Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

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

Youxiang Wang
Zhengzhou University
Jingfeng Chen
First Affiliated Hospital of Zhengzhou University
Shifeng Sheng
First Affiliated Hospital of Zhengzhou University
Shuaiyin Chen
Zhengzhou University
Suying Ding
fccdingsy@zzu.edu.cn

First Affiliated Hospital of Zhengzhou University

Article

Keywords: Gamma-glutamyl transferase, Frailty, Biological aging, Mendelian randomization, Metabolomics, UK Biobank

Posted Date: July 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10074789/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Against the backdrop of accelerated population aging, the effective identification and intervention of frailty have become an important priority. Gamma-glutamyl transferase (GGT) is considered a potential biomarker of biological aging. We aimed to investigate the association between GGT and frailty through prospective cohort and integrative genetic analyses.

Methods

A total of 85,716 participants from the UK Biobank (UKB) were included in the prospective cohort analysis. Frailty was defined using the frailty index (FI). Cox proportional hazards models were used to evaluate the association between GGT and incident frailty, and mediation analyses examined the role of metabolites. Genetic analyses included linkage disequilibrium score regression (LDSC), two-sample Mendelian randomization (MR), and summary-data-based MR (SMR).

Results

After multivariable adjustment, log-transformed GGT was positively associated with the risk of incident frailty (HR 1.21, 95% CI 1.14–1.27). Participants in the highest GGT group had a 30% higher risk of frailty than those in the lowest GGT group (HR 1.30, 95% CI 1.19–1.43). Metabolites related to lipoprotein metabolism, amino acid metabolism, glycolysis, and systemic inflammation jointly mediated 47.16% of the association between GGT and frailty. LDSC analysis revealed a significant positive genetic correlation between GGT and FI (rg = 0.32, P = 2.33×10^{-25}). MR analysis provided evidence for a positive relationship between genetically predicted GGT levels and FI (IVW: β = 0.046, 95% CI 0.022–0.070; P < 0.001). SMR analysis identified 36 genes shared between GGT and frailty. Representative shared genes included EP300, FCGR2B, ITGAL, RASIP1, FOS, and MAPK3. KEGG enrichment analysis revealed significant enrichment in pathways related to immune signaling, lipid metabolism and atherosclerosis, adherens junctions, growth hormone signaling, estrogen signaling, and osteoclast differentiation.

Conclusion

Elevated GGT was associated with an increased risk of frailty in both observational and genetic analyses. These findings suggest that GGT may serve as a promising biomarker for identifying individuals at high risk of frailty, with metabolic, immune, vascular, and musculoskeletal pathways potentially contributing to the underlying mechanisms.

Background

Frailty is a multidimensional aging-related syndrome characterized by diminished physiological reserve and impaired resilience to stressors[1,2]. It notably elevates the risk of unfavorable results, including falls, hospitalizations, and mortality[3,4]. Although frailty predominantly affects older adults, it can also develop earlier in life, particularly among individuals with multimorbidity or severe chronic diseases[5]. In the context of rapid global population aging, frailty has emerged as a significant public health issue worldwide, highlighting the need to identify easily accessible biomarkers that may enable earlier risk stratification and timely intervention.

In recent years, gamma-glutamyl transferase (GGT) has shifted from a conventional biomarker of alcohol consumption and liver function to being increasingly recognized as a marker implicated in a wide range of extrahepatic conditions[6,7]. Elevated GGT concentrations have been linked to cardiometabolic diseases and increased mortality risk[8–10]. Importantly, accumulating evidence suggests that GGT reflects systemic pathophysiological processes beyond liver injury, including oxidative stress, chronic inflammation, and metabolic dysregulation—mechanisms central to biological aging and frailty pathogenesis[7,11,12]. Despite substantial advances in the identification of blood biomarkers associated with frailty[13], the function of GGT in the emergence and worsening of frailty is not yet completely understood.

Existing studies are cross-sectional and based on a single population[12,14], thereby limiting causal inference and generalizability. Prospective longitudinal studies examining incident frailty, as well as investigations incorporating genetic evidence to strengthen causal interpretation, remain scarce. Moreover, the biological pathways through which elevated GGT may increase frailty risk have not been fully elucidated.

To address these gaps, we investigated the association between baseline GGT and incident frailty, explored the potential mediating effects of GGT-related metabolic signatures, and examined whether longitudinal changes in GGT were associated with subsequent frailty index (FI). We further performed integrative genetic analyses to characterize shared genetic architecture, evaluate potential causal relationships, and identify candidate genes underlying the GGT–frailty association.

Methods

Study population

The UK Biobank (UKB) is a large population-based biomedical resource that provides extensive de-identified genetic and health-related information on approximately 500,000 participants aged 37–73 years[15]. In the present study, 85,716 participants free of frailty at baseline and with follow-up frailty assessments were included to investigate the association between baseline GGT levels and incident frailty. In addition, 15,610 participants with GGT measurements available at both baseline and the first

repeat assessment (2012–2013) were included to evaluate the association between longitudinal changes in GGT and subsequent FI. Detailed inclusion and exclusion criteria are shown in Fig. 1.

GGT and metabolic biomarkers measurement

Serum GGT concentration was the primary exposure of interest. GGT levels were quantified using the Beckman Coulter AU5800 analyzer. Given the right-skewed distribution of GGT, values were natural log-transformed and analyzed both as a continuous variable and in quartiles. A total of 251 metabolic biomarkers were quantified using a high-throughput nuclear magnetic resonance (NMR). Detailed methodologies are documented in the UKB NMR companion file (https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=2082).

Construction of frailty index

In the UKB, the FI was calculated according to a previously validated deficit accumulation approach using 49 health-related variables, with frailty defined as an FI value ≥ 0.24[3]. Detailed scoring criteria provided in Supplementary Table 1.

Assessment of covariates

The covariates in this study included demographic variables such as sex, age, race/ethnicity, educational attainment, and socioeconomic status, along with other potential confounders, including BMI, smoking status, alcohol consumption, and physical activity.

Statistical analysis

Non-normally distributed continuous variables are reported as medians (interquartile ranges) and compared using the Mann–Whitney U test, whereas categorical variables are expressed as counts (percentages) and analyzed using the chi-square test. Missing covariates were imputed using the mice package.

The cumulative incidence of frailty across GGT categories was estimated using Kaplan–Meier curves. Cox proportional hazards models were used to estimate hazard ratios (HRs) for the associations between baseline GGT levels and incident frailty under three progressively adjusted models. The proportional hazards assumption was confirmed using Schoenfeld residuals (Supplementary Fig. 1). Restricted cubic spline (RCS) regression was applied to examine potential dose–response relationships, using the median value as the reference. Stratified analyses were conducted by sex, age, lifestyle factors, and disease history. Sensitivity analyses were performed after excluding participants with liver or gallbladder disease at baseline.

Metabolite processing was conducted in accordance with previously published literature[16]. Associations between 251 metabolites and log-transformed GGT levels were examined using linear regression models, while Cox proportional hazards models were applied to assess associations with incident frailty;

multiple testing was corrected using the Benjamini–Hochberg false discovery rate (FDR) method. Elastic net regression with 10-fold cross-validation (α = 0.5) was used to identify metabolites associated with log-GGT. Metabolites with non-zero coefficients at $\lambda_1$se were selected to construct a composite metabolic signature as a weighted sum, which was standardized to a z-score. The association between the metabolic signature and incident frailty was further evaluated using RCS models. Counterfactual-based mediation analyses were conducted using the CMAverse package, as previously described[17], to estimate the total, natural direct, and natural indirect effects of log-GGT on frailty through the metabolic signature, with Cox regression for the time-to-event outcome, linear regression for the mediator, assuming no exposure-mediator interaction, and bootstrap resampling (1 000 iterations) for confidence interval estimation.

We applied an ANCOVA model to assess the association between relative changes in GGT and subsequent FI, with adjustment for baseline FI. Relative change in GGT was defined as (GGT_{second}-GGT_{first})/GGT_{first}. FI at follow-up was treated as the dependent variable, with baseline FI included as a covariate to account for initial frailty status, reduce regression-to-the-mean bias, and improve statistical efficiency.

Genetic analyses

To characterize the genetic basis of the GGT–frailty association, we first applied linkage disequilibrium score regression (LDSC) to estimate genetic correlation between the two traits. We then performed two-sample Mendelian randomization (MR) analyses to evaluate potential causal relationships, using the inverse-variance weighted (IVW) method as the primary estimator. To identify shared functional genes, summary-data-based Mendelian randomization (SMR) analysis was conducted by integrating genome-wide association study (GWAS) summary statistics with quantitative trait locus (QTL) data. Finally, KEGG pathway enrichment analysis was performed using genes identified by SMR. Additional methodological details are provided in the Supplementary Methods.

All statistical analyses were conducted using R version 4.2.1 and the UKB Research Analysis Platform. All tests were two-tailed, with $P<0.05$ regarded as statistically significant.

Result

Baseline characteristics of participants

During a median follow-up of 12.5 years, 4,483 incident frailty cases were identified among 85,716 participants (Table 1). Compared with participants who remained non-frail, those who developed frailty were older, more likely to be female, had lower educational attainment, higher socioeconomic deprivation, higher prevalence of obesity, smoking, hypertension, diabetes, cardiovascular disease, and cancer, lower levels of physical activity, and higher baseline GGT concentrations (all P < 0.001).

Table 1
Baseline Characteristics of study participants stratified by frailty status in the UK Biobank

Characteristic	Non-frailty	Frailty	p-value
	N = 81,233	N = 4,483	
Age, Median (Q1, Q3)	55.00 (49.00, 61.00)	56.00 (49.00, 61.00)	< 0.001
Female, n (%)	41,467.00 (51.05)	2,826.00 (63.04)	< 0.001
Education level, n (%)			< 0.001
College	38,215.00 (47.04)	1,687.00 (37.63)	
Other levels	38,045.00 (46.83)	2,378.00 (53.04)	
Un-Known	4,973.00 (6.12)	418.00 (9.32)	
TDI, n (%)			< 0.001
Low	31,488.00 (38.76)	1,573.00 (35.09)	
Medium	27,644.00 (34.03)	1,450.00 (32.34)	
High	22,101.00 (27.21)	1,460.00 (32.57)	
Body mass index, n (%)			< 0.001
Normal	32,915.00 (40.52)	1,261.00 (28.13)	
Under	395.00 (0.49)	19.00 (0.42)	
Over	34,578.00 (42.57)	1,817.00 (40.53)	
Obese	13,345.00 (16.43)	1,386.00 (30.92)	
Smoking status, n (%)			< 0.001
Current	5,091.00 (6.27)	420.00 (9.37)	
Never	49,154.00 (60.51)	2,264.00 (50.50)	
Previous	26,988.00 (33.22)	1,799.00 (40.13)	
Drinking status, n (%)			< 0.001
Current	78,092.00 (96.13)	4,190.00 (93.46)	
Never	1,611.00 (1.98)	130.00 (2.90)	
Previous	1,530.00 (1.88)	163.00 (3.64)	
Physical activity, n (%)	51,500.00 (63.40)	2,507.00 (55.92)	< 0.001

Abbreviation: TDI, Townsend deprivation index; CVD, Cardiovascular diseases; GGT, gamma-glutamyl transferase.

Characteristic	Non-frailty N = 81,233	Frailty N = 4,483	p-value
Hypertension, n (%)	14,560.00 (17.92)	1,252.00 (27.93)	< 0.001
Diabetes, n (%)	1,658.00 (2.04)	226.00 (5.04)	< 0.001
CVD, n (%)	1,738.00 (2.14)	172.00 (3.84)	< 0.001
Cancer, n (%)	5,076.00 (6.25)	463.00 (10.33)	< 0.001
GGT, Median (Q1, Q3)	24.10 (17.30, 36.40)	25.90 (18.20, 40.30)	< 0.001

Abbreviation: TDI, Townsend deprivation index; CVD, Cardiovascular diseases; GGT, gamma-glutamyl transferase.

Association between GGT and incident frailty

Cumulative incidence analyses revealed significant differences in frailty risk across GGT categories (log-rank P < 0.001) (Fig. 2A). Across all three progressively adjusted models, higher baseline GGT levels were consistently associated with an increased risk of incident frailty (Fig. 2B). In the fully adjusted model (Model 3), each one-unit increase in log-transformed GGT was associated with a 21% increased risk of frailty (HR = 1.21, 95% CI: 1.14–1.27). Compared with participants in the lowest GGT quartile, the risk of frailty increased by 10%, 16%, and 30% in the second, third, and fourth quartiles, respectively (P for trend < 0.001). RCS analysis demonstrated a linear association between log-transformed GGT and frailty risk (Fig. 2C), supporting a dose–response relationship.

Metabolic biomarker analysis

Among the 251 metabolites analyzed, 130 were significantly associated with GGT levels and 177 were significantly associated with incident frailty after multiple-testing correction (Supplementary Table 2). Elastic net regression identified a metabolic signature comprising 99 metabolites associated with GGT levels (Fig. 3A). These metabolites were predominantly related to lipoprotein metabolism, fatty acid composition, amino acid metabolism, glycolysis-related pathways, ketone body metabolism, and inflammatory processes (Supplementary Table 3). Lipoprotein-related lipids and lipoprotein subclasses constituted the largest proportion of the identified metabolic signature (Fig. 3B).

Among the metabolites with the largest elastic net coefficients, several HDL-related measures, amino acids, and lipoprotein subclass markers contributed substantially to the metabolic signature (Fig. 3C). The GGT-related metabolic signature score was subsequently calculated as a weighted sum of the selected metabolites. RCS analysis demonstrated a significant positive association between the metabolic signature and incident frailty risk (overall P < 0.001; P for nonlinearity = 0.967) (Fig. 3D). Mediation analysis indicated that the GGT-related metabolic signature partially mediated the association between GGT and frailty, accounting for 47.16% (95% CI: 33.31–70.11) of the total effect (Fig. 3E).

Relative GGT change and FI at follow-up

Relative GGT change was positively associated with FI at follow-up when analyzed as a continuous variable. This association remained significant after adjustment for sociodemographic, lifestyle, and clinical factors (Model 3: β = 0.015, 95% CI: 0.006–0.024, P = 0.001). When categorized into quartiles, participants in the highest quartile of relative GGT change exhibited significantly higher FI values than those in the lowest quartile (Model 3: β = 0.048, 95% CI: 0.029–0.067, P < 0.001, Supplementary Table 4).

Subgroup analysis and sensitivity analysis

In stratified analyses, the association between GGT and incident frailty appeared to be stronger in older participants, current smokers, individuals with prior alcohol consumption, and those without pre-existing chronic conditions (Supplementary table 5). Sensitivity analyses after excluding participants with liver or gallbladder disease at baseline yielded consistent results (Supplementary Tables 6).

Genetic analysis

LDSC analysis demonstrated a significant positive genetic correlation between GGT and FI (rg = 0.32, P = 2.33×10^{-25}). MR analysis further supported a positive association between genetically predicted GGT levels and FI (Supplementary Table 7). Using the IVW method, the effect estimate was β = 0.033 (95% CI: 0.004–0.061; P = 0.025). After excluding variants associated with potential confounders, the association remained significant (IVW β = 0.035, 95% CI: 0.007–0.063; P = 0.014). Following removal of outlier variants using radial MR, the effect estimate increased (IVW β = 0.046, 95% CI: 0.022–0.070; P < 0.001), and consistent findings were observed using MR-PRESSO and additional sensitivity analyses (Supplementary Fig. 2).

Results of SMR analysis

SMR analysis identified 36 genes shared between GGT and frailty (Supplementary Table 8). Among these, 12 genes showed effect directions consistent with the positive genetic correlation between GGT and frailty, whereas 20 genes showed negative associations. Representative shared genes included EP300, FCGR2B, ITGAL, RASIP1, FOS, and MAPK3. KEGG pathway enrichment analysis of the SMR-identified shared genes revealed significant enrichment in pathways related to immune signaling, lipid and atherosclerosis, adherens junctions, growth hormone signaling, estrogen signaling, and osteoclast differentiation (Fig. 4, Supplementary Table 9).

Discussion

In this large prospective cohort study combined with metabolomic and integrative genetic analyses, we found that elevated GGT levels were associated with an increased risk of incident frailty. The association was further supported by genetic evidence. LDSC analysis demonstrated a significant positive genetic correlation between GGT and frailty, while MR analyses supported a positive association between genetically predicted GGT and frailty. Moreover, a GGT-related metabolic signature mediated

approximately 47% of the observed association, and SMR analyses identified multiple shared genes and biological pathways linking GGT to frailty. In addition, longitudinal increases in GGT were associated with higher subsequent FI, suggesting that changes in GGT over time may provide additional information regarding frailty progression beyond a single baseline measurement. Collectively, these findings suggest that GGT captures important aspects of biological vulnerability and may serve as an accessible biomarker of frailty risk and age-related decline in physiological reserve.

Previous studies have firmly established GGT as a key biomarker for liver function and cardiometabolic health, with strong associations to cardiovascular diseases[8,18], type 2 diabetes[19,20], hypertension[21,22], and cancer[23,24] risk—conditions that contribute substantially to health deficit accumulation and are integral components of the FI. In addition, elevated GGT levels have been linked to cognitive impairment and a higher risk of dementia[25–27]. However, studies specifically examining the relationship between GGT and frailty remain limited and have largely relied on single-cohort, cross-sectional designs[13,14]. A study based on the Korea National Health and Nutrition Examination Survey revealed that older men in the highest GGT quartile had a significantly higher FI and a 2.08-fold increased likelihood of frailty. However, no such association was observed in women, suggesting a sex-specific relationship[12]. In contrast, our study demonstrated a significant association between GGT and FI in both men and women, with results corroborated by longitudinal data. Differences in study design, age structure and frailty definitions may partly explain these discrepancies. Our findings are consistent with results from the Activity and Function of the Elderly (AFE) study [14] and extend previous evidence by providing longitudinal and genetic support for the association between GGT and frailty.

Recent work has begun to explore the role of GGT in broader aging assessments. A study incorporating GGT into a Gompertz law–based biological age model provided preliminary evidence supporting GGT as a marker of aging-related processes[10]. Nevertheless, integration of GGT into aging and frailty frameworks remains sparse. Extending prior research, our study demonstrates that GGT is not only associated with specific disease outcomes but is also closely linked to frailty, a multidimensional construct reflecting cumulative physiological dysregulation and biological aging. Supporting this interpretation, findings from the Swedish National Study on Aging and Care indicated that metabolic disorders are key drivers of comorbidity accumulation, with faster disease accumulation rates directly associated with higher GGT levels[28]. Our findings therefore support the concept that elevated GGT may reflect accelerated biological aging and increased susceptibility to frailty through the progressive accumulation of health deficits.

The onset and progression of frailty are influenced by multiple biological risk factors, including chronic inflammation, oxidative stress, metabolic dysfunction, disrupted proteostasis and genetic predisposition[11,13,29,30]. The association between GGT and frailty may be explained through several biological mechanisms. As a key enzyme in extracellular glutathione metabolism, elevated GGT reflects and may promote systemic oxidative stress, which accelerates cellular senescence and functional decline during aging[6,12]. Oxidative stress and inflammation are tightly coupled, and higher GGT levels are

consistently associated with markers of chronic low-grade inflammation, a condition that favors muscle catabolism and multisystem deterioration[31–33]. Moreover, GGT serves as an early indicator of metabolic dysfunction and is strongly linked to obesity, insulin resistance, and metabolic syndrome, even within the normal range. Metabolic dysregulation disrupts energy metabolism, endothelial function, and physiological homeostasis, thereby eroding physiological reserve[29,34,35]. Beyond its hepatic origin, GGT may therefore act as an integrative marker of systemic metabolic and inflammatory burden, reflecting the cumulative effects of biological aging and adverse lifestyle factors, which may underlie its observed associations with frailty development and progression.

The metabolomic analyses further provided mechanistic insights into this association. Nearly half of the relationship between GGT and frailty was mediated by a metabolic signature characterized predominantly by alterations in lipoprotein metabolism, fatty acid composition, amino acid metabolism, glycolysis-related metabolites, and inflammatory markers such as GlycA. Notably, higher GGT levels were associated with increased concentrations of triglyceride-rich lipoproteins, branched-chain amino acids, aromatic amino acids, lactate, and GlycA, together with lower levels of glycine, glutamine, and HDL-related metabolites. These findings are consistent with previous metabolomic studies demonstrating that frailty is characterized by disturbances in amino acid metabolism, lipid metabolism, inflammatory signaling, and insulin sensitivity, with metabolites such as branched-chain amino acids, aromatic amino acids, lactate, and GlycA emerging as key metabolic correlates of frailty and related functional decline[29,36,37]. Elevated GlycA levels may reflect chronic low-grade inflammation, whereas increased branched-chain amino acids and lactate have been linked to impaired insulin sensitivity, mitochondrial dysfunction, and reduced muscle function[36,37]. Collectively, these metabolic alterations have been associated with insulin resistance, chronic inflammation, vascular dysfunction, and biological aging, suggesting that metabolic dysregulation may represent a key intermediate mechanism through which elevated GGT contributes to frailty development[13,29]. The substantial mediation proportion observed in our study suggests that metabolomic alterations may capture early biological changes that precede the clinical manifestation of frailty.

The metabolomic findings were further complemented by the genetic analyses, which provided additional evidence supporting a biological link between GGT and frailty. LDSC demonstrated a substantial positive genetic correlation between GGT and frailty, indicating the presence of shared genetic determinants. Moreover, MR analyses supported a positive association between genetically predicted GGT and frailty, providing complementary genetic evidence for the observational and metabolomic findings.

SMR and pathway enrichment analyses offered further insights into the molecular mechanisms underlying this association. We identified multiple shared genes, including EP300, FCGR2B, ITGAL, RASIP1, FOS, and MAPK3, many of which have been implicated in immune regulation, inflammatory responses, vascular homeostasis, and cellular stress signaling[38–40]. KEGG enrichment analyses revealed significant enrichment of pathways related to immune signaling, lipid and atherosclerosis, adherens

junctions, growth hormone signaling, estrogen signaling, and osteoclast differentiation. These pathways are consistent with current concepts of frailty biology, which emphasize the contributions of chronic inflammation, metabolic dysfunction, endocrine dysregulation, vascular aging, and musculoskeletal decline to the development of frailty[29]. Notably, MAPK3, FOS, EP300, and FCGR2B appeared repeatedly across enriched pathways, suggesting that inflammatory and stress-response signaling networks may represent important molecular mechanisms linking elevated GGT to frailty.

This study has several strengths. First, it integrates prospective cohort, metabolomic, and genetic analyses within a unified framework, allowing triangulation of evidence across multiple methodological approaches. Second, the large sample size and long follow-up period provided sufficient statistical power to evaluate incident frailty. Third, the convergence of evidence from observational, metabolomic, and genetic analyses substantially strengthens the robustness and biological plausibility of the findings.

Several limitations should also be considered. First, despite the prospective design and extensive covariate adjustment, residual confounding cannot be completely excluded. Second, the FI may be subject to measurement error and cohort-specific operational definitions. Third, the metabolomic mediation analyses remain observational and do not establish causality between individual metabolites and frailty. Fourth, most genetic analyses were based on individuals of European ancestry, which may limit the generalizability of the findings to other populations. In addition, the SMR and pathway enrichment analyses were exploratory and require further validation in functional studies. Finally, further experimental and longitudinal studies are needed to clarify the causal mechanisms underlying the observed associations.

In conclusion, elevated serum GGT levels were associated with an increased risk of frailty and were supported by evidence from metabolomic and integrative genetic analyses. Metabolic dysregulation accounted for a substantial proportion of this association, while genetic analyses implicated immune, vascular, endocrine, and musculoskeletal pathways in the underlying mechanisms. These findings support the potential utility of GGT as a biomarker of biological aging and frailty risk and provide new insights into the biological mechanisms linking metabolic dysfunction to frailty development.

Declarations

Ethics approval and consent to participate

The study adhered to the Declaration of Helsinki. All individuals provided written informed consent at the outset of the study, and approval was obtained from the North West Multi-Center Research Ethics Committee (11/NW/0382).

Competing interests

All authors declare no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (72101236); China Postdoctoral Science Foundation (2022M722900); Henan province science and technology research project (242102311099); Collaborative Innovation Project of Zhengzhou City (XTCX2023006); Nursing team project of the First Affiliated Hospital of Zhengzhou University (HLKY2023005).

Author Contribution

YXW and SYC conceived the idea for the manuscript. YXW and JFC conducted the analysis. SFS, YY, TTL, and LW collected the data. All authors contributed to the interpretation of the findings. YXW and JFC wrote the first draft. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript. SYC and SYD 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.

Acknowledgement

We are grateful to UK Biobank participants. This research has been conducted using the UK Biobank Resource under Application Number 453339.

Data Availability

All data analyzed during the current study are publicly available upon request at https://biobank.ndph.ox.ac.uk/ukb/.

References

1. Hoogendijk, E. O. *et al.* Frailty: implications for clinical practice and public health. *Lancet* 394, 1365–1375 (2019).
2. Santulli, G. *et al.* Interplay between frailty and cardiometabolic disorders: from pathophysiology to clinical implications. *Cardiovasc. Diabetol.* 25, 1 (2025).
3. Yang, Y., Chen, L. & Filippidis, F. T. Accelerometer-measured physical activity, frailty, and all-cause mortality and life expectancy among middle-aged and older adults: a UK Biobank longitudinal study. *BMC Med.* 23, 125 (2025).
4. Fan, J. *et al.* Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. *The Lancet Public Health* 5, e650–e660 (2020).
5. Morales, D. R., Guthrie, B., Downes, T. J., McAllister, D. A. & Hanlon, P. Applicability of the electronic frailty index in younger and older adults in England: a population-based cohort study. *Lancet Healthy*

Longev 6, 100752 (2025).

6. Brennan, P. N., Dillon, J. F. & Tapper, E. B. Gamma-Glutamyl Transferase (γ-GT) - an old dog with new tricks? *Liver Int.* 42, 9–15 (2022).
7. Corti, A., Belcastro, E., Dominici, S., Maellaro, E. & Pompella, A. The dark side of gamma-glutamyltransferase (GGT): Pathogenic effects of an 'antioxidant' enzyme. *Free Radic. Biol. Med.* 160, 807–819 (2020).
8. Rhee, S. Y. Potential of γ-Glutamyl Transferase as a Novel Risk Factor for Cardiovascular Disease. *Endocrinol. Metab.* 38, 667–668 (2023).
9. Ho, F. K. *et al.* Association of gamma-glutamyltransferase levels with total mortality, liver-related and cardiovascular outcomes: A prospective cohort study in the UK Biobank. *EClinicalMedicine* 48, 101435 (2022).
10. Hao, M. *et al.* Gompertz Law-Based Biological Age (GOLD BioAge): A Simple and Practical Measurement of Biological Ageing to Capture Morbidity and Mortality Risks. *Adv. Sci.* e01765 (2025) doi:10.1002/advs.202501765.
11. Jiang, M. *et al.* A multidimensional epidemiological perspective on frailty dynamics and prevention. *Trends Endocrinol. Metab.* S104327602500147X (2025) doi:10.1016/j.tem.2025.07.001.
12. Kang, M., Jung, H. & Kim, B. Elevated Serum Gamma-Glutamyl Transferase as a Risk Factor for Frailty in Older Men: A Nationwide Population-Based Study. *J cachexia sarcopenia muscle* 16, e70034 (2025).
13. Fritzenschaft, L., Boehm, F., Rothenbacher, D., Denkinger, M. & Dallmeier, D. Association of blood biomarkers with frailty–A mapping review. *Ageing Res. Rev.* 109, 102761 (2025).
14. Boehm, F. J. *et al.* Sex- and system-specific analysis of blood-based biomarkers and frailty in older adults—the Activity and Function of the Elderly study. *Age Ageing* 54, afaf255 (2025).
15. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 12, e1001779 (2015).
16. Guo, J. *et al.* Metabolic signature of EAT-Lancet diet in relation to risk of frailty: a prospective cohort study. *npj Sci. Food* 9, 255 (2025).
17. Suo, X. *et al.* Frailty Mediated the Associations of Fine Particulate Matter With Depression and Anxiety: Findings From the UK Biobank. *J. Gerontol. A. Biol. Sci. Med. Sci.* 80, glaf047 (2025).
18. Baek, H.-S. *et al.* Long-Term Cumulative Exposure to High γ-Glutamyl Transferase Levels and the Risk of Cardiovascular Disease: A Nationwide Population-Based Cohort Study. *Endocrinol. Metab.* 38, 770–781 (2023).
19. Bi, Y. *et al.* To explore association between gamma-glutamyl transferase and type 2 diabetes using a real-world study and mendelian randomization analysis. *Front. Endocrinol.* 13, 899008 (2022).
20. Thai, N. Q. N. *et al.* Longitudinal Analysis of Liver Chemistry Trajectories and Risk of Type 2 Diabetes in Children With Metabolic Dysfunction-Associated Steatotic Liver Disease: A Multicenter Cohort Study. *Diabetes Care* dc251532 (2025) doi:10.2337/dc25-1532.

21. Fard, M. T., Najafi, F., Rezaeian, S., Kohsari, M. & Moradinazar, M. Association between serum liver enzymes and hypertension using propensity score matching analysis: evidence from a large kurdish prospective cohort study. *BMC Cardiovasc. Disord.* 22, 476 (2022).
22. Liu, Y.-H. *et al.* Liver-function parameters are associated with incident hypertension in a large Taiwanese population follow-up study. *J. Hum. Hypertens.* 37, 496–501 (2022).
23. Song, J. *et al.* Sleep and liver function biomarkers in relation to risk of incident liver cancer: a nationwide prospective cohort study. *BMC Med.* 22, 261 (2024).
24. Mok, Y., Son, D.-K., Yun, Y. D., Jee, S. H. & Samet, J. M. γ-Glutamyltransferase and cancer risk: The Korean cancer prevention study. *Int. J. Cancer* 138, 311–319 (2015).
25. Lee, Y.-B. *et al.* Gamma-glutamyl transferase variability and risk of dementia: A nationwide study. *Int. J. Geriatr. Psychiatry* 35, 1105–1114 (2020).
26. Zhou, Q. *et al.* Prevalence of Frailty Among Chinese Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. *Int. J. Public Health* 68, 1605964 (2023).
27. Praetorius Björk, M. & Johansson, B. Gamma-Glutamyltransferase (GGT) as a biomarker of cognitive decline at the end of life: contrasting age and time to death trajectories. *Int. Psychogeriatr.* 30, 981–990 (2018).
28. Ornago, A. M. *et al.* Shared and specific blood biomarkers for multimorbidity. *Nat. Med.* https://doi.org/10.1038/s41591-025-04038-2 (2026) doi:10.1038/s41591-025-04038-2.
29. Mishra, M., Wu, J., Kane, A. E. & Howlett, S. E. The intersection of frailty and metabolism. *Cell Metab.* 36, 893–911 (2024).
30. Hodgins, M. L., Maxwell, S. P., Howlett, S. E. & Rockwood, K. Blood biomarkers of frailty and cognition: A scoping review. *Neurobiol. Aging* 161, 14–30 (2026).
31. Costamagna, D., Costelli, P., Sampaolesi, M. & Penna, F. Role of Inflammation in Muscle Homeostasis and Myogenesis. *Mediators Inflammation* 2015, 805172 (2015).
32. Formanowicz, D. Decoding Chronicity: Oxidative Stress and Inflammation as Systems Hubs. *Biomedicines* 13, 2976 (2025).
33. Mitrić, A. & Castellano, I. Targeting gamma-glutamyl transpeptidase: A pleiotropic enzyme involved in glutathione metabolism and in the control of redox homeostasis. *Free Radical Biol. Med.* 208, 672–683 (2023).
34. Perazza, L. R., Brown-Borg, H. M. & Thompson, L. V. Physiological Systems in Promoting Frailty. *Compr. Physiol.* 12, 3575–3620 (2022).
35. Abdullah, G., Akpan, A., Phelan, M. M. & Wright, H. L. New insights into healthy ageing, inflammageing and frailty using metabolomics. *Front. Aging* 5, 1426436 (2024).
36. Xiao, L. *et al.* Metabolomic characterization of frailty identifies subtype-specific management strategies. *npj Digital Med.* 8, 746 (2025).
37. Bougel, C. *et al.* Serum metabolomic signatures associated with frailty-related phenotypes in a cohort of older people. *GeroScience* https://doi.org/10.1007/s11357-026-02116-y (2026)

doi:10.1007/s11357-026-02116-y.

38. Yu, Y.-L. *et al.* STAT1 epigenetically regulates LCP2 and TNFAIP2 by recruiting EP300 to contribute to the pathogenesis of inflammatory bowel disease. *Clin. Epigenet.* 13, 127 (2021).
39. Xu, K., Chong, D. C., Rankin, S. A., Zorn, A. M. & Cleaver, O. Rasip1 is required for endothelial cell motility, angiogenesis and vessel formation. *Dev. Biol.* 329, 269–279 (2009).
40. Zarei, S., Taghian, F., Sharifi, G. & Abedi, H. Novel prevention insights into depletion of oxidative stress status through regular exercise and grape seed effective substance in heart ischemia rat model. *Food Sci. Nutr.* 10, 833–845 (2022).

Figures

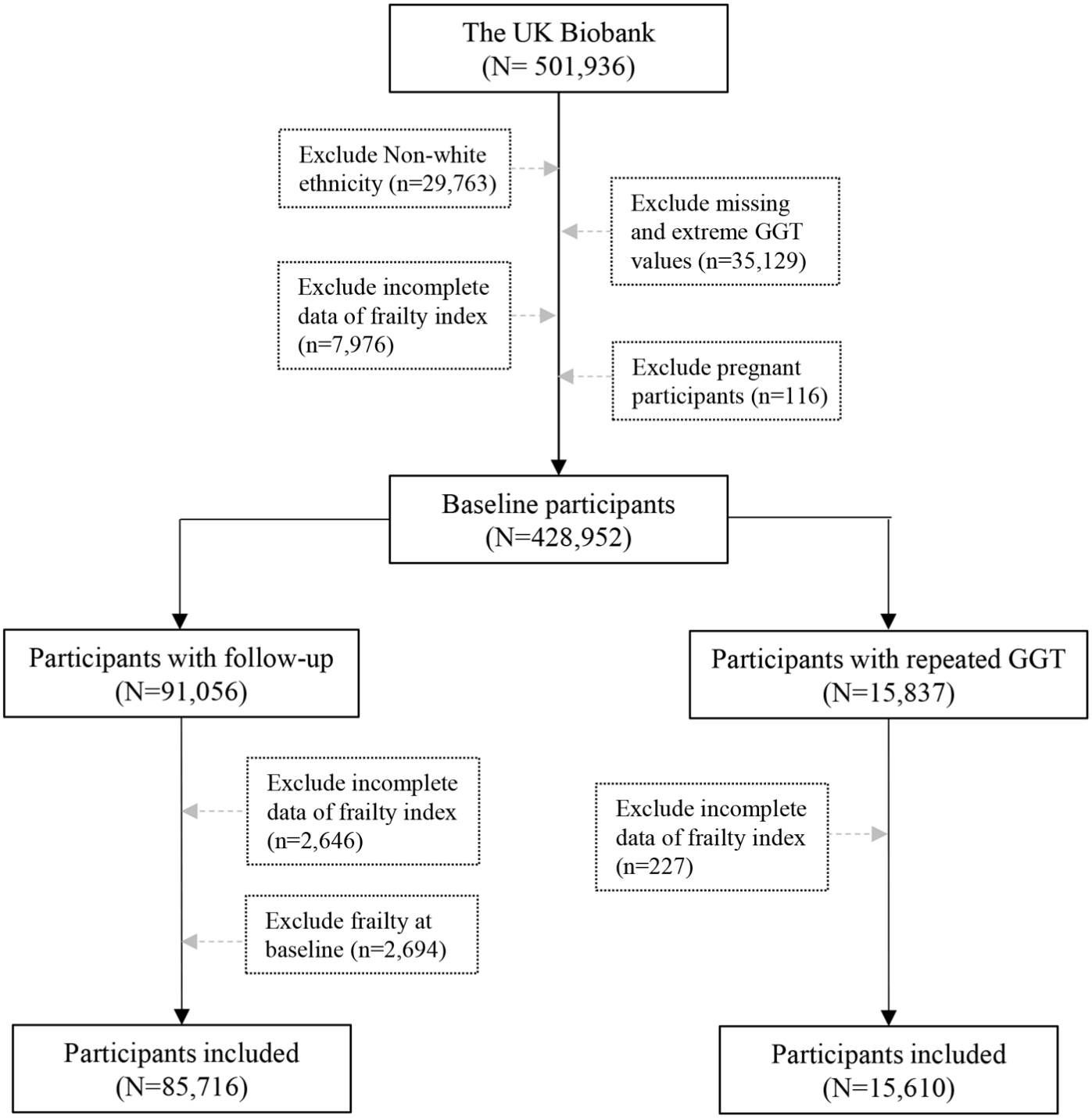
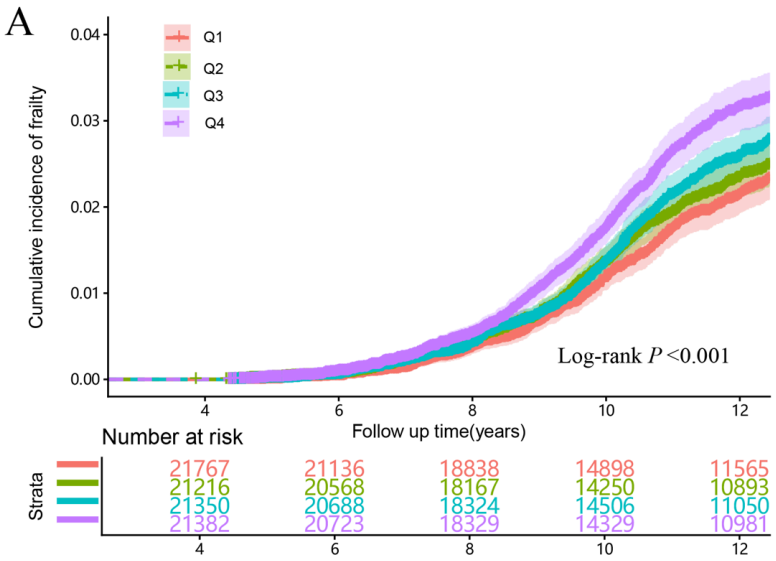
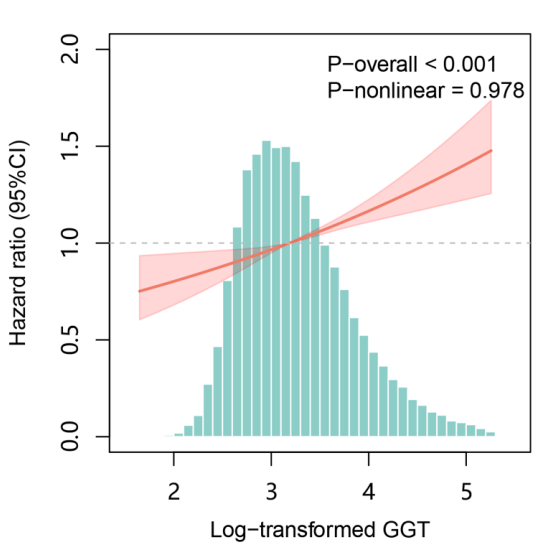


Figure 1

Flowchart of participant screening. GGT, gamma-glutamyl transferase



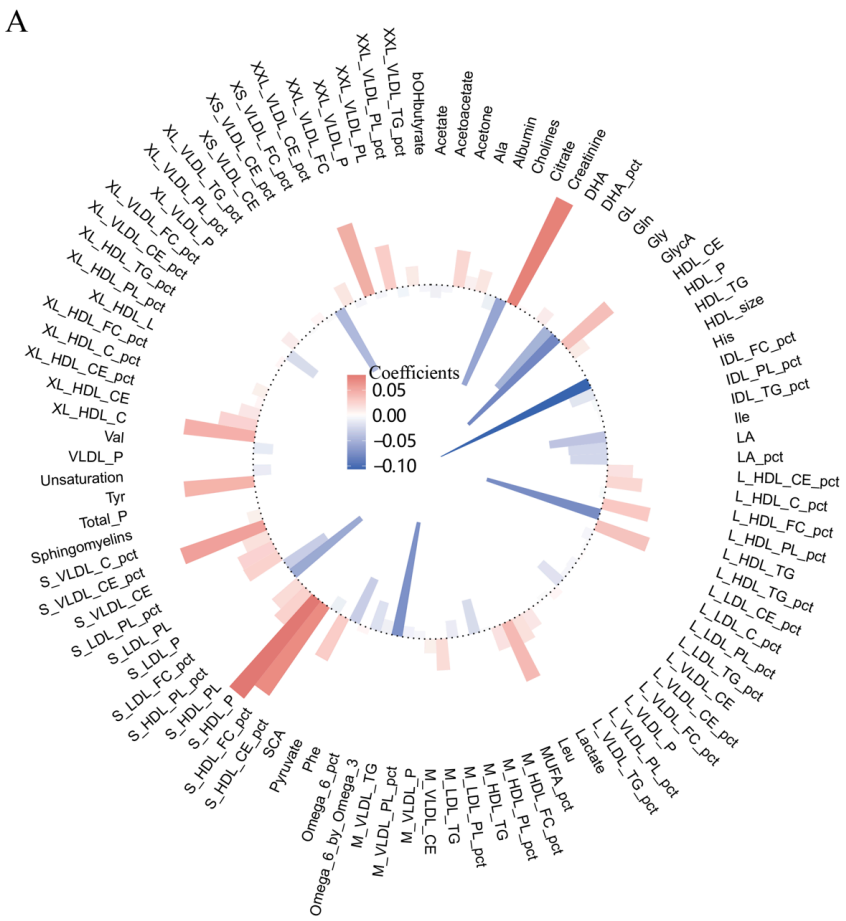


B

GGT	Total	Event N	Model 1 HR(95% CI)	Model 1 P	Model 2 HR(95% CI)	Model 2 P	Model 3 HR(95% CI)	Model 3 P
Continuous	85716	4483	1.27 (1.21 , 1.34)	<0.001	1.44 (1.36 , 1.51)	<0.001	1.21 (1.14 , 1.27)	<0.001
Quartile								
Q1	21767	1002	Reference		Reference		Reference	
Q2	21217	1047	1.13 (1.03 , 1.23)	0.007	1.20 (1.10 , 1.31)	<0.001	1.10 (1.00 , 1.20)	0.041
Q3	21350	1126	1.22 (1.12 , 1.32)	<0.001	1.41 (1.29 , 1.54)	<0.001	1.16 (1.06 , 1.27)	0.001
Q4	21382	1308	1.41 (1.30 , 1.54)	<0.001	1.74 (1.59 , 1.90)	<0.001	1.30 (1.19 , 1.43)	<0.001
P for Trend				<0.001		<0.001		<0.001

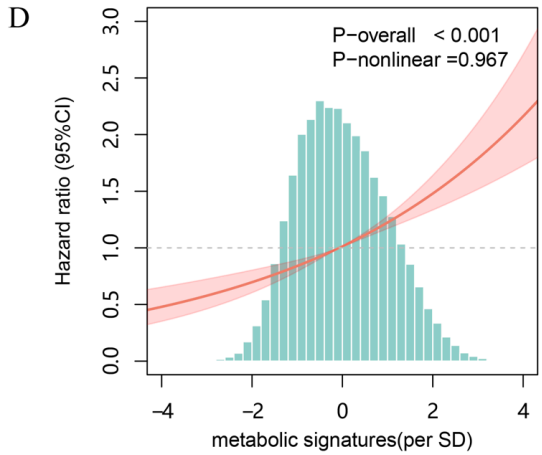
Figure 2

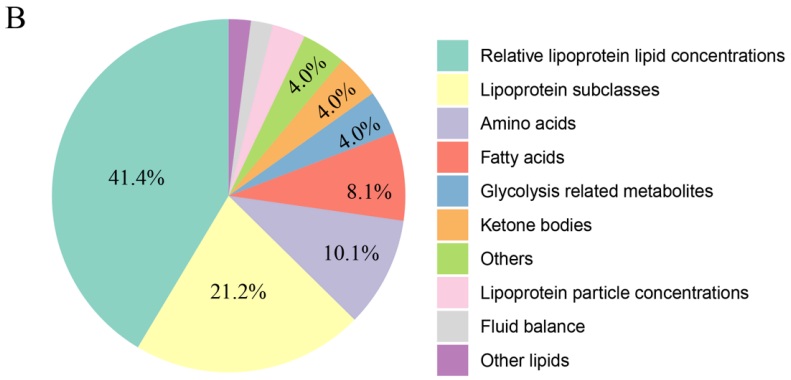
Association between gamma-glutamyl transferase and incident frailty in the UK Biobank. A: Cumulative incidence curves across different GGT level groups; B: Results of Cox proportional hazards regression analysis. C: Dose–response relationship between GGT and incident frailty; Model 1: unadjusted; Model 2: adjusted for age, sex, education level, and Townsend deprivation index; Model 3: further adjusted for BMI, physical activity, smoking status, and alcohol intake.



C

Metabolites	Coefficients	Beta (95% CI)	HR (95% CI)
HDL_size	-0.107	-0.06(-0.06,-0.05)	0.86(0.83,0.89)
Gly	-0.080	-0.06(-0.06,-0.06)	0.96(0.93,0.99)
L_HDL_TG	-0.076	0.06(0.06,0.07)	1.01(0.98,1.04)
M_VLDL_TG	-0.075	0.11(0.10,0.11)	1.09(1.06,1.12)
Citrate	-0.060	-0.03(-0.03,-0.02)	0.97(0.94,1.00)
S_LDL_FC_pct	-0.057	-0.08(-0.09,-0.08)	0.90(0.88,0.93)
Gln	-0.050	-0.06(-0.07,-0.06)	0.97(0.94,1.00)
XS_VLDL_CE_pct	-0.046	-0.07(-0.08,-0.07)	0.85(0.83,0.88)
Ile	-0.037	0.03(0.02,0.03)	1.01(0.98,1.04)
S_LDL_P	-0.032	0.07(0.07,0.07)	1.01(0.98,1.04)
L_HDL_TG_pct	0.035	0.09(0.09,0.10)	1.13(1.09,1.17)
GlycA	0.038	0.12(0.11,0.12)	1.14(1.11,1.18)
Leu	0.041	0.03(0.03,0.04)	1.00(0.97,1.03)
Tyr	0.045	0.05(0.04,0.05)	0.98(0.95,1.01)
XL_HDL_C	0.046	-0.05(-0.06,-0.05)	0.85(0.82,0.88)
XXL_VLDL_FC	0.048	0.11(0.11,0.11)	1.11(1.07,1.14)
S_VLDL_CE_pct	0.057	-0.04(-0.04,-0.03)	0.93(0.90,0.96)
S_HDL_FC_pct	0.069	0.00(-0.01,0.00)	0.92(0.89,0.95)
Creatinine	0.075	0.02(0.01,0.02)	1.06(1.02,1.10)
S_HDL_P	0.080	0.09(0.08,0.09)	1.03(1.00,1.06)





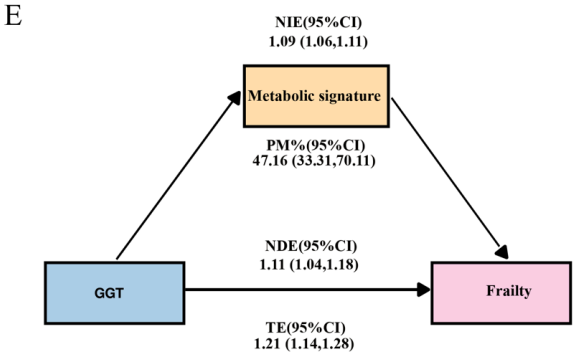


Figure 3

Association between gamma-glutamyl transferase, metabolites and incident frailty in the UK Biobank. A: GGT-related metabolites identified using elastic net regression; B: Classification of GGT-related metabolites; C: Associations of the top 20 metabolites with GGT and incident frailty; D: Dose–response relationship between the GGT-related metabolic signature and incident frailty; E: GGT-related metabolites identified in the mediation analysis between GGT and incident frailty.

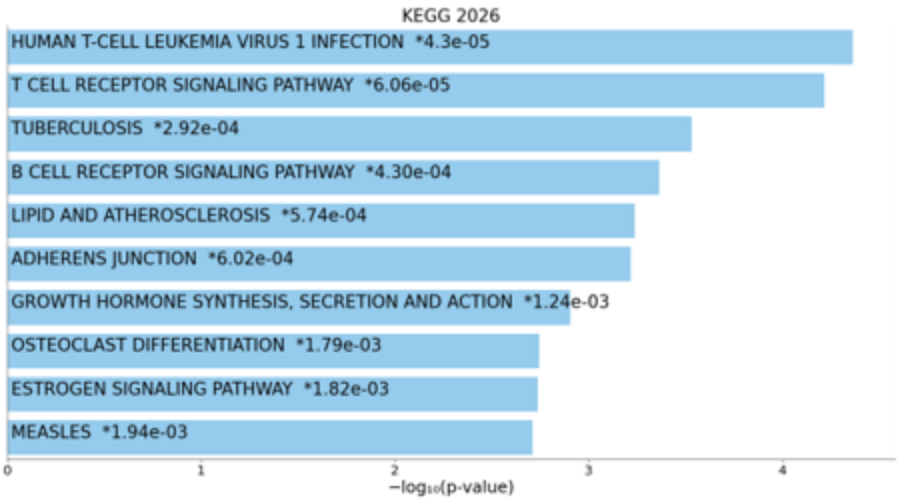


Figure 4

Pathway enrichment analyses

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20260618Supplementarymaterial.pdf