Association of gamma-glutamyltransferase levels across and beyond the 'normal' range with total mortality, liver-related, and cardiovascular outcomes: a prospective cohort study in the UK Biobank

ONLINE-ONLY SUPPLEMENT

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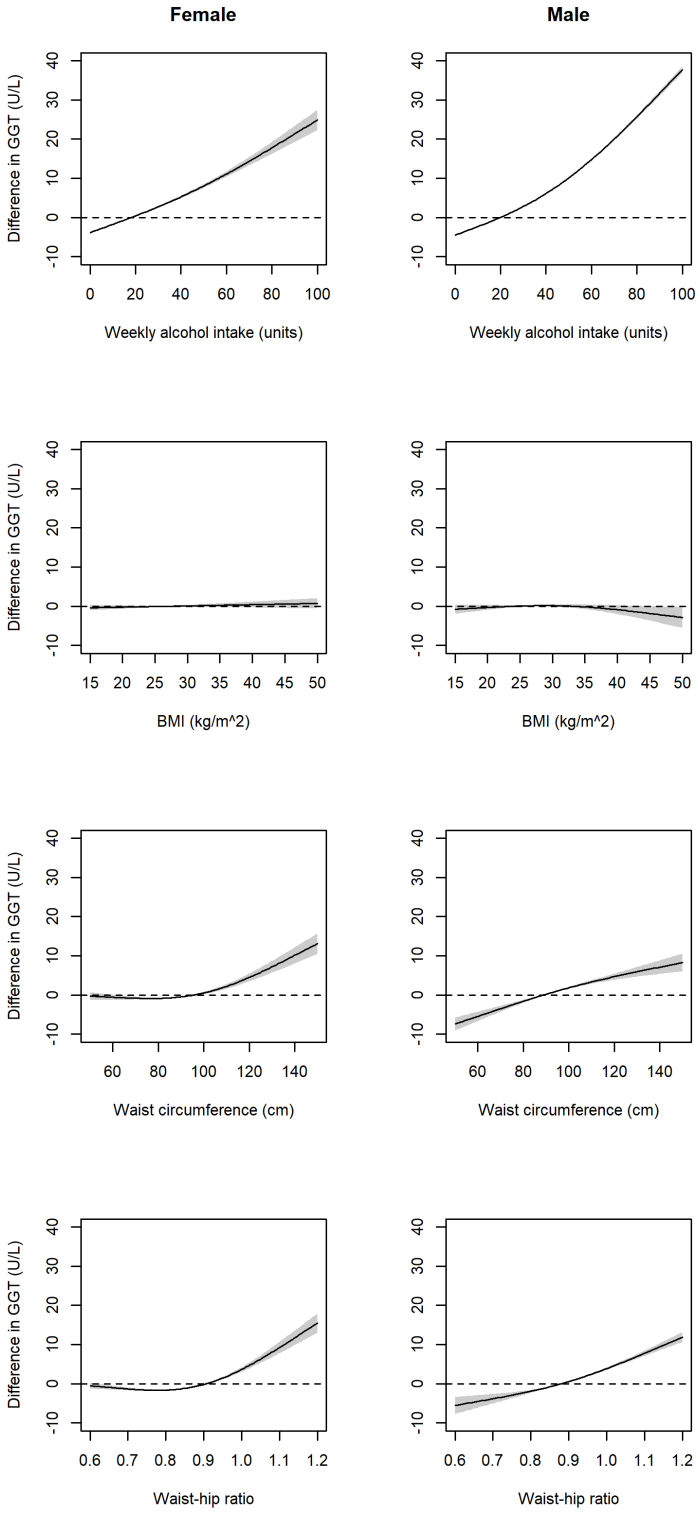
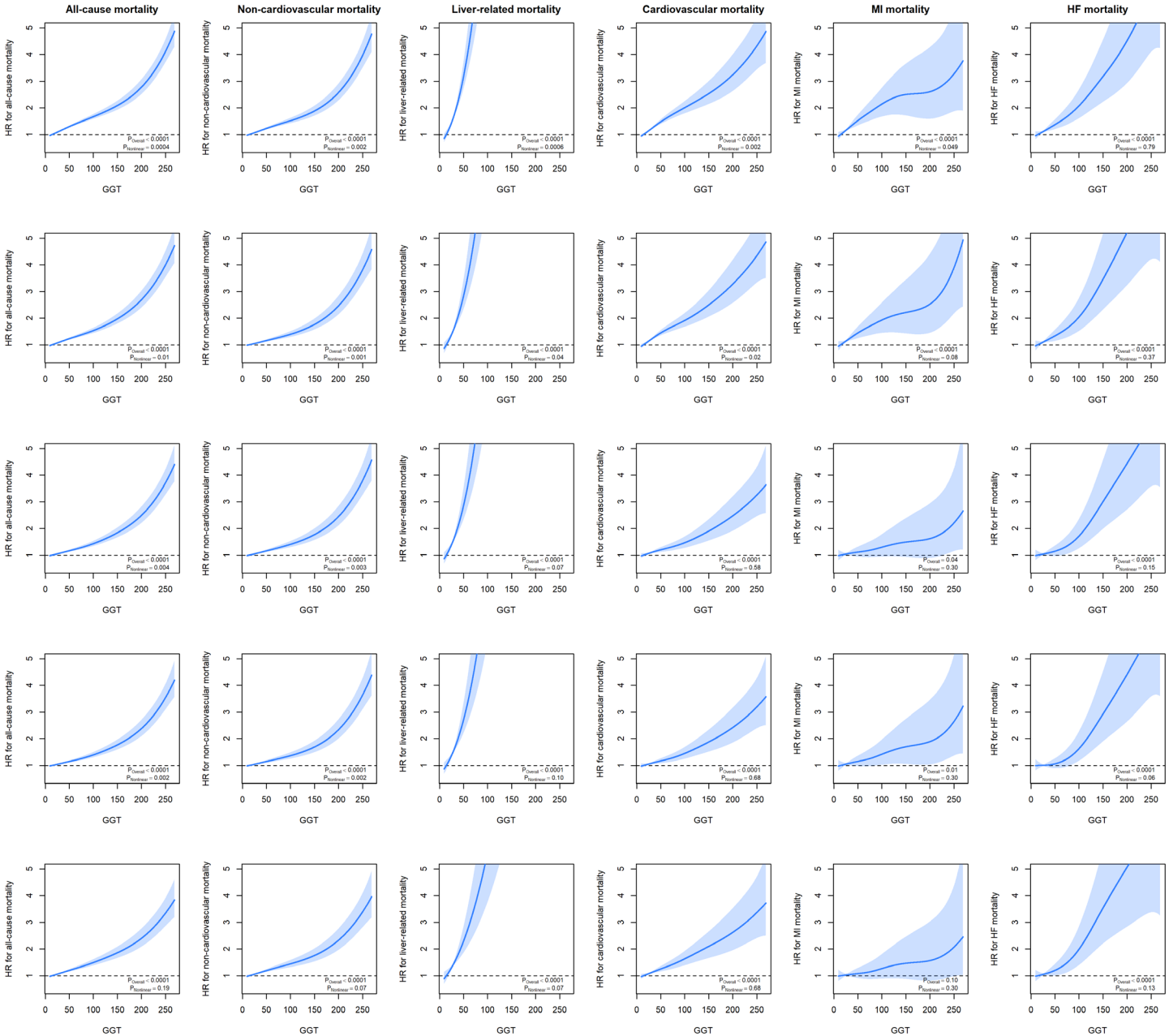
Figure S1. Nonlinear association of alcohol intake, BMI, and waist circumference with GGT



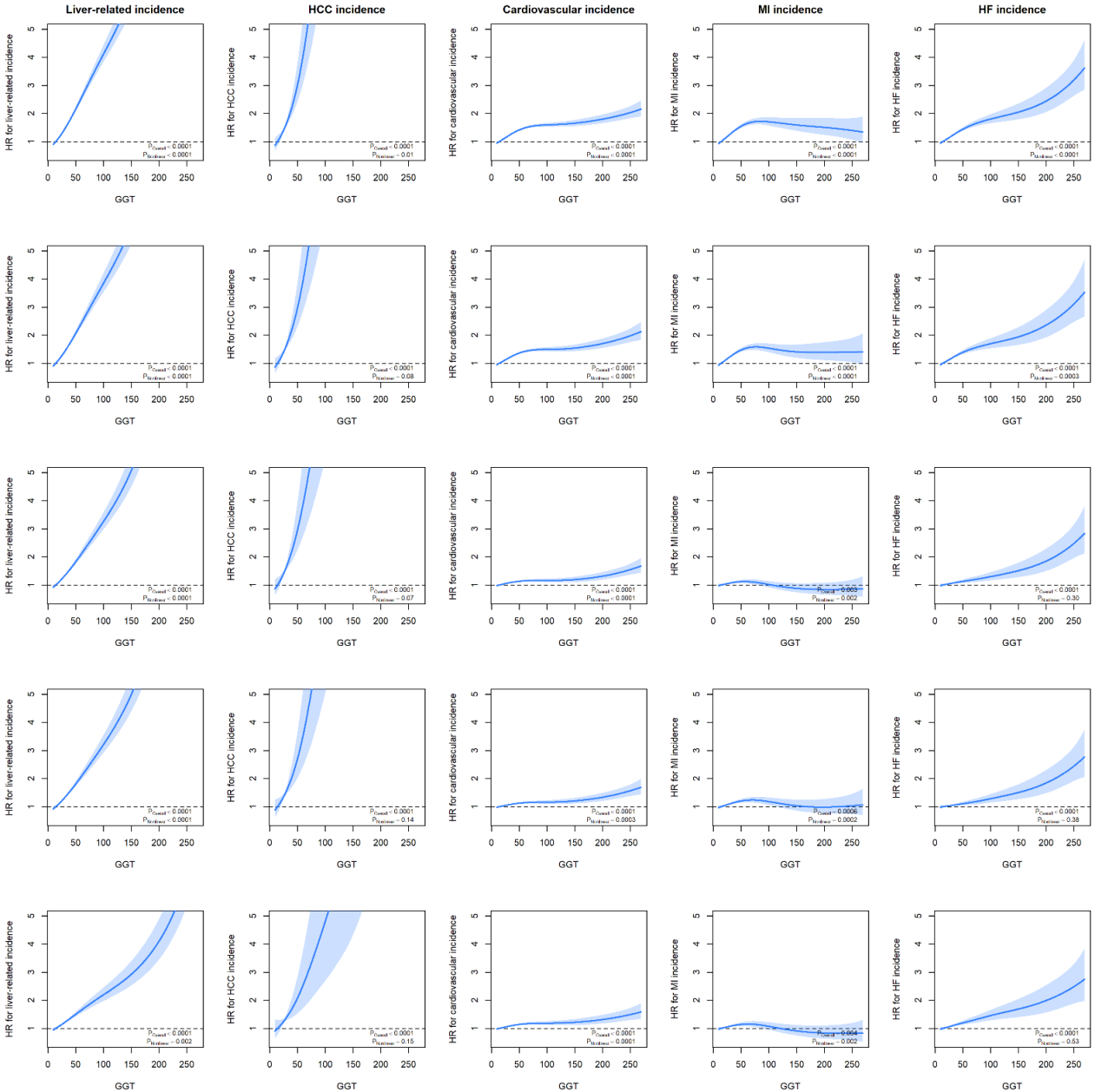
The figure shows the differences in GGT (U/L) for each of the risk factors compared with the mean values. E.g. among female, compared with the mean value (20 units/week), alcohol consumption of 60 units/week was associated with 10 U/L increase in GGT. Adjusted for each other and for age, sex, ethnicity, 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

Figure S2. Association of GGT with fatal events by model adjustment



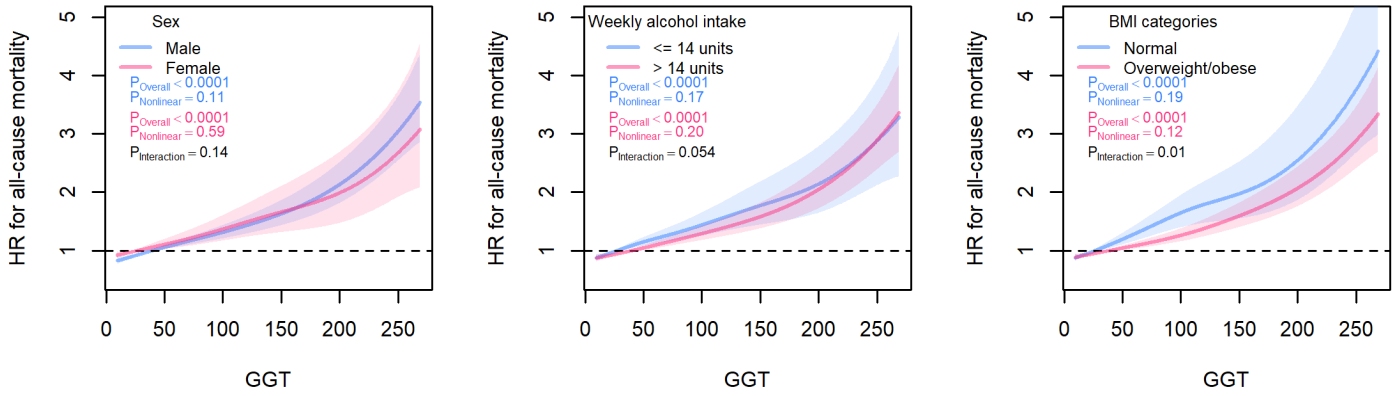
Each row represents a model adjustment model. M1: Age, sex, ethnicity, and deprivation index; M2: M1 + physical activity, dietary intake, and smoking; M3: M2 + BMI categories, waist circumference, systolic blood pressure, prevalent diabetes, total cholesterol; M4: M3 + units of weekly alcohol intake; M5: M4 + other liver function markers

Figure S3. Association of GGT with all incident events by model adjustment



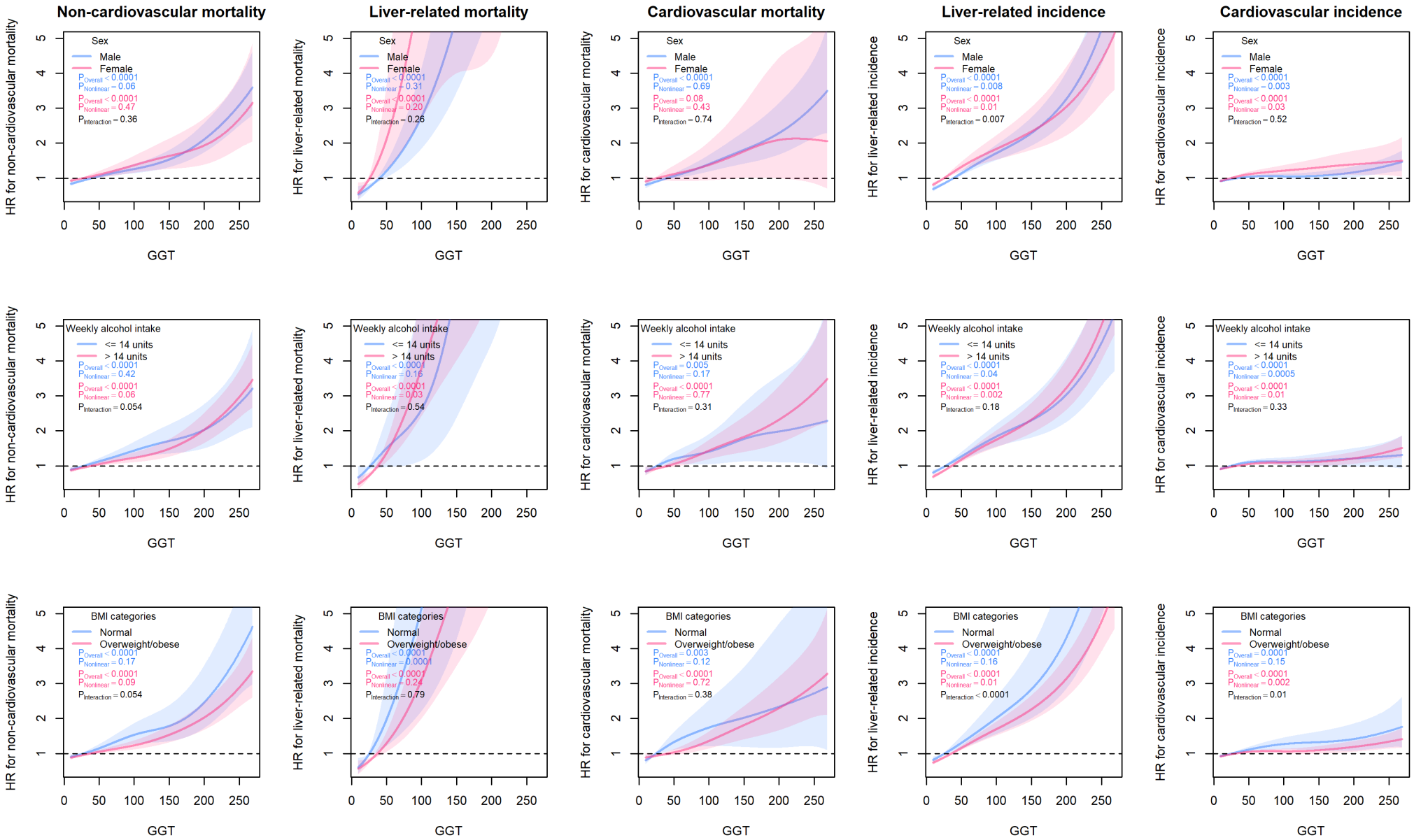
Each row represents a model adjustment model. M1: Age, sex, ethnicity, and deprivation index; M2: M1 + physical activity, dietary intake, and smoking; M3: M2 + BMI categories, waist circumference, and systolic blood pressure, prevalent diabetes, total cholesterol; M4: M3 + units of weekly alcohol intake; M5: M4 + other liver function markers

Figure S4. Association of GGT with all-cause mortality by subgroups by sex, alcohol units and BMI



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

Figure S5. Association of GGT and CVD outcomes by subgroups



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

Table S1. Numbers of events across sex specific GGT quintiles

		Sex-specific GGT quintile group				
	Overall	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
Fatal events						
Liver-related	343	17 (5)	18 (5.2)	31 (9)	39 (11.4)	238 (69.4)
MI	497	73 (14.7)	80 (16.1)	108 (21.7)	117 (23.5)	119 (23.9)
Stroke	699	106 (15.2)	139 (19.9)	152 (21.7)	139 (19.9)	163 (23.3)
HF	452	71 (15.7)	88 (19.5)	79 (17.5)	88 (19.5)	126 (27.9)
CV	2442	359 (14.7)	446 (18.3)	495 (20.3)	531 (21.7)	611 (25)
All-cause mortality	12098	2012 (16.6)	2203 (18.2)	2492 (20.6)	2473 (20.4)	2918 (24.1)
Incidence (fatal & nonfatal)						
Liver-related	4798	556 (11.6)	677 (14.1)	735 (15.3)	966 (20.1)	1864 (38.8)
HCC	160	5 (3.1)	17 (10.6)	13 (8.1)	18 (11.2)	107 (66.9)
MI	4973	754 (15.2)	922 (18.5)	1077 (21.7)	1144 (23)	1076 (21.6)
Stroke	5673	958 (16.9)	1097 (19.3)	1187 (20.9)	1208 (21.3)	1223 (21.6)
HF	4382	680 (15.5)	825 (18.8)	862 (19.7)	969 (22.1)	1046 (23.9)
CV	23414	3769 (16.1)	4525 (19.3)	4895 (20.9)	5119 (21.9)	5106 (21.8)

Table S2. Linear association of GGT with fatal and all CVD events

	Fatal events		All incident events	
	HR (95% CI)	P	HR (95% CI)	P
Per SD increase				
All-cause	1.18 (1.15-1.20)	< 0.0001	-	-
Liver-related	1.62 (1.50-1.75)	< 0.0001	1.27 (1.23-1.30)	< 0.0001
Hepatocellular carcinoma	-	-	1.51 (1.35-1.69)	< 0.0001
CV	1.19 (1.14-1.25)	< 0.0001	1.06 (1.04-1.08)	< 0.0001
Myocardial infarction	1.11 (0.99-1.24)	0.08	0.98 (0.94-1.02)	0.34
Heart failure	1.34 (1.22-1.48)	< 0.0001	1.14 (1.10-1.19)	< 0.0001
Per quintile increase				
All-cause	1.07 (1.05-1.09)	< 0.0001	-	-
Liver-related	1.53 (1.32-1.78)	< 0.0001	1.18 (1.14-1.22)	< 0.0001
Hepatocellular carcinoma	-	-	1.53 (1.24-1.89)	< 0.0001
CV	1.09 (1.05-1.14)	< 0.0001	1.05 (1.03-1.06)	< 0.0001
Myocardial infarction	1.06 (0.96-1.16)	0.25	1.04 (1.01-1.08)	0.006
Heart failure	1.08 (0.98-1.19)	0.14	1.07 (1.03-1.10)	< 0.0001

One SD increase correspond to 27.9 and 36.8 U/L increase of GGT in female and male respectively. 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 test

Table S3. Linear association of GGT with fatal and all CVD events including participants with other chronic illnesses and/or receiving statin treatment

	Fatal events		All incident events	
	HR (95% CI)	P	HR (95% CI)	P
Per SD increase				
All-cause	1.15 (1.13-1.17)	< 0.0001	-	-
Liver-related	1.45 (1.38-1.53)	< 0.0001	1.25 (1.23-1.28)	< 0.0001
Hepatocellular carcinoma	-	-	1.48 (1.38-1.60)	< 0.0001
Cardiovascular	1.15 (1.12-1.19)	< 0.0001	1.07 (1.06-1.08)	< 0.0001
Myocardial infarction	1.08 (1.00-1.17)	0.04	1.00 (0.97-1.03)	0.96
Heart failure	1.22 (1.15-1.30)	< 0.0001	1.13 (1.11-1.16)	< 0.0001
Per quintile increase				
All-cause	1.06 (1.05-1.08)	< 0.0001	-	-
Liver-related	1.56 (1.41-1.72)	< 0.0001	1.19 (1.16-1.22)	< 0.0001
Hepatocellular carcinoma	-	-	1.67 (1.43-1.96)	< 0.0001
Cardiovascular	1.10 (1.07-1.13)	< 0.0001	1.05 (1.04-1.06)	< 0.0001
Myocardial infarction	1.07 (1.00-1.14)	0.06	1.03 (1.01-1.06)	0.006
Heart failure	1.11 (1.04-1.18)	0.001	1.07 (1.05-1.10)	< 0.0001

One SD increase correspond to 27.9 and 36.8 U/L increase of GGT in female and male respectively. 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 test

Table S4. Linear association of GGT with fatal and all CVD events excluding events in the first two years of follow-up

	Fatal events		All incident events	
	HR (95% CI)	P	HR (95% CI)	P
Per SD increase				
All-cause	1.17 (1.14-1.20)	< 0.0001	-	-
Liver-related	1.64 (1.51-1.78)	< 0.0001	1.26 (1.22-1.29)	< 0.0001
Hepatocellular carcinoma	-	-	1.52 (1.34-1.71)	< 0.0001
Cardiovascular	1.19 (1.13-1.25)	< 0.0001	1.06 (1.03-1.08)	< 0.0001
Myocardial infarction	1.11 (0.99-1.25)	0.08	0.98 (0.93-1.03)	0.38
Heart failure	1.33 (1.21-1.47)	< 0.0001	1.15 (1.10-1.19)	< 0.0001
Per quintile increase				
All-cause	1.06 (1.04-1.09)	< 0.0001	-	-
Liver-related	1.54 (1.32-1.80)	< 0.0001	1.17 (1.13-1.21)	< 0.0001
Hepatocellular carcinoma	-	-	1.52 (1.22-1.89)	0.0002
Cardiovascular	1.08 (1.04-1.13)	0.0005	1.04 (1.03-1.06)	< 0.0001
Myocardial infarction	1.07 (0.97-1.18)	0.17	1.04 (1.01-1.07)	0.02
Heart failure	1.07 (0.97-1.19)	0.18	1.06 (1.03-1.10)	0.0005

One SD increase correspond to 27.9 and 36.8 U/L increase of GGT in female and male respectively. 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 test

Table S5. Population attributable fractions of GGT

	Fatal events	All incident events
All-cause	12.88 (11.06-14.75)	
Liver-related	41.51 (32.74-49.52)	20.36 (17.96-22.68)
Hepatocellular carcinoma	-	38.27 (25.5-49.27)
Cardiovascular	13.43 (9.58-17.19)	3.88 (2.50- 5.25)
Myocardial infarction	7.90 (-0.08-15.65)	1.64 (-1.55- 4.60)
Heart failure	22.81 (14.12-31.22)	9.89 (6.90-12.80)

Estimated based on HR shown in Table S1 and the distribution of GGT in the study sample. 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 test