (e.g. total and HDL cholesterol [ΔC=0.004],[43] high sensitivity C-reactive protein [ΔC=0.006],[44] and glomerular filtration rate based on creatinine and cystatin C [ΔC=0.005][45]) being investigated to improve risk scores in recent high profile papers, accepting differing risk models were being compared. Furthermore, the NRI for GGT (1.24% for events) appeared to be stronger than when total and HDL cholesterol were added to the office-based risk prediction (0.79% for events[46]). Since GGT is cheap and commonly available at the same time as other routine tests, more people at risk of a fatal CVD event could be identified based on elevations in GGT leading to formal risk screening and intervention. Interestingly, GGT may also have a role in the prognosis of patients undergoing percutaneous coronary interventions, as shown in multiple mortality and heart failure outcomes.[47–49]

The present study showed that alcohol intake was strongly and linearly associated with GGT even when sociodemographic, lifestyle, other liver function markers, and obesity were adjusted for. There were also significant positive interactions between alcohol intake and WC on GGT. This is consistent with, and meaningfully expands, a previous report showing prospective association between alcohol intake and obesity (as indicated by BMI) with liver disease,[50] since our analyses mutually adjusted for WC and BMI. This suggests that central obesity, rather than general obesity, might be a stronger risk factor for elevated GGT though this warrants further studies. It was also notable that whereas waist levels were linearly associated with GGT levels in across the entire range in men, only once waist circumference levels extended beyond around 100 cm did GGT levels rise in women. This difference in part reflects greater capacity to store subcutaneous fat in females and is in keeping with lower risks for diabetes[51] and NAFLD[52] compared to men, at similar BMI levels. Given these associations, a relationship of GGT with liver-related mortality might be expected hence the need to determine the aetiology of liver disease and to risk-stratify for liver fibrosis.

This study suggests GGT levels to be associated with liver related outcome and with a broad range of CV conditions. While adjustment for traditional cardiometabolic risk factors attenuated the association of GGT with incident CV including IHD, MI, stroke, and atrial fibrillation, the association with incident heart failure remained strong. This finding is in keeping with previous studies which have shown that individuals free from heart failure and MI at baseline with a GGT concentration ≥ 16 U/L in men and 9 U/L in women had a 71% increased risk of heart failure compared to individuals with GGT concentrations below these values, even after adjustment for traditional CV risk factors and liver aminotransferases.[53] Extending these findings, we have shown that this association is even stronger for fatal

Fatal events	C-index (%)			NRI (%)	
	GGT + SCORE model	Change from SCORE only model	P	Event (Up) (10-year mortality risk ≥5%)	Non-event (Down) (10-year mortality risk <5%)
CV composite	0.7866 (0.7760 to 0.7968)	0.0104 (0.0074 to 0.0134)	< 0.0001	1.24 (0.14 to 2.34)	−0.13 (−0.23 to −0.02)
IHD	0.8039 (0.7908 to 0.8164)	0.0032 (0.0004 to 0.0060)	0.03	0.41 (−0.96 to 1.79)	−0.20 (−0.29 to −0.08)
MI	0.7833 (0.7582 to 0.8064)	0.0065 (0.0019 to 0.0111)	0.006	0.56 (−2.21 to 3.61)	−0.11 (−0.20 to −0.02)
HF	0.7805 (0.7539 to 0.8049)	0.0174 (0.0088 to 0.0261)	< 0.0001	−0.59 (−2.69 to 1.63)	−0.09 (−0.21 to 0.03)
Stroke	0.7743 (0.7534 to 0.7938)	0.0059 (0.0009 to 0.0109)	0.02	0.02 (−1.78 to 1.85)	0.04 (−0.04 to 0.13)

***Table 2*: C-indices and NRI for GGT in additional to SCORE.**
SCORE is based on sex, age, systolic blood pressure, total and HDL cholesterol, and smoking status. Model was trained with 60% randomly selected data subset and C-indices were estimated for the remaining 40% data subset for validation.
CV: cardiovascular disease; IHD: ischaemic heart disease, MI: myocardial infarction; HF: heart failure.

heart failure, increasing in a linear fashion with a HR approaching near **four-fold** at GGT concentrations just over 150 U/L.

The patterns we observe in UK Biobank are similar to those of an international consortium previously reported for alcohol intake.[54] Both GGT concentrations and reported alcohol intake are more strongly associated with CV events, other than MI, including stronger associations with fatal CV events. Thus, we consider that the associations reported herein may in part relate to excess alcohol intake in many individuals, a measure difficult to establish with accuracy as many people will under-report or under-recognise their true alcohol intake. However, GGT concentrations also depend on genetic determinants[55] as well as liver fat accumulation and diabetes,[56,57] and thus the associations we report may reflect other overlapping factors. While there is insufficient evidence to support actively seeking out GGT as a disease predictor, where GGT results are available and elevated, clinicians should take the opportunity to address risk factors for liver-related and CV mortality risks. Whether we should more often measure GGT in clinical practice is something worthy of further study.

In conclusion, GGT is independently associated with increased CV events and all-cause mortality as well as liver related outcomes. GGT modestly improves the 10-year prediction of *fatal CV events* beyond established predictors. Clinicians should be made aware of the link of even apparently modest elevations of GGT with all-cause, non-CV and CV-related deaths, and should consider optimising liver and CV risk management in this group, including the (re)emphasis of advice on factors such as alcohol intake, weight change or activity levels. They should also conduct formal liver (as per guidance) and CV risk assessments in such patients if not already done, especially if GGT levels remain meaningfully elevated despite relevant lifestyle advice.

Contributors

FKH, PW, JPP and NS conceived the idea for the paper. FKH conducted the analysis. All authors contributed to the interpretation of the findings. FKH, LDF, CACM, PW, and NS jointly wrote the first draft. All authors critically revised the paper for intellectual content and data and approved the final version of the manuscript. FKH, PW and NS are guarantors of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

UK Biobank data can be requested by bona fide researchers for approved projects, including replication, through https://www.ukbiobank.ac.uk/.

Declaration of interests

PW has received research grants from Roche Diagnostics, AstraZeneca and Boehringer Ingelheim outside the submitted work, and NS has received grants from AstraZeneca, Boehringer Ingelheim, and Roche Diagnostics, and personal fees from Afimmune, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi outside the submitted work. JGFC has received research grants from Bayer, Pharmacosmos and Vifor outside the submitted work All the other authors declare no conflict of interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101435.

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