

Title: Elevated serum gamma-glutamyl transferase and frailty risk: evidence from prospective cohort, metabolomic, and integrative genetic evidence

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Supplementary methods: Detailed methods of Mendelian randomization study

This study made use of publicly accessible, de-identified summary data. Informed consent was secured from every participant in the initial research, with each study receiving approval from the local ethics board. The exposure and outcome analyzed in this study were derived from distinct populations, ensuring no overlap in samples. The core assumptions of Mendelian randomization (MR) include three key principles^[1]: the correlation assumption, which requires a strong association between instrumental variables and exposure factors; the independence assumption, meaning that instrumental variables are uncorrelated with any confounding factors; and the exclusion restriction assumption, which stipulates that instrumental variables affect the outcome solely through the exposure factors, without a direct association with the outcome itself.

All analyses were performed using R studio (version 4.3.3) with the TwoSampleMR package (version 0.6.8), MendelianRandomization package (version 0.8.0), RadialMR package (version 1.1) and MendelR package^[2].

Exposure data

The genome-wide association studies (GWAS) data for gamma-glutamyl transferase (GGT) were collected from the FinnGen cohort^[3]. The analysis included 257,813 participants, and individual phenotypic values were defined as the median of repeated laboratory measurements. The mean GGT concentration was 49.66 U/L, with a standard deviation of 97.63. Details of the phenotype definition are available in the FinnGen Risteys database (<https://risteys.finnngen.fi/lab-tests/3026910>).

Outcome data

GWAS summary statistics for the frailty index (FI) were obtained from the study by Janice L. Atkins and colleagues, which included 175,226 participants comprising UK Biobank individuals (n = 164,610) and Swedish TwinGene participants (n = 10,616)^[4]. Participants were of European descent, with UK Biobank individuals aged 60–70 years (mean 64.1, SD 2.8; 51.3% female) and TwinGene participants aged 41–87 years (mean 58.3, SD 7.9; 52.5% female). FI was constructed based on 49 and 44 self-reported deficits for UK Biobank and TwinGene, respectively, and was analysed as a continuous variable. The mean FI was 0.129

(SD 0.075) in UK Biobank and 0.121 (SD 0.080) in TwinGene. As this study used summary-level data, covariate adjustment was performed in the original GWAS analyses. Specifically, the UK Biobank GWAS adjusted for age, sex, assessment centre, genotyping array, and population structure using linear mixed models, while the TwinGene GWAS adjusted for age, sex, and principal components of ancestry. These adjustments help to control for confounding and population stratification, supporting the validity of the two-sample MR design. Heterogeneity across contributing cohorts in the outcome GWAS meta-analysis was assessed using I^2 statistics and heterogeneity p-values. The dataset is available through the IEU OpenGWAS database (ebi-a-GCST90020053).

Genetic correlation analysis

To assess the genetic overlap between GGT and biomarkers of biological aging, linkage disequilibrium score regression (LDSC) was conducted using the “ldsc” R package. Prior to the analysis, SNPs were filtered based on the HapMap3 reference panel. LD scores were calculated using the European-ancestry reference panel from the 1000 Genomes Project.

Selection of genetic instruments

Genetic instruments were selected using a stringent genome-wide significance threshold ($P = 5 \times 10^{-8}$)^[5], yielding 189 SNPs. Samples of European ancestry from the 1000 Genomes Project were evaluated for linkage disequilibrium (LD) using the PLINK clustering method. For quality assurance of the instrument, only standard SNPs that are within 10,000 kb of the index variant and have an r^2 value under 0.001 were preserved^[6]. To minimize bias from weak instruments, F-statistics were calculated, and SNPs with F statistics <10 were excluded to ensure that the retained instrument SNPs had sufficient statistical power^[7].

The selected SNPs were then extracted from the outcome GWAS dataset (ebi-a-GCST90020053), resulting in 170 SNPs. No SNPs were excluded based on associations with the outcome ($P < 5 \times 10^{-5}$). Harmonisation of exposure and outcome datasets led to the removal of 5 SNPs due to allele inconsistencies (rs11857386, rs13395911, rs2414679, rs28601761, rs55722209), leaving 165 SNPs for analysis. All remaining SNPs passed the Steiger filtering test, and a total of 165 SNPs were included in the final Mendelian randomization analysis.

Two-sample MR analysis

In the univariate MR analysis, we utilized the inverse variance-weighted (IVW) estimates as primary outcome measure. Additionally, we performed supplementary analyses using MR-Egger, Weighted median, Weighted mode methods and MR-PRESSO. SNPs that were genome-wide significantly associated ($P < 5 \times 10^{-8}$) with potential confounders of the GGT–frailty association, including type 2 diabetes, lipid traits, smoking behavior, cardiovascular disease, and body fat distribution, were excluded. A radial MR approach was utilized to identify and exclude SNPs that significantly contributed to horizontal pleiotropy and heterogeneity. This process improved the quality of the IVW radial regression plots^[8]. Heterogeneity was evaluated using Cochran's Q test^[9], while potential horizontal pleiotropy was assessed with the Egger intercept test^[10]. In addition, a leave-one-out sensitivity analysis was performed to examine whether the overall causal estimates were disproportionately driven by any single SNP.

Summary-data-based MR analysis

To investigate the genetic regulatory mechanisms linking GGT with biological aging, we performed SMR analysis by integrating GWAS summary statistics with quantitative trait loci (QTL) data to identify gene expression signals associated with GGT, GrimAge acceleration (GrimAgeAcc), and telomere length. The blood cis-eQTL dataset from the eQTLGen Consortium, comprising 37 datasets and 31,684 blood samples from individuals of European ancestry^[11], was used as the reference dataset. The heterogeneity in dependent instruments (HEIDI) test was applied to distinguish pleiotropic or potentially causal associations from associations driven by linkage. Associations with $P_{\text{SMR}} < 0.01$ and $P_{\text{HEIDI}} > 0.01$ were considered statistically significant^[12]. SMR analysis was conducted using the Online SMR Analysis platform, an integrative tool for analyzing GWAS and xQTL data to identify genes associated with complex traits, available at <https://yanglab.westlake.edu.cn/smr-portal/>. We further performed KEGG pathway enrichment analysis using Enrichr (<https://maayanlab.cloud/Enrichr/>) based on the SMR-identified shared genes associated with both GGT and frailty.

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Supplementary table 1 List of 49 frailty index items included in the UK Biobank

Item	Variant	Scoring
Sensory	1 Glaucoma	yes=1, no=0
	2 Cataracts	yes=1, no=0
	3 Hearing difficulty	yes=1, completely deaf=1, no=0
Cranial	4 Migraine	yes=1, no=0
	5 Dental problems	yes=1, no=0
Mental wellbeing	6 Self-rated health	excellent=0, good=0.25, fair=0.5, poor=1
	Fatigue: frequency of tiredness /	not at all=0, several days=0.25, more than half the days=0.5,
	7 lethargy in last two weeks	nearly every day=1
	Sleep: experience of	never/rarely=0, sometimes=0.5,
	8 sleeplessness/insomnia	usually=1
	Depressed feelings: frequency in last	not at all=0, several days=0.5, more than half the days=0.75,
	9 two weeks	nearly every day=1
	10 Self-described nervous personality	yes=1, no=0
	11 Severe anxiety/ panic attacks	yes=1, no=0
	12 Common to feel loneliness	yes=1, no=0
	13 Sense of misery (ever/never)	yes=1, no=0
	Infirmity: long-standing illness or	
Infirmity	14 disability	yes=1, no=0
	15 Falls in last year	no falls=0, only one fall=0.5, more than one fall=1
	Fractures/broken bones in last five	
Cardiometabolic	16 years	yes=1, no=0
	17 Diabetes	yes=1, no=0
	18 Myocardial infarction	yes=1, no=0
	19 Angina	yes=1, no=0
	20 Stroke	yes=1, no=0
	21 High blood pressure	yes=1, no=0
	22 Hypothyroidism	yes=1, no=0
	23 Deep-vein thrombosis	yes=1, no=0
Respiratory	24 High cholesterol	yes=1, no=0
	25 Breathing: wheeze in last year	yes=1, no=0
	26 Pneumonia	yes=1, no=0
	27 Chronic bronchitis/emphysema	yes=1, no=0
Musculoskeletal	28 Asthma	yes=1, no=0
	29 Rheumatoid arthritis	yes=1, no=0
	30 Osteoarthritis	yes=1, no=0
	31 Gout	yes=1, no=0
Immunological	32 Osteoporosis	yes=1, no=0
	33 Hayfever, allergic rhinitis or eczema	yes=1, no=0

Cancer	34	Psoriasis	yes=1, no=0
	35	Any cancer diagnosis	yes=1, no=0
		Multiple cancers diagnosed (number reported)	no cancer, one cancer =0, more than one cancer=1
Pain	36		
	37	Chest pain	yes=1, no=0
	38	Head and/or neck pain	yes=1, no=0
	39	Back pain	yes=1, no=0
	40	Stomach/abdominal pain	yes=1, no=0
	41	Hip pain	yes=1, no=0
	42	Knee pain	yes=1, no=0
	43	Whole-body pain	yes=1, no=0
Gastrointestinal	44	Facial pain	yes=1, no=0
	45	Sciatica	yes=1, no=0
	46	Gastric reflux	yes=1, no=0
	47	Hiatus hernia	yes=1, no=0
	48	Gall stones	yes=1, no=0
	49	Diverticulitis	yes=1, no=0

Note: do not know/prefer not to answer=missing.

Supplementary table 2 Association of 251 metabolites with gamma-glutamyl transferase and incident frailty

Metabolites	GGT			Frailty	
	Coefficient	Beta (95% CI)	Adjusted <i>P</i> value	HR (95% CI)	Adjusted <i>P</i> value
Acetate	-0.008	-0.02(-0.02, -0.01)	2.65E-22	1.03(1.00,1.06)	0.07393107
Acetoacetate	-0.004	0.01(0.01,0.02)	1.18E-13	1.05(1.02,1.09)	0.004052424
Acetone	0.024	-0.01(-0.02, -0.01)	3.98E-12	0.98(0.95,1.01)	0.219468908
Ala	0.008	0.03(0.03,0.03)	1.17E-62	1.01(0.98,1.04)	0.741086481
Albumin	0.014	0.03(0.03,0.04)	1.08E-86	0.95(0.92,0.98)	0.00283371
ApoA1	-	0.05(0.04,0.05)	9.90E-134	0.94(0.91,0.97)	0.00029768
ApoB	-	0.06(0.06,0.07)	1.85E-278	0.99(0.97,1.02)	0.765037828
ApoB_by_ApoA1	-	0.03(0.03,0.04)	3.36E-72	1.03(0.99,1.06)	0.138409932
bOHbutyrate	-0.004	0.01(0.01,0.02)	1.18E-11	1.00(0.97,1.03)	0.897253731
Cholines	-0.009	0.08(0.08,0.09)	<1E-300	0.98(0.95,1.01)	0.146237211
Citrate	-0.060	-0.03(-0.03, -0.02)	1.14E-57	0.97(0.94,1.00)	0.036782304
Clinical_LDL_C	-	0.05(0.04,0.05)	1.18E-168	0.97(0.94,1.00)	0.035209671
Creatinine	0.075	0.02(0.01,0.02)	8.33E-17	1.06(1.02,1.10)	0.003259923
DHA	0.002	0.04(0.04,0.05)	6.86E-123	0.94(0.91,0.97)	0.000189022
DHA_pct	8.64E-05	-0.02(-0.03, -0.02)	2.41E-36	0.90(0.87,0.93)	1.08E-09
GL	0.010	0.05(0.04,0.05)	4.63E-154	1.09(1.06,1.12)	5.22E-10
Gln	-0.050	-0.06(-0.07, -0.06)	<1E-300	0.97(0.94,1.00)	0.040402567
Glucose	-	0.03(0.02,0.03)	4.94E-55	1.07(1.04,1.11)	1.61E-06
Gly	-0.080	-0.06(-0.06, -0.06)	2.26E-233	0.96(0.93,0.99)	0.026610283
GlycA	0.038	0.12(0.11,0.12)	<1E-300	1.14(1.11,1.18)	1.18E-17
HDL_C	-	0.00(0.00,0.01)	0.17372321	0.88(0.85,0.92)	1.27E-10
HDL_CE	0.012	0.00(-0.01,0.00)	0.19669343	0.88(0.85,0.91)	4.84E-11
HDL_FC	-	0.02(0.02,0.03)	3.70E-26	0.90(0.87,0.93)	2.03E-08
HDL_L	-	0.03(0.03,0.04)	1.50E-57	0.92(0.89,0.95)	4.29E-06
HDL_P	4.81E-05	0.06(0.06,0.06)	7.16E-234	0.95(0.92,0.98)	0.005922055
HDL_PL	-	0.04(0.04,0.05)	3.78E-99	0.94(0.90,0.97)	0.000267135
HDL_size	-0.107	-0.06(-0.06, -0.05)	4.46E-150	0.86(0.83,0.89)	4.21E-14
HDL_TG	-0.000	0.10(0.10,0.11)	<1E-300	1.08(1.05,1.12)	5.69E-08
His	-0.016	-0.01(-0.02, -0.01)	8.32E-13	0.99(0.96,1.02)	0.410248975
IDL_C	-	0.04(0.03,0.04)	1.05E-93	0.94(0.91,0.96)	3.09E-05

IDL_C_pct	-	-0.05(-0.05, -0.04)	6.15E-147	0.89(0.87,0.92)	6.80E-15
IDL_CE	-	0.04(0.03,0.04)	1.03E-98	0.94(0.91,0.97)	4.80E-05
IDL_CE_pct	-	-0.03(-0.04, -0.03)	3.57E-75	0.91(0.88,0.93)	2.46E-11
IDL_FC	-	0.03(0.03,0.04)	1.30E-75	0.93(0.91,0.96)	1.40E-05
IDL_FC_pct	-0.003	-0.05(-0.05, -0.04)	2.54E-148	0.92(0.89,0.94)	1.30E-08
IDL_L	-	0.05(0.04,0.05)	7.94E-151	0.95(0.92,0.98)	0.001090026
IDL_P	-	0.04(0.04,0.05)	4.25E-138	0.96(0.94,0.99)	0.025010349
IDL_PL	-	0.04(0.04,0.05)	3.23E-126	0.95(0.92,0.98)	0.001247123
IDL_PL_pct	-0.002	-0.03(-0.04, -0.03)	1.18E-80	1.02(0.99,1.05)	0.278599828
IDL_TG	-	0.11(0.10,0.11)	<1E-300	1.09(1.06,1.12)	1.76E-08
IDL_TG_pct	0.000	0.07(0.07,0.07)	<1E-300	1.14(1.11,1.17)	2.74E-19
Ile	-0.037	0.03(0.02,0.03)	5.02E-46	1.01(0.98,1.04)	0.410248975
L_HDL_C	-	-0.05(-0.05, -0.04)	3.11E-105	0.85(0.81,0.88)	3.34E-16
L_HDL_C_pct	0.023	-0.10(-0.11, -0.10)	<1E-300	0.88(0.85,0.90)	2.33E-18
L_HDL_CE	-	-0.05(-0.05, -0.05)	2.93E-120	0.84(0.81,0.88)	1.02E-16
L_HDL_CE_pct	0.016	-0.11(-0.11, -0.10)	<1E-300	0.88(0.85,0.90)	1.49E-17
L_HDL_FC	-	-0.03(-0.04, -0.03)	2.79E-59	0.86(0.82,0.89)	3.68E-14
L_HDL_FC_pct	-0.003	-0.02(-0.03, -0.02)	3.66E-41	0.97(0.95,0.99)	0.003975179
L_HDL_L	-	-0.03(-0.04, -0.03)	5.63E-52	0.86(0.83,0.89)	1.12E-13
L_HDL_P	-	-0.03(-0.04, -0.03)	1.98E-55	0.85(0.82,0.89)	1.15E-14
L_HDL_PL	-	-0.02(-0.03, -0.02)	4.04E-30	0.87(0.84,0.91)	7.86E-12
L_HDL_PL_pct	0.031	0.09(0.08,0.09)	<1E-300	1.15(1.11,1.18)	7.71E-19
L_HDL_TG	-0.076	0.06(0.06,0.07)	3.84E-274	1.01(0.98,1.04)	0.410248975
L_HDL_TG_pct	0.035	0.09(0.09,0.10)	<1E-300	1.13(1.09,1.17)	4.94E-12
L_LDL_C	-	0.05(0.05,0.05)	3.38E-184	0.96(0.94,0.99)	0.019386539
L_LDL_C_pct	-0.002	-0.04(-0.05, -0.04)	7.39E-137	0.93(0.92,0.94)	4.80E-26
L_LDL_CE	-	0.06(0.05,0.06)	6.87E-226	0.97(0.94,1.00)	0.076130744
L_LDL_CE_pct	-0.006	0.02(0.01,0.02)	2.73E-25	0.97(0.94,1.00)	0.067745047
L_LDL_FC	-	0.03(0.03,0.04)	5.58E-85	0.94(0.91,0.97)	0.000119283
L_LDL_FC_pct	-	-0.09(-0.09, -0.08)	<1E-300	0.87(0.84,0.89)	5.15E-21
L_LDL_L	-	0.06(0.05,0.06)	1.36E-233	0.97(0.94,1.00)	0.076788389
L_LDL_P	-	0.05(0.05,0.05)	9.01E-177	0.99(0.96,1.02)	0.410248975
L_LDL_PL	-	0.05(0.05,0.06)	6.36E-205	0.97(0.94,1.00)	0.053868485

L_LDL_PL_pct	0.002	-0.04(-0.04, -0.04)	1.33E-111	1.00(0.97,1.03)	0.852654571
L_LDL_TG	-	0.12(0.11,0.12)	<1E-300	1.09(1.06,1.12)	3.09E-09
L_LDL_TG_pct	-0.004	0.06(0.06,0.07)	6.86E-288	1.14(1.11,1.17)	1.68E-17
L_VLDL_C	-	0.10(0.10,0.11)	<1E-300	1.08(1.05,1.12)	5.58E-07
L_VLDL_C_pct	-	-0.04(-0.04, -0.03)	2.35E-95	0.92(0.89,0.95)	3.94E-07
L_VLDL_CE	-0.004	0.09(0.09,0.09)	<1E-300	1.06(1.03,1.10)	0.000124074
L_VLDL_CE_pct	-0.018	-0.06(-0.06, -0.05)	3.46E-202	0.89(0.86,0.92)	9.10E-12
L_VLDL_FC	-	0.11(0.11,0.12)	<1E-300	1.10(1.07,1.14)	2.00E-09
L_VLDL_FC_pct	0.005	0.01(0.01,0.01)	8.94E-11	1.00(0.97,1.04)	0.800332188
L_VLDL_L	-	0.11(0.11,0.11)	<1E-300	1.10(1.07,1.13)	3.72E-09
L_VLDL_P	-0.003	0.11(0.11,0.12)	<1E-300	1.10(1.07,1.13)	1.69E-09
L_VLDL_PL	-	0.11(0.11,0.12)	<1E-300	1.11(1.07,1.14)	1.58E-10
L_VLDL_PL_pct	0.001	0.01(0.01,0.02)	5.04E-15	1.02(0.98,1.06)	0.322272345
L_VLDL_TG	-	0.11(0.10,0.11)	<1E-300	1.10(1.07,1.13)	3.11E-09
L_VLDL_TG_pct	0.012	0.00(0.00,0.01)	0.0297815	1.02(0.99,1.05)	0.319689185
LA	-0.025	0.06(0.05,0.06)	4.75E-240	0.98(0.95,1.01)	0.256884109
LA_pct	-0.024	-0.1(-0.11, -0.1)	<1E-300	0.85(0.83,0.88)	7.66E-22
Lactate	0.017	0.03(0.03,0.03)	3.34E-70	1.03(1.00,1.06)	0.080995569
LDL_C	-	0.06(0.05,0.06)	2.28E-249	0.98(0.95,1.01)	0.168123895
LDL_CE	-	0.07(0.06,0.07)	<1E-300	0.99(0.96,1.02)	0.478829043
LDL_FC	-	0.04(0.03,0.04)	4.80E-96	0.95(0.92,0.98)	0.001247123
LDL_L	-	0.06(0.06,0.07)	<1E-300	0.99(0.96,1.02)	0.410248975
LDL_P	-	0.06(0.06,0.06)	6.09E-256	0.99(0.97,1.02)	0.745074163
LDL_PL	-	0.06(0.06,0.06)	1.54E-254	0.98(0.96,1.01)	0.322272345
LDL_size	-	-0.05(-0.05, -0.04)	7.01E-140	0.94(0.91,0.97)	7.32E-05
LDL_TG	-	0.12(0.12,0.12)	<1E-300	1.10(1.07,1.13)	2.77E-10
Leu	0.041	0.03(0.03,0.04)	4.11E-79	1.00(0.97,1.03)	0.816295488
M_HDL_C	-	0.03(0.02,0.03)	3.38E-47	0.93(0.90,0.96)	5.53E-05
M_HDL_C_pct	-	-0.08(-0.09, -0.08)	<1E-300	0.89(0.86,0.92)	5.02E-13
M_HDL_CE	-	0.02(0.02,0.03)	3.95E-36	0.93(0.90,0.96)	4.76E-05
M_HDL_CE_pct	-	-0.09(-0.09, -0.08)	<1E-300	0.90(0.88,0.93)	1.72E-10
M_HDL_FC	-	0.04(0.04,0.05)	1.46E-103	0.93(0.90,0.97)	0.000170755
M_HDL_FC_pct	-0.002	0.00(0.00,0.00)	0.77984804	0.88(0.85,0.91)	9.70E-13

M_HDL_L	-	0.05(0.05,0.06)	5.47E-173	0.96(0.93,0.99)	0.026610283
M_HDL_P	-	0.05(0.04,0.05)	5.98E-120	0.94(0.91,0.98)	0.001212515
M_HDL_PL	-	0.06(0.06,0.07)	1.60E-245	0.98(0.95,1.01)	0.208563423
M_HDL_PL_pct	-0.022	0.06(0.06,0.07)	2.82E-232	1.13(1.10,1.17)	1.12E-13
M_HDL_TG	-0.001	0.10(0.10,0.11)	<1E-300	1.09(1.05,1.12)	4.61E-08
M_HDL_TG_pct	-	0.09(0.08,0.09)	<1E-300	1.11(1.08,1.15)	5.23E-11
M_LDL_C	-	0.07(0.07,0.08)	<1E-300	1.01(0.98,1.04)	0.742453883
M_LDL_C_pct	-	-0.02(-0.02, -0.01)	8.89E-21	0.92(0.89,0.94)	7.97E-10
M_LDL_CE	-	0.08(0.08,0.09)	<1E-300	1.02(0.99,1.05)	0.246383077
M_LDL_CE_pct	-	0.07(0.07,0.08)	<1E-300	1.05(1.02,1.08)	0.006171828
M_LDL_FC	-	0.04(0.04,0.05)	9.20E-140	0.97(0.94,1.00)	0.052069563
M_LDL_FC_pct	-	-0.10(-0.10, -0.10)	<1E-300	0.88(0.85,0.91)	4.25E-16
M_LDL_L	-	0.08(0.07,0.08)	<1E-300	1.01(0.98,1.04)	0.460542968
M_LDL_P	-	0.07(0.07,0.08)	<1E-300	1.01(0.98,1.04)	0.633775356
M_LDL_PL	-	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.62689684
M_LDL_PL_pct	-0.011	-0.06(-0.07, -0.06)	8.95E-283	0.98(0.95,1.01)	0.140741595
M_LDL_TG	0.020	0.12(0.12,0.13)	<1E-300	1.10(1.07,1.13)	3.41E-11
M_LDL_TG_pct	-	0.06(0.05,0.06)	1.09E-222	1.12(1.09,1.15)	2.27E-13
M_VLDL_C	-	0.04(0.04,0.05)	3.99E-144	0.98(0.95,1.00)	0.130577117
M_VLDL_C_pct	-	-0.07(-0.07, -0.07)	1.38E-291	0.87(0.84,0.89)	2.70E-18
M_VLDL_CE	0.009	0.02(0.02,0.03)	1.32E-41	0.95(0.92,0.98)	0.001305
M_VLDL_CE_pct	-	-0.08(-0.08, -0.07)	<1E-300	0.86(0.83,0.89)	7.77E-19
M_VLDL_FC	-	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.569055611
M_VLDL_FC_pct	-	-0.05(-0.05, -0.04)	4.03E-146	0.88(0.85,0.91)	1.52E-15
M_VLDL_L	-	0.09(0.09,0.10)	<1E-300	1.05(1.02,1.08)	0.003259923
M_VLDL_P	-0.005	0.08(0.08,0.09)	<1E-300	1.03(1.00,1.06)	0.051602417
M_VLDL_PL	-	0.08(0.08,0.08)	<1E-300	1.03(1.00,1.06)	0.107985554
M_VLDL_PL_pct	-0.007	-0.03(-0.04, -0.03)	3.61E-69	0.89(0.87,0.92)	5.76E-13
M_VLDL_TG	-0.075	0.11(0.10,0.11)	<1E-300	1.09(1.06,1.12)	4.22E-08
M_VLDL_TG_pct	-	0.06(0.06,0.07)	2.76E-237	1.15(1.12,1.19)	1.55E-17
MUFA	-	0.12(0.12,0.13)	<1E-300	1.12(1.09,1.15)	1.15E-13
MUFA_pct	0.016	0.10(0.09,0.10)	<1E-300	1.21(1.17,1.25)	2.43E-28
non_HDL_C	-	0.06(0.06,0.07)	4.57E-291	0.98(0.95,1.01)	0.278599828

Omega_3	-	0.07(0.07,0.08)	<1E-300	0.99(0.96,1.02)	0.640952803
Omega_3_pct	-	0.02(0.02,0.03)	5.78E-34	0.95(0.92,0.98)	0.002987361
Omega_6	-	0.07(0.07,0.08)	<1E-300	1.00(0.97,1.03)	0.904670142
Omega_6_by_Omega_3	-0.009	-0.05(-0.06, -0.05)	6.75E-207	1.01(0.98,1.04)	0.497419702
Omega_6_pct	-0.019	-0.13(-0.14, -0.13)	<1E-300	0.87(0.85,0.90)	8.82E-17
Phe	0.004	0.01(0.01,0.02)	2.14E-14	1.04(1.01,1.07)	0.01846459
Phosphatidylc	-	0.08(0.08,0.09)	<1E-300	0.97(0.94,1.00)	0.108841695
Phosphoglyc	-	0.09(0.09,0.10)	<1E-300	0.99(0.96,1.02)	0.681281923
PUFA	-	0.08(0.08,0.09)	<1E-300	1.00(0.97,1.03)	0.984382818
PUFA_by_MUFA	-	-0.11(-0.11, -0.11)	<1E-300	0.83(0.80,0.86)	2.18E-25
PUFA_pct	-	-0.12(-0.12, -0.12)	<1E-300	0.86(0.83,0.88)	5.48E-21
Pyruvate	-0.031	0.01(0.00,0.01)	9.27E-05	1.08(1.05,1.12)	9.84E-07
Remnant_C	-	0.07(0.06,0.07)	<1E-300	0.99(0.96,1.02)	0.461183622
S_HDL_C	-	0.08(0.07,0.08)	<1E-300	1.02(0.99,1.05)	0.358033977
S_HDL_C_pct	-	-0.06(-0.07, -0.06)	2.71E-296	0.93(0.90,0.95)	5.93E-07
S_HDL_CE	-	0.07(0.06,0.07)	<1E-300	1.01(0.98,1.04)	0.413041926
S_HDL_CE_pct	-0.009	-0.06(-0.07, -0.06)	1.84E-287	0.94(0.92,0.97)	0.000221476
S_HDL_FC	-	0.10(0.10,0.10)	<1E-300	1.02(0.99,1.05)	0.273262168
S_HDL_FC_pct	0.069	0.00(-0.01,0.00)	0.25462206	0.92(0.89,0.95)	5.30E-06
S_HDL_L	-	0.11(0.10,0.11)	<1E-300	1.05(1.02,1.08)	0.003108585
S_HDL_P	0.080	0.09(0.08,0.09)	<1E-300	1.03(1.00,1.06)	0.109554507
S_HDL_PL	0.027	0.11(0.10,0.11)	<1E-300	1.05(1.02,1.08)	0.003259923
S_HDL_PL_pct	0.021	0.02(0.02,0.02)	3.91E-26	1.00(0.97,1.03)	0.999843103
S_HDL_TG	-	0.12(0.12,0.13)	<1E-300	1.13(1.10,1.17)	2.24E-15
S_HDL_TG_pct	-	0.09(0.08,0.09)	<1E-300	1.13(1.10,1.17)	3.02E-14
S_LDL_C	-	0.07(0.06,0.07)	<1E-300	1.00(0.97,1.03)	0.956731248
S_LDL_C_pct	-	0.01(0.00,0.01)	0.00025486	0.94(0.92,0.97)	8.34E-05
S_LDL_CE	-	0.08(0.07,0.08)	<1E-300	1.01(0.98,1.04)	0.406917514
S_LDL_CE_pct	-	0.08(0.08,0.09)	<1E-300	1.05(1.01,1.08)	0.007347441
S_LDL_FC	-	0.03(0.02,0.03)	1.80E-52	0.96(0.93,0.99)	0.010862169
S_LDL_FC_pct	-0.057	-0.08(-0.09, -0.08)	<1E-300	0.90(0.88,0.93)	4.20E-12
S_LDL_L	-	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.741137912
S_LDL_P	-0.032	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.679010786

S_LDL_PL	0.025	0.05(0.05,0.06)	5.18E-200	0.99(0.96,1.02)	0.640952803
S_LDL_PL_pct	0.025	-0.08(-0.09, -0.08)	<1E-300	0.95(0.92,0.98)	0.001208132
S_LDL_TG	-	0.12(0.12,0.12)	<1E-300	1.11(1.07,1.14)	1.69E-11
S_LDL_TG_pct	-	0.08(0.08,0.08)	<1E-300	1.12(1.09,1.15)	3.67E-15
S_VLDL_C	-	0.07(0.07,0.08)	<1E-300	1.03(1.00,1.06)	0.119149065
S_VLDL_C_pct	0.009	-0.05(-0.05, -0.04)	7.82E-153	0.90(0.87,0.93)	1.51E-11
S_VLDL_CE	0.017	0.08(0.07,0.08)	<1E-300	1.04(1.01,1.07)	0.028933465
S_VLDL_CE_pct	0.057	-0.04(-0.04, -0.03)	2.67E-93	0.93(0.90,0.96)	2.78E-06
S_VLDL_FC	-	0.07(0.06,0.07)	<1E-300	1.01(0.98,1.04)	0.639192787
S_VLDL_FC_pct	-	-0.06(-0.06, -0.05)	4.97E-203	0.87(0.84,0.90)	1.59E-17
S_VLDL_L	-	0.10(0.10,0.10)	<1E-300	1.07(1.04,1.10)	3.38E-05
S_VLDL_P	-	0.10(0.09,0.10)	<1E-300	1.07(1.04,1.11)	9.25E-06
S_VLDL_PL	-	0.08(0.08,0.09)	<1E-300	1.04(1.01,1.07)	0.029430225
S_VLDL_PL_pct	-	-0.06(-0.06, -0.05)	4.05E-208	0.88(0.85,0.90)	3.19E-16
S_VLDL_TG	-	0.11(0.11,0.11)	<1E-300	1.11(1.07,1.14)	8.72E-11
S_VLDL_TG_pct	-	0.05(0.05,0.05)	3.70E-175	1.12(1.09,1.16)	2.71E-13
SCA	0.030	0.04(0.03,0.04)	2.59E-101	1.01(0.98,1.04)	0.453824767
SFA	-	0.13(0.12,0.13)	<1E-300	1.07(1.04,1.10)	2.86E-06
SFA_pct	-	0.09(0.08,0.09)	<1E-300	1.05(1.02,1.08)	0.003806519
Sphingomyelins	0.001	0.06(0.05,0.06)	4.61E-216	0.95(0.92,0.98)	0.00263858
TG_by_PG	-	0.10(0.10,0.10)	<1E-300	1.14(1.10,1.18)	5.82E-14
Total_BCAA	-	0.04(0.04,0.05)	7.47E-124	1.01(0.98,1.04)	0.65387031
Total_C	-	0.06(0.06,0.06)	2.26E-252	0.95(0.92,0.98)	0.00237595
Total_CE	-	0.06(0.05,0.06)	4.77E-230	0.95(0.92,0.98)	0.000762749
Total_FA	-	0.12(0.11,0.12)	<1E-300	1.07(1.04,1.10)	1.57E-05
Total_FC	-	0.06(0.06,0.07)	<1E-300	0.97(0.94,0.99)	0.029488762
Total_L	-	0.09(0.09,0.10)	<1E-300	1.00(0.97,1.03)	0.852654571
Total_P	2.12E-06	0.07(0.06,0.07)	<1E-300	0.95(0.92,0.99)	0.007259188
Total_PL	-	0.09(0.09,0.09)	<1E-300	0.98(0.95,1.01)	0.192072523
Total_TG	-	0.12(0.12,0.12)	<1E-300	1.11(1.08,1.14)	2.98E-11
Tyr	0.045	0.05(0.04,0.05)	2.26E-158	0.98(0.95,1.01)	0.188044648
Unsaturation	-0.011	-0.05(-0.05, -0.04)	7.38E-142	0.89(0.86,0.92)	2.39E-12
Val	-0.012	0.05(0.05,0.06)	1.60E-185	1.01(0.98,1.04)	0.684615669

VLDL_C	-	0.08(0.08,0.09)	<1E-300	1.03(1.00,1.07)	0.033731957
VLDL_CE	-	0.07(0.07,0.07)	<1E-300	1.02(0.99,1.05)	0.298704576
VLDL_FC	-	0.10(0.09,0.10)	<1E-300	1.06(1.03,1.09)	0.000429292
VLDL_L	-	0.11(0.11,0.11)	<1E-300	1.09(1.05,1.12)	1.53E-07
VLDL_P	-2.34E-05	0.09(0.09,0.10)	<1E-300	1.05(1.02,1.09)	0.001106195
VLDL_PL	-	0.10(0.10,0.11)	<1E-300	1.07(1.04,1.11)	8.17E-06
VLDL_size	-	0.10(0.09,0.10)	<1E-300	1.12(1.08,1.16)	1.44E-10
VLDL_TG	-	0.12(0.11,0.12)	<1E-300	1.11(1.07,1.14)	5.23E-11
XL_HDL_C	0.046	-0.05(-0.06, -0.05)	2.95E-148	0.85(0.82,0.88)	4.19E-16
XL_HDL_C_pct	0.005	0.01(0.01,0.02)	1.43E-12	1.04(1.01,1.08)	0.011488891
XL_HDL_CE	0.025	-0.05(-0.06, -0.05)	3.92E-143	0.84(0.81,0.88)	9.01E-17
XL_HDL_CE_pct	0.013	-0.02(-0.02, -0.01)	1.56E-18	0.96(0.93,0.98)	0.003284309
XL_HDL_FC	-	-0.05(-0.06, -0.05)	2.52E-153	0.88(0.85,0.91)	1.69E-12
XL_HDL_FC_pct	0.009	0.04(0.04,0.05)	8.11E-89	1.14(1.11,1.18)	4.14E-14
XL_HDL_L	1.35E-05	-0.05(-0.05, -0.04)	3.13E-122	0.86(0.83,0.89)	1.68E-14
XL_HDL_P	-	-0.03(-0.04, -0.03)	5.64E-58	0.87(0.83,0.90)	2.97E-13
XL_HDL_PL	-	-0.05(-0.06, -0.05)	1.39E-136	0.86(0.83,0.89)	3.95E-14
XL_HDL_PL_pct	0.000	-0.03(-0.04, -0.03)	1.07E-90	0.96(0.94,0.98)	6.50E-05
XL_HDL_TG	-	0.08(0.08,0.08)	<1E-300	1.04(1.02,1.07)	0.004341769
XL_HDL_TG_pct	0.003	0.12(0.11,0.12)	<1E-300	1.16(1.12,1.20)	4.11E-18
XL_VLDL_C	-	0.11(0.10,0.11)	<1E-300	1.09(1.06,1.12)	6.76E-08
XL_VLDL_C_pct	-	-0.05(-0.06, -0.05)	6.16E-204	0.88(0.85,0.91)	5.17E-13
XL_VLDL_CE	-	0.10(0.09,0.10)	<1E-300	1.08(1.04,1.11)	4.85E-06
XL_VLDL_CE_pct	-0.021	-0.07(-0.07, -0.07)	<1E-300	0.88(0.85,0.90)	1.66E-15
XL_VLDL_FC	-	0.11(0.11,0.11)	<1E-300	1.10(1.07,1.13)	1.46E-09
XL_VLDL_FC_pct	0.010	-0.04(-0.04, -0.04)	4.16E-112	0.90(0.87,0.93)	1.23E-10
XL_VLDL_L	-	0.12(0.11,0.12)	<1E-300	1.11(1.08,1.14)	2.39E-11
XL_VLDL_P	-0.000	0.12(0.11,0.12)	<1E-300	1.11(1.07,1.14)	7.79E-11
XL_VLDL_PL	-	0.11(0.11,0.12)	<1E-300	1.11(1.07,1.14)	1.23E-10
XL_VLDL_PL_pct	-0.002	0.01(0.00,0.01)	5.51E-07	1.00(0.98,1.03)	0.904670142
XL_VLDL_TG	-	0.12(0.11,0.12)	<1E-300	1.12(1.08,1.15)	2.35E-12
XL_VLDL_TG_pct	0.006	0.05(0.04,0.05)	1.39E-163	1.12(1.09,1.16)	1.42E-12
XS_VLDL_C	-	0.05(0.04,0.05)	3.16E-145	0.97(0.94,1.00)	0.04531023

XS_VLDL_C_pct	-	-0.07(-0.08, -0.07)	<1E-300	0.86(0.83,0.89)	2.41E-21
XS_VLDL_CE	-0.003	0.04(0.03,0.04)	3.38E-96	0.95(0.93,0.98)	0.003875618
XS_VLDL_CE_pct	-0.046	-0.07(-0.08, -0.07)	<1E-300	0.85(0.83,0.88)	3.17E-22
XS_VLDL_FC	-	0.06(0.06,0.07)	1.84E-283	1.00(0.97,1.03)	0.999843103
XS_VLDL_FC_pct	0.014	-0.04(-0.04, -0.03)	1.64E-108	0.92(0.90,0.95)	2.74E-08
XS_VLDL_L	-	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.460542968
XS_VLDL_P	-	0.07(0.07,0.07)	<1E-300	1.01(0.98,1.04)	0.577965876
XS_VLDL_PL	-	0.07(0.07,0.07)	<1E-300	1.02(0.99,1.05)	0.173389805
XS_VLDL_PL_pct	-	0.01(0.01,0.01)	3.14E-07	1.10(1.06,1.13)	1.13E-08
XS_VLDL_TG	-	0.11(0.11,0.11)	<1E-300	1.10(1.07,1.13)	2.89E-10
XS_VLDL_TG_pct	-	0.08(0.07,0.08)	<1E-300	1.16(1.12,1.19)	1.66E-20
XXL_VLDL_C	-	0.11(0.11,0.11)	<1E-300	1.11(1.08,1.14)	1.20E-11
XXL_VLDL_C_pct	-	-0.03(-0.03, -0.03)	6.29E-78	0.95(0.93,0.98)	0.003259923
XXL_VLDL_CE	-	0.11(0.11,0.11)	<1E-300	1.11(1.08,1.14)	8.34E-12
XXL_VLDL_CE_pct	-0.004	-0.02(-0.03, -0.02)	3.36E-45	0.97(0.94,1.00)	0.096526828
XXL_VLDL_FC	0.048	0.11(0.11,0.11)	<1E-300	1.11(1.07,1.14)	3.50E-11
XXL_VLDL_FC_pct	-	-0.03(-0.04, -0.03)	1.54E-83	0.93(0.91,0.96)	1.57E-05
XXL_VLDL_L	-	0.11(0.11,0.11)	<1E-300	1.11(1.07,1.14)	1.51E-11
XXL_VLDL_P	-0.004	0.11(0.11,0.11)	<1E-300	1.10(1.07,1.13)	9.24E-11
XXL_VLDL_PL	0.029	0.11(0.11,0.11)	<1E-300	1.11(1.08,1.14)	5.49E-12
XXL_VLDL_PL_pct	-0.006	0.02(0.02,0.02)	7.56E-31	1.06(1.03,1.09)	0.000276744
XXL_VLDL_TG	-	0.11(0.10,0.11)	<1E-300	1.10(1.07,1.13)	3.97E-11
XXL_VLDL_TG_pct	0.012	0.02(0.02,0.02)	7.45E-37	1.02(0.99,1.05)	0.244474061

Note: - The biomarkers that were not selected by the elastic network regression.

Supplementary table 3 Metabolite categories based on the UK Biobank

Metabolite	Shortened name	Group
Total Cholesterol	Total_C	Cholesterol
Total Cholesterol Minus HDL-C	non_HDL_C	Cholesterol
Remnant Cholesterol (Non-HDL, Non-LDL -Cholesterol)	Remnant_C	Cholesterol
VLDL Cholesterol	VLDL_C	Cholesterol
Clinical LDL Cholesterol	Clinical_LDL_C	Cholesterol
LDL Cholesterol	LDL_C	Cholesterol
HDL Cholesterol	HDL_C	Cholesterol
Total Triglycerides	Total_TG	Triglycerides
Triglycerides in VLDL	VLDL_TG	Triglycerides
Triglycerides in LDL	LDL_TG	Triglycerides
Triglycerides in HDL	HDL_TG	Triglycerides
Total Phospholipids in Lipoprotein Particles	Total_PL	Phospholipids
Phospholipids in VLDL	VLDL_PL	Phospholipids
Phospholipids in LDL	LDL_PL	Phospholipids
Phospholipids in HDL	HDL_PL	Phospholipids
Total Esterified Cholesterol	Total_CE	Cholesteryl esters
Cholesteryl Esters in VLDL	VLDL_CE	Cholesteryl esters
Cholesteryl Esters in LDL	LDL_CE	Cholesteryl esters
Cholesteryl Esters in HDL	HDL_CE	Cholesteryl esters
Total Free Cholesterol	Total_FC	Free cholesterol
Free Cholesterol in VLDL	VLDL_FC	Free cholesterol
Free Cholesterol in LDL	LDL_FC	Free cholesterol
Free Cholesterol in HDL	HDL_FC	Free cholesterol
Total Lipids in Lipoprotein Particles	Total_L	Total lipids
Total Lipids in VLDL	VLDL_L	Total lipids
Total Lipids in LDL	LDL_L	Total lipids
Total Lipids in HDL	HDL_L	Total lipids

Total Concentration of Lipoprotein Particles	Total_P	Lipoprotein particle concentrations
Concentration of VLDL Particles	VLDL_P	Lipoprotein particle concentrations
Concentration of LDL Particles	LDL_P	Lipoprotein particle concentrations
Concentration of HDL Particles	HDL_P	Lipoprotein particle concentrations
Average Diameter for VLDL Particles	VLDL_size	Lipoprotein particle sizes
Average Diameter for LDL Particles	LDL_size	Lipoprotein particle sizes
Average Diameter for HDL Particles	HDL_size	Lipoprotein particle sizes
Phosphoglycerides	Phosphoglyc	Other lipids
Triglycerides to Phosphoglycerides ratio	TG_by_PG	Other lipids
Total Cholines	Cholines	Other lipids
Phosphatidylcholines	Phosphatidylc	Other lipids
Sphingomyelins	Sphingomyelins	Other lipids
Apolipoprotein B	ApoB	Apolipoproteins
Apolipoprotein A1	ApoA1	Apolipoproteins
Apolipoprotein B to Apolipoprotein A1 ratio	ApoB_by_ApoA1	Apolipoproteins
Total Fatty Acids	Total_FA	Fatty acids
Degree of Unsaturation	Unsaturation	Fatty acids
Omega-3 Fatty Acids	Omega_3	Fatty acids
Omega-6 Fatty Acids	Omega_6	Fatty acids
Polyunsaturated Fatty Acids	PUFA	Fatty acids
Monounsaturated Fatty Acids	MUFA	Fatty acids
Saturated Fatty Acids	SFA	Fatty acids
Linoleic Acid	LA	Fatty acids
Docosahexaenoic Acid	DHA	Fatty acids
Omega-3 Fatty Acids to Total Fatty Acids percentage	Omega_3_pct	Fatty acids
Omega-6 Fatty Acids to Total Fatty Acids percentage	Omega_6_pct	Fatty acids
Polyunsaturated Fatty Acids to Total Fatty Acids percentage	PUFA_pct	Fatty acids
Monounsaturated Fatty Acids to Total Fatty Acids percentage	MUFA_pct	Fatty acids
Saturated Fatty Acids to Total Fatty Acids percentage	SFA_pct	Fatty acids

Linoleic Acid to Total Fatty Acids percentage	LA_pct	Fatty acids
Docosahexaenoic Acid to Total Fatty Acids percentage	DHA_pct	Fatty acids
Polyunsaturated Fatty Acids to Monounsaturated Fatty Acids ratio	PUFA_by_MUFA	Fatty acids
Omega-6 Fatty Acids to Omega-3 Fatty Acids ratio	Omega_6_by_Omega_3	Fatty acids
Alanine	Ala	Amino acids
Glutamine	Gln	Amino acids
Glycine	Gly	Amino acids
Histidine	His	Amino acids
Total Concentration of Branched-Chain Amino Acids (Leucine + Isoleucine + Valine)	Total_BCAA	Amino acids
Isoleucine	Ile	Amino acids
Leucine	Leu	Amino acids
Valine	Val	Amino acids
Phenylalanine	Phe	Amino acids
Tyrosine	Tyr	Amino acids
Glucose	Glucose	Glycolysis related metabolites
Lactate	Lactate	Glycolysis related metabolites
Pyruvate	Pyruvate	Glycolysis related metabolites
Citrate	Citrate	Glycolysis related metabolites
3-Hydroxybutyrate	bOHbutyrate	Ketone bodies
Acetate	Acetate	Ketone bodies
Acetoacetate	Acetoacetate	Ketone bodies
Acetone	Acetone	Ketone bodies
Creatinine	Creatinine	Fluid balance
Albumin	Albumin	Fluid balance
Glycoprotein Acetyls	GlycA	Inflammation
Concentration of Chylomicrons and Extremely Large VLDL Particles	XXL_VLDL_P	Lipoprotein subclasses
Total Lipids in Chylomicrons and Extremely Large VLDL	XXL_VLDL_L	Lipoprotein subclasses
Phospholipids in Chylomicrons and Extremely Large VLDL	XXL_VLDL_PL	Lipoprotein subclasses
Cholesterol in Chylomicrons and Extremely Large VLDL	XXL_VLDL_C	Lipoprotein subclasses

Cholesteryl Esters in Chylomicrons and Extremely Large VLDL	XXL_VLDL_CE	Lipoprotein subclasses
Free Cholesterol in Chylomicrons and Extremely Large VLDL	XXL_VLDL_FC	Lipoprotein subclasses
Triglycerides in Chylomicrons and Extremely Large VLDL	XXL_VLDL_TG	Lipoprotein subclasses
Concentration of Very Large VLDL Particles	XL_VLDL_P	Lipoprotein subclasses
Total Lipids in Very Large VLDL	XL_VLDL_L	Lipoprotein subclasses
Phospholipids in Very Large VLDL	XL_VLDL_PL	Lipoprotein subclasses
Cholesterol in Very Large VLDL	XL_VLDL_C	Lipoprotein subclasses
Cholesteryl Esters in Very Large VLDL	XL_VLDL_CE	Lipoprotein subclasses
Free Cholesterol in Very Large VLDL	XL_VLDL_FC	Lipoprotein subclasses
Triglycerides in Very Large VLDL	XL_VLDL_TG	Lipoprotein subclasses
Concentration of Large VLDL Particles	L_VLDL_P	Lipoprotein subclasses
Total Lipids in Large VLDL	L_VLDL_L	Lipoprotein subclasses
Phospholipids in Large VLDL	L_VLDL_PL	Lipoprotein subclasses
Cholesterol in Large VLDL	L_VLDL_C	Lipoprotein subclasses
Cholesteryl Esters in Large VLDL	L_VLDL_CE	Lipoprotein subclasses
Free Cholesterol in Large VLDL	L_VLDL_FC	Lipoprotein subclasses
Triglycerides in Large VLDL	L_VLDL_TG	Lipoprotein subclasses
Concentration of Medium VLDL Particles	M_VLDL_P	Lipoprotein subclasses
Total Lipids in Medium VLDL	M_VLDL_L	Lipoprotein subclasses
Phospholipids in Medium VLDL	M_VLDL_PL	Lipoprotein subclasses
Cholesterol in Medium VLDL	M_VLDL_C	Lipoprotein subclasses
Cholesteryl Esters in Medium VLDL	M_VLDL_CE	Lipoprotein subclasses
Free Cholesterol in Medium VLDL	M_VLDL_FC	Lipoprotein subclasses
Triglycerides in Medium VLDL	M_VLDL_TG	Lipoprotein subclasses
Concentration of Small VLDL Particles	S_VLDL_P	Lipoprotein subclasses
Total Lipids in Small VLDL	S_VLDL_L	Lipoprotein subclasses
Phospholipids in Small VLDL	S_VLDL_PL	Lipoprotein subclasses
Cholesterol in Small VLDL	S_VLDL_C	Lipoprotein subclasses
Cholesteryl Esters in Small VLDL	S_VLDL_CE	Lipoprotein subclasses

Free Cholesterol in Small VLDL	S_VLDL_FC	Lipoprotein subclasses
Triglycerides in Small VLDL	S_VLDL_TG	Lipoprotein subclasses
Concentration of Very Small VLDL Particles	XS_VLDL_P	Lipoprotein subclasses
Total Lipids in Very Small VLDL	XS_VLDL_L	Lipoprotein subclasses
Phospholipids in Very Small VLDL	XS_VLDL_PL	Lipoprotein subclasses
Cholesterol in Very Small VLDL	XS_VLDL_C	Lipoprotein subclasses
Cholesteryl Esters in Very Small VLDL	XS_VLDL_CE	Lipoprotein subclasses
Free Cholesterol in Very Small VLDL	XS_VLDL_FC	Lipoprotein subclasses
Triglycerides in Very Small VLDL	XS_VLDL_TG	Lipoprotein subclasses
Concentration of IDL Particles	IDL_P	Lipoprotein subclasses
Total Lipids in IDL	IDL_L	Lipoprotein subclasses
Phospholipids in IDL	IDL_PL	Lipoprotein subclasses
Cholesterol in IDL	IDL_C	Lipoprotein subclasses
Cholesteryl Esters in IDL	IDL_CE	Lipoprotein subclasses
Free Cholesterol in IDL	IDL_FC	Lipoprotein subclasses
Triglycerides in IDL	IDL_TG	Lipoprotein subclasses
Concentration of Large LDL Particles	L_LDL_P	Lipoprotein subclasses
Total Lipids in Large LDL	L_LDL_L	Lipoprotein subclasses
Phospholipids in Large LDL	L_LDL_PL	Lipoprotein subclasses
Cholesterol in Large LDL	L_LDL_C	Lipoprotein subclasses
Cholesteryl Esters in Large LDL	L_LDL_CE	Lipoprotein subclasses
Free Cholesterol in Large LDL	L_LDL_FC	Lipoprotein subclasses
Triglycerides in Large LDL	L_LDL_TG	Lipoprotein subclasses
Concentration of Medium LDL Particles	M_LDL_P	Lipoprotein subclasses
Total Lipids in Medium LDL	M_LDL_L	Lipoprotein subclasses
Phospholipids in Medium LDL	M_LDL_PL	Lipoprotein subclasses
Cholesterol in Medium LDL	M_LDL_C	Lipoprotein subclasses
Cholesteryl Esters in Medium LDL	M_LDL_CE	Lipoprotein subclasses
Free Cholesterol in Medium LDL	M_LDL_FC	Lipoprotein subclasses

Triglycerides in Medium LDL	M_LDL_TG	Lipoprotein subclasses
Concentration of Small LDL Particles	S_LDL_P	Lipoprotein subclasses
Total Lipids in Small LDL	S_LDL_L	Lipoprotein subclasses
Phospholipids in Small LDL	S_LDL_PL	Lipoprotein subclasses
Cholesterol in Small LDL	S_LDL_C	Lipoprotein subclasses
Cholesteryl Esters in Small LDL	S_LDL_CE	Lipoprotein subclasses
Free Cholesterol in Small LDL	S_LDL_FC	Lipoprotein subclasses
Triglycerides in Small LDL	S_LDL_TG	Lipoprotein subclasses
Concentration of Very Large HDL Particles	XL_HDL_P	Lipoprotein subclasses
Total Lipids in Very Large HDL	XL_HDL_L	Lipoprotein subclasses
Phospholipids in Very Large HDL	XL_HDL_PL	Lipoprotein subclasses
Cholesterol in Very Large HDL	XL_HDL_C	Lipoprotein subclasses
Cholesteryl Esters in Very Large HDL	XL_HDL_CE	Lipoprotein subclasses
Free Cholesterol in Very Large HDL	XL_HDL_FC	Lipoprotein subclasses
Triglycerides in Very Large HDL	XL_HDL_TG	Lipoprotein subclasses
Concentration of Large HDL Particles	L_HDL_P	Lipoprotein subclasses
Total Lipids in Large HDL	L_HDL_L	Lipoprotein subclasses
Phospholipids in Large HDL	L_HDL_PL	Lipoprotein subclasses
Cholesterol in Large HDL	L_HDL_C	Lipoprotein subclasses
Cholesteryl Esters in Large HDL	L_HDL_CE	Lipoprotein subclasses
Free Cholesterol in Large HDL	L_HDL_FC	Lipoprotein subclasses
Triglycerides in Large HDL	L_HDL_TG	Lipoprotein subclasses
Concentration of Medium HDL Particles	M_HDL_P	Lipoprotein subclasses
Total Lipids in Medium HDL	M_HDL_L	Lipoprotein subclasses
Phospholipids in Medium HDL	M_HDL_PL	Lipoprotein subclasses
Cholesterol in Medium HDL	M_HDL_C	Lipoprotein subclasses
Cholesteryl Esters in Medium HDL	M_HDL_CE	Lipoprotein subclasses
Free Cholesterol in Medium HDL	M_HDL_FC	Lipoprotein subclasses
Triglycerides in Medium HDL	M_HDL_TG	Lipoprotein subclasses

Concentration of Small HDL Particles	S_HDL_P	Lipoprotein subclasses
Total Lipids in Small HDL	S_HDL_L	Lipoprotein subclasses
Phospholipids in Small HDL	S_HDL_PL	Lipoprotein subclasses
Cholesterol in Small HDL	S_HDL_C	Lipoprotein subclasses
Cholesteryl Esters in Small HDL	S_HDL_CE	Lipoprotein subclasses
Free Cholesterol in Small HDL	S_HDL_FC	Lipoprotein subclasses
Triglycerides in Small HDL	S_HDL_TG	Lipoprotein subclasses
Phospholipids to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	XXL_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	XXL_VLDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	XXL_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	XXL_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Chylomicrons and Extremely Large VLDL percentage	XXL_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Very Large VLDL percentage	XL_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Very Large VLDL percentage	XL_VLDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Very Large VLDL percentage	XL_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Very Large VLDL percentage	XL_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Very Large VLDL percentage	XL_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Large VLDL percentage	L_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Large VLDL percentage	L_VLDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Large VLDL percentage	L_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Large VLDL percentage	L_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Large VLDL percentage	L_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Medium VLDL percentage	M_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Medium VLDL percentage	M_VLDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Medium VLDL percentage	M_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Medium VLDL percentage	M_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Medium VLDL percentage	M_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Small VLDL percentage	S_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Small VLDL percentage	S_VLDL_C_pct	Relative lipoprotein lipid concentrations

Cholesteryl Esters to Total Lipids in Small VLDL percentage	S_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Small VLDL percentage	S_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Small VLDL percentage	S_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Very Small VLDL percentage	XS_VLDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Very Small VLDL percentage	XS_VLDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Very Small VLDL percentage	XS_VLDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Very Small VLDL percentage	XS_VLDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Very Small VLDL percentage	XS_VLDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in IDL percentage	IDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in IDL percentage	IDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in IDL percentage	IDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in IDL percentage	IDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in IDL percentage	IDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Large LDL percentage	L_LDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Large LDL percentage	L_LDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Large LDL percentage	L_LDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Large LDL percentage	L_LDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Large LDL percentage	L_LDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Medium LDL percentage	M_LDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Medium LDL percentage	M_LDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Medium LDL percentage	M_LDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Medium LDL percentage	M_LDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Medium LDL percentage	M_LDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Small LDL percentage	S_LDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Small LDL percentage	S_LDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Small LDL percentage	S_LDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Small LDL percentage	S_LDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Small LDL percentage	S_LDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Very Large HDL percentage	XL_HDL_PL_pct	Relative lipoprotein lipid concentrations

Cholesterol to Total Lipids in Very Large HDL percentage	XL_HDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Very Large HDL percentage	XL_HDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Very Large HDL percentage	XL_HDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Very Large HDL percentage	XL_HDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Large HDL percentage	L_HDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Large HDL percentage	L_HDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Large HDL percentage	L_HDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Large HDL percentage	L_HDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Large HDL percentage	L_HDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Medium HDL percentage	M_HDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Medium HDL percentage	M_HDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Medium HDL percentage	M_HDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Medium HDL percentage	M_HDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Medium HDL percentage	M_HDL_TG_pct	Relative lipoprotein lipid concentrations
Phospholipids to Total Lipids in Small HDL percentage	S_HDL_PL_pct	Relative lipoprotein lipid concentrations
Cholesterol to Total Lipids in Small HDL percentage	S_HDL_C_pct	Relative lipoprotein lipid concentrations
Cholesteryl Esters to Total Lipids in Small HDL percentage	S_HDL_CE_pct	Relative lipoprotein lipid concentrations
Free Cholesterol to Total Lipids in Small HDL percentage	S_HDL_FC_pct	Relative lipoprotein lipid concentrations
Triglycerides to Total Lipids in Small HDL percentage	S_HDL_TG_pct	Relative lipoprotein lipid concentrations
Glucose-lactate	GL	Glycolysis related metabolites
Spectrometer-corrected alanine	SCA	Amino acids

Supplementary table 4 The longitudinal dynamic of serum gamma-glutamyl transferase and frailty index in the UK Biobank

Relative GGT change	Model 1		Model 2		Model 3	
	β (95%CI)	P	β (95%CI)	P	β (95%CI)	P
Continuous	0.014(0.005,0.023)	0.003	0.014(0.005,0.024)	0.002	0.015(0.006,0.024)	0.001
Quartile						
Q1	0 (Ref)		0 (Ref)		0 (Ref)	
Q2	-0.013(-0.032,0.007)	0.200	-0.014(-0.033,0.005)	0.162	-0.006(-0.025,0.013)	0.533
Q3	-0.016(-0.036,0.003)	0.094	-0.016(-0.035,0.004)	0.110	-0.006(-0.026,0.013)	0.522
Q4	0.037(0.018,0.056)	<0.001	0.040(0.021,0.059)	<0.001	0.048(0.029,0.067)	<0.001
P for Trend		<0.001		<0.001		<0.001

The relative change in GGT was calculated as the difference between the repeat and baseline measurements divided by the baseline value;

Model 1 adjusted for baseline frailty index;

Model 2 additionally adjusted for age, sex, Townsend Deprivation Index, and educational level;

Model 3 further adjusted for BMI, smoking status, alcohol consumption, and physical activity;

Abbreviation: GGT, gamma-glutamyl transferase; CI, confidence interval.

Supplementary table 5 Stratified analysis of the association between gamma-glutamyl transferase and incident frailty in the UK Biobank

Subgroups		Event N	Total	HR (95%CI)	P
Age	≥65 years	469	8110	1.43(1.19, 1.71)	<0.001
	< 65 years	4014	77606	1.20(1.13, 1.27)	<0.001
Sex	Female	2826	44293	1.21(1.13, 1.30)	<0.001
	Male	1657	41423	1.21(1.10, 1.32)	<0.001
Body mass index	Normal	1261	34176	1.13(1.01, 1.27)	0.034
	Under	19	414	0.41(0.12, 1.45)	0.166
	Over	1817	36395	1.24(1.14, 1.35)	<0.001
	Obese	1386	14731	1.20(1.09, 1.32)	<0.001
Smoking status	Never	2264	51418	1.20(1.11, 1.30)	<0.001
	Previous	1799	28787	1.19(1.09, 1.30)	<0.001
	Current	420	5511	1.34(1.11, 1.60)	0.002
Drinking status	Never	130	1741	1.16(0.83, 1.62)	0.388
	Previous	163	1693	1.41(1.08, 1.84)	0.011
	Current	4190	82282	1.20(1.14, 1.27)	<0.001
Physical activity	Yes	2507	54007	1.25(1.16, 1.35)	<0.001
	Non	1976	31709	1.16(1.07, 1.26)	<0.001
Hypertension	No	3231	69904	1.20(1.13, 1.28)	<0.001
	Yes	1252	15812	1.11(1.00, 1.23)	0.041
Diabetes	No	4257	83832	1.22(1.15, 1.29)	<0.001
	Yes	226	1884	0.87(0.69, 1.11)	0.262
Cardiovascular diseases	No	4311	83806	1.22(1.15, 1.29)	<0.001
	Yes	172	1910	1.03(0.78, 1.36)	0.830
Cancer	No	4020	80177	1.21(1.14, 1.28)	<0.001
	Yes	463	5539	1.12(0.95, 1.33)	0.182

The analyses were adjusted for age, sex, education levels, Townsend deprivation index, body mass index, smoking status, alcohol consumption, and physical activity.

Supplementary table 6 Association between gamma-glutamyl transferase and incident frailty excluding participants with liver or gallbladder disease at baseline in the UK Biobank

GGT	Total	Event N	Model 1		Model 2		Model 3	
			HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Continuous	82183	4141	1.25(1.190, 1.32)	<0.001	1.41(1.33, 1.48)	<0.001	1.18(1.11, 1.25)	<0.001
Quartile								
Q1	20639	919	Reference		Reference		Reference	
Q2	20573	989	1.12(1.03, 1.23)	0.011	1.19(1.09, 1.31)	<0.001	1.09(1.00, 1.20)	0.057
Q3	20506	1042	1.21(1.11, 1.32)	<0.001	1.39(1.27, 1.53)	<0.001	1.15(1.05, 1.27)	0.004
Q4	20465	1191	1.38(1.27, 1.51)	<0.001	1.68(1.53, 1.85)	<0.001	1.26(1.15, 1.39)	<0.001
P for Trend				<0.001		<0.001		<0.001

Model 1: unadjusted;

Model 2: adjusted for age, sex, education level, and Townsend deprivation index;

Model 3: further adjusted for BMI, physical activity, smoking status, and alcohol intake.

Supplementary table 7 Genetically predicted gamma-glutamyl transferase and frailty index by Mendelian randomization analysis

Method	MR result				Heterogeneity test		Pleiotropy test	
	SNP	SE	β(95%CI)	P	Q	P	Egger intercept	P
Preliminary analysis								
Inverse variance weighted	165	0.01	0.033(0.004, 0.061)	0.025	295.962	<0.001	0.001	0.141
Weighted median	165	0.02	0.027(-0.019, 0.072)	0.252				
Weighted mode	165	0.02	0.031(-0.011, 0.073)	0.156				
MR Egger	165	0.03	0.002(-0.048, 0.051)	0.948				
MR PRESSO	165	0.01	0.033(0.004, 0.061)	0.026				
Excluding confounding SNPs								
Inverse variance weighted	152	0.01	0.035(0.007, 0.063)	0.014	243.388	<0.001	0.001	0.092
Weighted median	152	0.02	0.026(-0.022, 0.073)	0.287				
Weighted mode	152	0.02	0.026(-0.017, 0.070)	0.239				
MR Egger	152	0.02	0.001(-0.047, 0.049)	0.956				
MR PRESSO	152	0.01	0.035(0.007, 0.063)	0.015				
Removing outliers by Radial method								
Inverse variance weighted	133	0.01	0.046(0.022, 0.070)	<0.001	124.650	0.663	0.001	0.127
Weighted median	133	0.02	0.029(-0.016, 0.074)	0.213				
Weighted mode	133	0.02	0.038(-0.007, 0.083)	0.1				
MR Egger	133	0.02	0.020(-0.021, 0.061)	0.337				
MR PRESSO	133	0.01	0.046(0.023, 0.070)	<0.001				

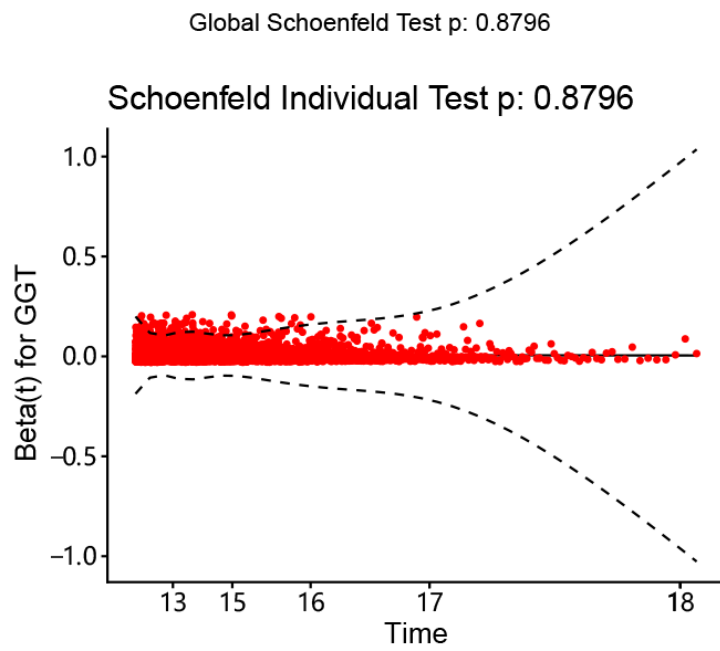
Supplementary table 8 SMR results showing genes associated with both GGT and frailty index

No.	Gene	Gamma-glutamyl transferase					Frailty index				
		topSNP	bsMR	sesMR	PSMR	P _{HEIDI}	topSNP	bsMR	sesMR	PSMR	P _{HEIDI}
1	ANAPC4	rs1533133	0.017	0.005	1.04E-03	0.077	rs1533133	0.019	0.007	4.03E-03	0.512
2	ARMC7	rs4789146	-0.041	0.013	1.25E-03	0.083	rs4789146	-0.051	0.017	2.66E-03	0.262
3	C15orf62	rs75973365	0.153	0.048	1.53E-03	0.211	rs75973365	0.148	0.053	5.65E-03	0.025
4	CCDC90B	rs647069	0.109	0.038	3.94E-03	0.059	rs647069	0.178	0.049	2.51E-04	0.075
5	CORO1A	rs7199462	-0.087	0.020	1.68E-05	0.183	rs7199462	-0.089	0.026	5.26E-04	0.278
6	DCTPP1	rs12373113	-0.161	0.051	1.56E-03	0.180	rs12373113	-0.170	0.064	7.78E-03	0.405
7	DPM3	rs10157801	0.370	0.045	1.57E-16	0.252	rs10157801	-0.104	0.040	9.38E-03	0.472
8	EP300	rs13058113	0.031	0.011	5.51E-03	0.157	rs13058113	0.046	0.015	2.62E-03	0.027
9	FCGR2B	rs61804206	0.031	0.004	5.64E-12	0.012	rs61804206	0.018	0.006	3.47E-03	0.399
10	FOS	rs7149592	-0.151	0.057	8.35E-03	0.036	rs7149592	-0.236	0.077	2.22E-03	0.747
11	GDPD3	rs57149692	-0.068	0.015	3.96E-06	0.106	rs57149692	-0.060	0.019	2.03E-03	0.058
12	HSPA4	rs72801474	0.028	0.010	6.30E-03	0.017	rs72801474	0.034	0.011	1.98E-03	0.746
13	HSPA6	rs12142755	-0.073	0.016	9.07E-06	0.016	rs12142755	-0.052	0.019	6.50E-03	0.460
14	ITGAL	rs11574938	0.045	0.013	3.08E-04	0.085	rs11574938	0.054	0.016	7.64E-04	0.759
15	KAZN	rs10803327	0.015	0.005	4.88E-03	0.020	rs10803327	0.017	0.006	6.69E-03	0.045
16	KPNA2	rs62086903	-0.339	0.059	8.00E-09	0.086	rs62086903	-0.149	0.055	6.64E-03	0.579
17	LMF2	rs762671	-0.054	0.020	7.99E-03	0.073	rs762671	-0.069	0.023	2.85E-03	0.578
18	LRPPRC	rs11900511	-0.022	0.008	8.94E-03	0.025	rs11900511	-0.054	0.011	8.15E-07	0.399
19	MAFF	rs4820323	-0.059	0.020	3.07E-03	0.290	rs4820323	-0.067	0.026	9.73E-03	0.395
20	MAPK3	rs55732507	-0.024	0.005	2.52E-06	0.910	rs55732507	-0.021	0.007	2.04E-03	0.271
21	NCK1	rs80201571	0.068	0.025	6.15E-03	0.098	rs80201571	0.086	0.033	8.26E-03	0.060
22	PBX4	rs1476459	0.110	0.022	3.90E-07	0.026	rs1476459	-0.077	0.027	4.79E-03	0.452
23	PPP2R3A	rs12695644	0.102	0.026	9.72E-05	0.218	rs12695644	0.153	0.032	2.27E-06	0.012
24	PRMT6	rs1623927	-0.021	0.004	1.06E-06	0.194	rs1623927	-0.014	0.005	9.36E-03	0.831
25	RASIP1	rs1231281	0.407	0.051	1.73E-15	0.043	rs1231281	0.127	0.042	2.86E-03	0.815
26	SMARCD2	rs11656575	-0.045	0.009	7.86E-07	0.150	rs11656575	-0.035	0.011	1.95E-03	0.782
27	SP1	rs10876447	0.030	0.009	1.32E-03	0.092	rs10876447	0.030	0.011	7.84E-03	0.144
28	SPATC1	rs56261297	-0.050	0.015	8.46E-04	0.479	rs56261297	-0.058	0.019	2.52E-03	0.190
29	STRADA	rs11079508	-0.122	0.026	3.08E-06	0.094	rs11079508	-0.102	0.031	9.96E-04	0.089
30	TBC1D10B	rs12930787	-0.110	0.039	4.23E-03	0.022	rs12930787	-0.129	0.048	7.18E-03	0.112
31	TM4SF19	rs73212184	-0.045	0.015	2.36E-03	0.161	rs73212184	0.049	0.019	8.60E-03	0.182
32	TMOD2	rs7174808	-0.012	0.005	7.13E-03	0.063	rs7174808	-0.030	0.006	7.13E-07	0.114
33	TRIM73	rs62477685	-0.015	0.005	1.58E-03	0.024	rs62477685	-0.021	0.006	4.80E-04	0.045
34	YIF1A	rs2155030	-0.074	0.018	3.19E-05	0.029	rs2155030	-0.060	0.023	9.10E-03	0.109
35	ZDHHC18	rs17162315	-0.050	0.008	2.21E-09	0.020	rs17162315	0.031	0.011	3.44E-03	0.241
36	ZNF771	rs7204270	-0.196	0.051	1.38E-04	0.582	rs7204270	-0.202	0.063	1.32E-03	0.360

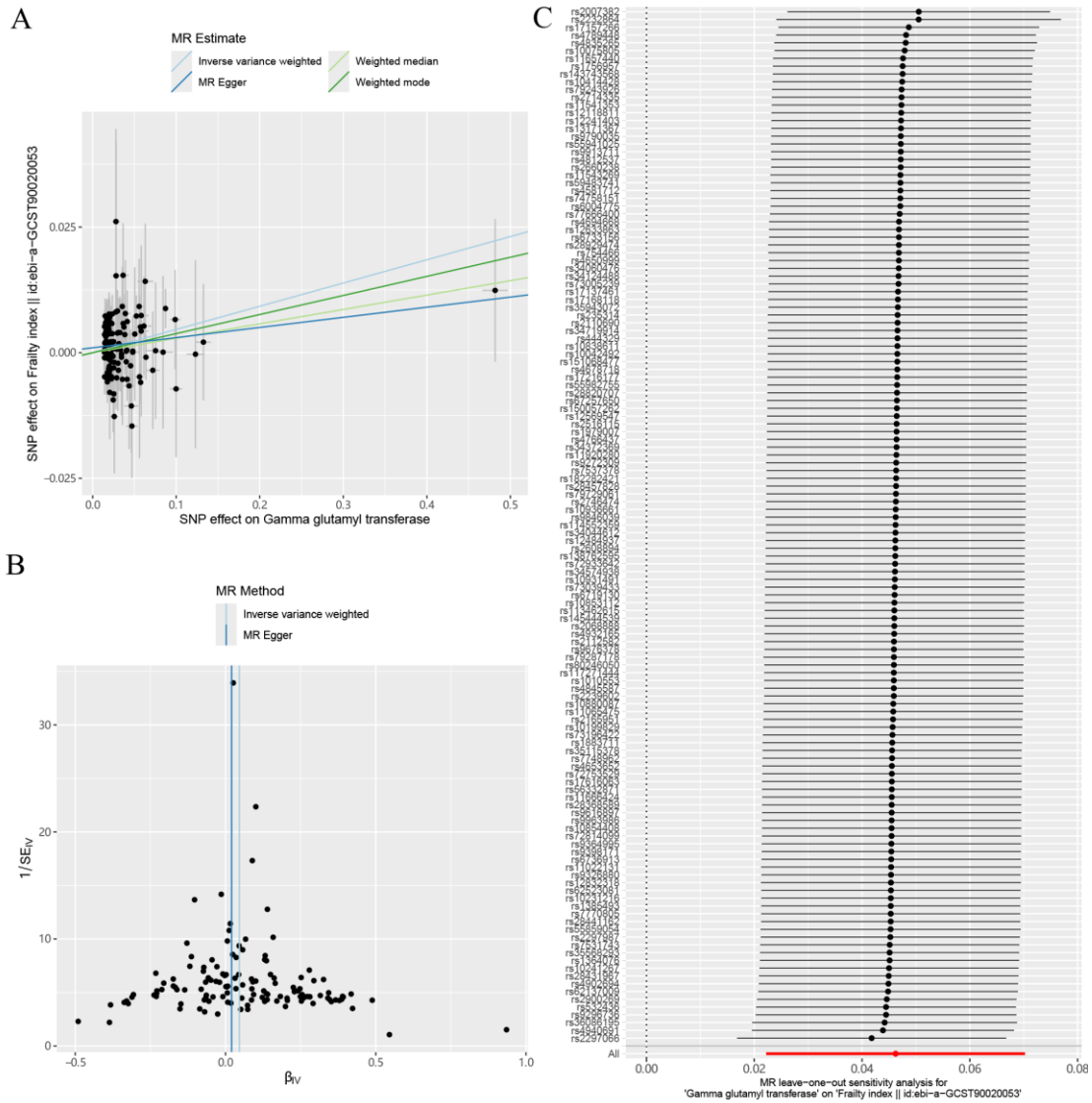
Abbreviations: HEIDI, heterogeneity in the dependent instrument; SMR, summary-based Mendelian randomization; SNP, single nucleotide polymorphism.

Supplementary table 9 Pathway enrichment analyses

Term	P	Adjusted P	Genes
Human t-cell leukemia virus 1 infection	4.30E-05	0.005	EP300; ANAPC4; FOS; ITGAL; MAPK3
T cell receptor signaling pathway	6.06E-05	0.005	FOS; PPP2R3A; MAPK3; NCK1
Tuberculosis	2.92E-04	0.015	EP300; FCGR2B; CORO1A; MAPK3
B cell receptor signaling pathway	4.30E-04	0.016	FOS; FCGR2B; MAPK3
Lipid and atherosclerosis	5.74E-04	0.016	HSPA4; HSPA6; FOS; MAPK3
Adherens junction	6.02E-04	0.016	EP300; RASIP1; MAPK3
Growth hormone synthesis, secretion and action	1.24E-03	0.028	EP300; FOS; MAPK3
Osteoclast differentiation	1.79E-03	0.031	FOS; FCGR2B; MAPK3
Estrogen signaling pathway	1.82E-03	0.031	HSPA6; FOS; MAPK3
Measles	1.94E-03	0.031	HSPA6; FOS; FCGR2B
Hepatitis b	3.01E-03	0.043	EP300; FOS; MAPK3
Influenza a	3.56E-03	0.047	EP300; KPNA2; MAPK3
Kaposi sarcoma-associated herpesvirus infection	5.14E-03	0.056	EP300; FOS; MAPK3
Chemical carcinogenesis - receptor activation	5.14E-03	0.056	FOS; KPNA2; MAPK3
Pathogenic escherichia coli infection	5.37E-03	0.056	FOS; MAPK3; NCK1
Long-term potentiation	6.10E-03	0.058	EP300; MAPK3
Renal cell carcinoma	6.29E-03	0.058	EP300; MAPK3
Prolactin signaling pathway	6.85E-03	0.060	FOS; MAPK3
Camp signaling pathway	7.36E-03	0.060	EP300; FOS; MAPK3
Leishmaniasis	8.26E-03	0.060	FOS; MAPK3
Pertussis	8.47E-03	0.060	FOS; MAPK3
Antigen processing and presentation	8.68E-03	0.060	HSPA4; HSPA6
ErbB signaling pathway	9.78E-03	0.060	MAPK3; NCK1



Supplementary figure 1 Test of the proportional hazards assumption using Schoenfeld Residuals.



Supplementary figure 2 Sensitivity analysis of Mendelian randomization.

A: Scatter plot; B: Funnel plot; C: Leave-one-out plot.