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The J-shaped relationship between the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio and mortality risk in U.S. adults

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ABSTRACT

Background: Research has investigated the gamma-glutamyltransferase to high-density lipoprotein cholesterol (GGT/HDL-C) ratio concerning metabolic diseases. This study aims to explore its effects on mortality, including cardiovascular disease (CVD) mortality.

Methods: A retrospective cohort study was conducted utilizing data from the National Health and Nutrition Examination Survey (1999–2018), comprising 50,462 U.S. adults. Survival outcomes were assessed through Kaplan-Meier curves, and a multivariable Cox proportional hazards model was employed to analyze the relationship between GGT/HDL-C levels and mortality risk. Restricted cubic splines and hierarchical analyses were utilized to explore potential non-linear associations and interactions, respectively.

Results: During a median follow-up period of 114.4 months, 7573 deaths were recorded, including 1956 deaths related to CVD. The relationship between the GGT/HDL-C ratio and the likelihood of all-cause death and CVD death showed a J-shaped curve in the restricted cubic spline analysis. Below a lnGGT/HDL-C of 2.3 (GGT/HDL-C of 10.0), no significant correlation with all-cause mortality was identified, while the threshold for CVD death was established at lnGGT/HDL-C of 2.5. Beyond these thresholds, each unit increase in lnGGT/HDL-C was associated with a 36.3 % higher risk of all-cause mortality [HR (95 % CI), 1.36 (1.26, 1.47)] and a 67.1 % increased risk of death from CVD [HR (95 % CI), 1.67 (1.42, 1.97)]. Consistent findings were observed across various subgroups, with participants younger than 65 showing a more pronounced association.

Conclusions: The GGT/HDL-C ratio exhibits a J-shaped correlation with the risk of all-cause mortality and CVD mortality among U.S. adults. This ratio may be utilized for assessing mortality risk.

1. Introduction

Gamma-glutamyltransferase (GGT) is a serum marker primarily used to assess liver function. However, emerging research has unveiled its broader implications, linking GGT levels to various health measures like blood pressure, cholesterol levels, and blood sugar (Lee et al., 2007). Additionally, GGT holds predictive value for conditions including type 2 diabetes, metabolic syndrome, and hypertension (Franzini et al., 2017; Kwak et al., 2023; Kim et al., 2012; Lee et al., 2003), while also showing close ties to atherosclerosis and heart disease (Lee et al., 2007; Ndrepepa and Kastrati, 2016; Ndrepepa et al., 2018; Baek et al., 2023). In contrast, high-density lipoprotein cholesterol (HDL-C) plays a role in reducing inflammation, acts as an antioxidant, and helps prevent blood clotting. Lower levels of HDL-C are frequently observed in individuals with coronary artery disease as well as metabolic syndrome, indicating its protective role against atherosclerosis (Barbalho et al., 2019; Fadaei et al., 2019; Cho et al., 2017).

Recent attention has focused on the GGT/HDL-C ratio as a promising new measurement, offering resistance to interference and ease of assessment. Studies have demonstrated its effectiveness in predicting the onset of diabetes and other metabolic diseases, outperforming individual markers (Xie et al., 2022a; Feng et al., 2020a; Li et al., 2022; Zhao et al., 2023; Hu et al., 2022; Xie et al., 2022b; Feng et al., 2020b). Despite this, research on its relationship with survival outcomes remains

Abbreviations: GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; CVD, cardiovascular disease; NHANES, The National Health and Nutrition Examination Survey; MAP, mean arterial blood pressure; HbA1c, glycosylated hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase.

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limited. Therefore, this cohort study utilizes the National Health and Nutrition Examination Survey (NHANES) database to retrospectively analyze the association between the GGT/HDL-C ratio and the risk of all-cause and cardiovascular disease (CVD) death among U.S. adults.

2. Subjects and methods

2.1. Study population

NHANES utilizes a sophisticated, stratified probabilistic method (Zipf et al., 2013) for participant selection, ensuring the data collected is representative of the entire U.S. population. The survey involves comprehensive household interviews to gather demographic as well as medical history details. Additionally, participants undergo physical exams and provide blood specimens at the Mobile Examination Center (MEC). Serum samples are then analyzed by the Division of Laboratory Sciences at the National Center for Environmental Health, Centers for Disease Control and Prevention. In-depth technical details on sample design can be found in the NHANES Survey Methods and Analytic Guidelines (pages 20–21). The original study protocol, formally approved by the Ethics Review Committee (protocol #2005–06; #2011–17), is accessible on the NHANES Ethics Review Committee website (https://www.cdc.gov/nchs/nhanes/irba98.htm). Ethics approval for the NHANES survey was obtained from the ethics review board, and all participants provided informed consent. Valid follow-up data collected by NHANES from 1999 to 2018 across 10 survey cycles were used for the research. Participants under 18 years old, those lacking follow-up death data, or individuals without GGT or HDL-C measurements were excluded. Fig. 1 illustrates the selection process for a total of 50,462 participants.

2.2. Data collection and definitions

In this observational cohort study, we gathered baseline data encompassing demographic information, anthropometric measurements, biomarker data, comorbidities, and medication details, adhering to the study protocol. Race/ethnicity was divided into non-Hispanic white, non-Hispanic black, Mexican American, or other race. For drinking status, participants were classified as alcohol drinkers if they had consumed at least 12 alcoholic beverages per year throughout their lifetime (Ruan et al., 2022). Smoking status was divided into never, former, and current categories, using established definitions (Kim et al., 2019). Hypertension diagnosis was established based on antihypertensive medication usage, self-reported hypertension, or blood pressure measurements equal to or greater than 140 mmHg (systolic) and 90 mmHg (diastolic). Diabetes diagnosis followed the criteria outlined by the American Diabetes Association, identifying individuals through self-report, insulin or oral hypoglycemic drug use, fasting blood glucose levels of 126 mg/dl or higher, or glycosylated hemoglobin (HbA1c) levels of 6.5 % or greater. CVD diagnosis was confirmed via self-reported interviews using a standardized questionnaire on medical history. By asking participants if they had ever been diagnosed with conditions such as congestive heart failure, coronary heart disease, angina pectoris, myocardial infarction, or stroke by a healthcare professional, researchers were able to confirm the presence of CVD.

The NHANES dataset from 1999 to 2018 was connected to the National Death Index (NDI) database to procure mortality details, maintaining follow-up until December 31, 2019. A probabilistic matching technique is utilized by the National Center for Health Statistics to establish total mortality rates by examining NHANES respondents against NDI death records.

2.3. Statistical analysis

Normally distributed continuous variables were described using the mean and standard deviation, whereas skewed variables were expressed as the median and interquartile range (25th–75th percentile). Categorical variables were described as percentages. Continuous and categorical data were compared using the *t*-test and χ^2 test as appropriate. The Mann-Whitney *U* test was used to compare continuous variables that exhibited skewed distributions. Since the GGT/HDL-C ratio data were significantly skewed, a natural logarithm transformation (ln) was applied before statistical analysis. The lnGGT/HDL-C was then divided into three tertile groups: Tertile 1 (< 1.9), Tertile 2 (1.9–2.6), and Tertile 3 (≥ 2.6), with Tertile 1 as the reference group.

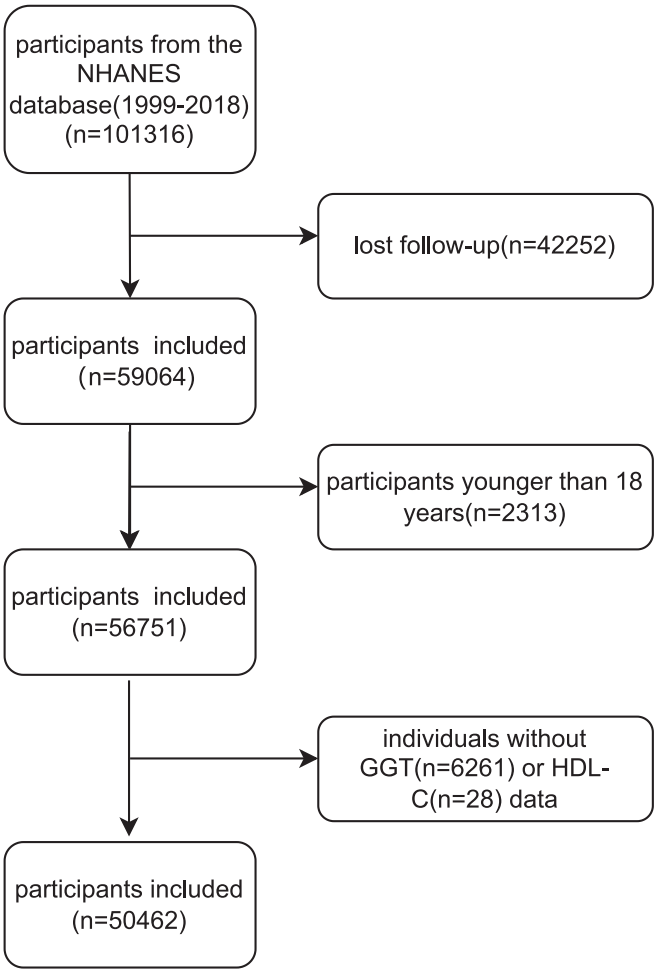

Fig. 1. Title: Participant selection flowchart: The National Health and Nutrition Examination Survey (1999–2018) for U.S. adults. Footnotes: NHANES: National Health and Nutrition Examination Survey; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol.

Restricted cubic splines were employed to analyze the nonlinear relationship between lnGGT/HDL-C and mortality risk. Following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, this study conducted a multivariable regression analysis that developed three models to adjust for confounders in a stepwise manner. This approach facilitates a detailed examination of the relationship between lnGGT/HDL-C and mortality risk. The crude model considered lnGGT/HDL-C alone, while Adjusted Model 1 incorporated gender, age, and race/ethnicity. Adjusted Model 2 further adjusted for drinking status, smoking status, body mass index (BMI), mean arterial blood pressure (MAP), alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol, fasting triglycerides, as well as comorbidities (hypertension, diabetes, and CVD). This study utilized multiple imputation to address missing values in covariates. Separate analyses were conducted using data before and after imputation to assess the stability of the results. Deaths occurring within a 2-year

follow-up period were excluded to minimize bias.

Person-months were defined as the period from the MEC examination date to the occurrence of death or the follow-up deadline (December 31, 2019), whichever came first. HR adjusted for multiple variables and the corresponding 95 % CI was calculated. An analysis was conducted in strata to explore the correlation between lnGGT/HDL-C and mortality across various demographic and health variables.

Sample size was determined based on available data without prior statistical power calculation. Statistical analysis was carried out utilizing R software (version 4.2.1) and the R survey package (version 4.1–1), as well as Free Statistics software (version 1.7.1). Two-sided *p*-values lower than 0.05 were deemed statistically significant.

3. Results

3.1. Baseline characteristics of participants stratified by GGT/HDL-C ratio

Table 1 presents the demographic characteristics of the 50,462 subjects, with 48.4 % being male and a mean age of 48.7 ± 18.7 years. Those with elevated GGT/HDL-C ratios were predominantly male, non-Hispanic white, had lower education levels, engaged in smoking and alcohol consumption, and had a higher incidence of comorbidities such as hypertension, diabetes, and CVD. Participants with higher GGT/HDL-C levels showed a correlation with elevated BMI, MAP, as well as various blood indicators including ALT, alkaline phosphatase, total cholesterol, fasting triglycerides, uric acid, and fasting blood glucose. Additionally, this group exhibited lower levels of vitamin D. The study found that the all-cause mortality rates in the three groups with low to high GGT/HDL-C ratios were 8.4 %, 14.3 %, and 22.2 %, respectively ($p < 0.01$). Similarly, the cardiovascular disease mortality rates were 0.9 %, 3.4 %, and 7.3 %, respectively ($p < 0.01$).

3.2. Survival analysis curves for all-cause mortality and CVD mortality based on the GGT/HDL-C ratio

Throughout the observational period totaling 5,773,035 person-months (with a median duration of 114.4 months), 7573 incidents of all-cause death and 1956 cases of CVD death were recorded. Mortality rates for various GGT/HDL-C groups are depicted in Fig. 2. Significant differences were found in both all-cause (Fig. 2A) and CVD (Fig. 2B) mortality among the groups analyzed ($p < 0.01$ for the log-rank test). It is evident that individuals in the highest GGT/HDL-C tertile exhibit the lowest survival rates.

Associations of the GGT/HDL-C ratio with all-cause and CVD mortality.

Table 2 illustrates the correlation between lnGGT/HDL-C and both all-cause and CVD mortality. The unadjusted and fully adjusted multivariable HRs with 95 % CIs for all-cause mortality among participants in Tertile 3 compared to those in the Tertile 1 group were 1.62 (95 % CI = 1.52, 1.72) and 1.29 (95 % CI = 1.10, 1.51), respectively. For CVD mortality, the unadjusted model showed a risk of 1.81 (95 % CI = 1.60, 2.05) for the Tertile 3 group compared to the Tertile 1 group, while the fully adjusted model indicated a risk of 1.25 (95 % CI = 1.14, 1.37). Examining the lnGGT/HDL-C ratio as a continuous variable revealed that for each unit increase, there was a 23 % higher risk of all-cause death [HR (95 % CI), 1.23 (1.19, 1.28)], along with a 47 % increased risk of CVD death [HR (95 % CI), 1.47 (1.39, 1.55)].

In the fully adjusted Model 2, the relationship between the GGT/HDL-C level and the risk of death from all causes exhibited a J-shaped curve in the restricted cubic spline analysis (nonlinear, $p < 0.01$), as illustrated in Fig. 3A. Two-stage linear regression analysis showed an insignificant association between all-cause death and lnGGT/HDL-C when lnGGT/HDL-C was below 2.3 (GGT/HDL-C equaled 10.0). However, beyond this threshold, each unit increase led to a 36.3 % increase in mortality risk (95 % CI = 1.26, 1.47, see Table 3). These disparities

Table 1
Baseline characteristics of U.S. participants from the National Health and Nutrition Examination Survey (1999–2018) categorized by the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio (n = 50,462).

Variables	Total (n = 50,462)	Tertile 1 (n = 16,776) lnGGT/HDL-C < 1.9	Tertile 2 (n = 16,839) 1.9 ≤ lnGGT/HDL-C < 2.6	Tertile 3 (n = 16,847) lnGGT/HDL-C ≥ 2.6	*P*
Gender, n(%)					< 0.01
Male	24,400 (48.4)	4930 (29.4)	8433 (50.1)	11,037 (65.5)	
Female	26,062 (51.6)	11,846 (70.6)	8406 (49.9)	5810 (34.5)	
Age, years	48.7 ± 18.7	46.1 ± 19.8	49.5 ± 18.8	50.4 ± 17.2	< 0.01
Race/Ethnicity, n (%)					< 0.01
Non-Hispanic white	9062 (18.0)	2372 (14.1)	2978 (17.7)	3712 (22)	
Non-Hispanic black	4213 (8.3)	1522 (9.1)	1473 (8.7)	1218 (7.2)	
Hispanic	22,283 (44.2)	7535 (44.9)	7393 (43.9)	7355 (43.7)	
Others	14,904 (29.5)	5347 (31.9)	4995 (29.7)	4562 (27.1)	
Marital status, n (%)					< 0.01
Partnered	29,328 (60.6)	9100 (58)	9825 (60.4)	10,403 (63.2)	
Others	19,093 (39.4)	6593 (42)	6441 (39.6)	6059 (36.8)	
Education, n(%)					< 0.01
Less than high school	5940 (12.2)	1393 (8.9)	1989 (12.1)	2558 (15.3)	
High school or equivalent	18,544 (38.0)	5248 (33.4)	6286 (38.4)	7010 (41.9)	
College or above	24,342 (49.9)	9083 (57.8)	8108 (49.5)	7151 (42.8)	
Drinking status, n (%)					< 0.01
No	9653 (19.8)	4698 (28.8)	3277 (20.2)	1678 (10.4)	
Yes	39,098 (80.2)	11,634 (71.2)	12,981 (79.8)	14,483 (89.6)	
Smoking status, n (%)					< 0.01
Never	28,042 (55.6)	10,923 (65.1)	9305 (55.3)	7814 (46.4)	
Former	13,405 (26.6)	3819 (22.8)	4612 (27.4)	4974 (29.5)	
Current	9015 (17.9)	2034 (12.1)	2922 (17.4)	4059 (24.1)	
BMI, kg/m^2	28.9 ± 6.8	27.0 ± 6.4	29.2 ± 6.9	30.4 ± 6.6	< 0.01
SBP, mmHg	124.8 ± 19.7	120.6 ± 19.3	125.4 ± 19.7	128.4 ± 19.3	< 0.01
MAP, mmHg	88.3 ± 12.6	85.3 ± 12.1	88.6 ± 12.4	91.1 ± 12.7	< 0.01
Laboratory parameters					
ALT, U/L	20.0 (16.0, 28.0)	17.0 (14.0, 21.0)	20.0 (16.0, 26.0)	27.0 (20.0, 38.0)	< 0.01
AST, U/L	22.0 (19.0, 27.0)	21.0 (18.0, 24.0)	22.0 (19.0, 26.0)	25.0 (21.0, 32.0)	< 0.01
LDL-C, mg/dl	114.7 ± 36.0	109.3 ± 34.7	115.3 ± 35.1	119.9 ± 37.7	< 0.01
HbA1c, (%)	5.7 ± 1.1	5.5 ± 0.8	5.7 ± 1.0	5.9 ± 1.3	< 0.01
Total cholesterol, mg/dl	195.1 ± 42.9	191.0 ± 41.3	193.0 ± 41.6	201.3 ± 45.0	< 0.01

(*continued on next page*)

Table 1 (*continued*)

Variables	Total (n = 50,462)	Tertile 1 (*n* = 16,776) lnGGT/HDL-C < 1.9	Tertile 2 (n = 16,839) 1.9 ≤ lnGGT/HDL-C < 2.6	Tertile 3 (n = 16,847) lnGGT/HDL-C ≥ 2.6	*P*
Fasting triglycerides, mg/dl	118.0 (79.0, 181.0)	91.0 (63.0, 133.0)	125.0 (85.0, 185.0)	160.0 (108.0, 244.0)	< 0.01
Fasting Glucose, mg/dl	107.9 ± 36.3	100.2 ± 23.8	108.1 ± 35.8	115.8 ± 44.9	< 0.01
Uric acid, umol/l	322.0 ± 87.0	288.4 ± 75.8	324.2 ± 83.6	353.1 ± 88.8	< 0.01
25(OH)vitamin D, nmol/l	59.8 (43.4, 77.4)	64.5 (46.8, 83.7)	59.4 (43.4, 76.2)	55.7 (40.6, 70.6)	< 0.01
eGFR, ml/min	95.9 ± 23.7	98.6 ± 24.1	94.8 ± 23.7	94.5 ± 23.1	< 0.01
Comorbidities					
Hypertension, n (%)					< 0.01
No	29,695 (58.8)	11,399 (67.9)	9634 (57.2)	8662 (51.4)	
Yes	20,767 (41.2)	5377 (32.1)	7205 (42.8)	8185 (48.6)	
Diabetes, n(%)					< 0.01
No	42,418 (84.1)	15,128 (90.2)	14,087 (83.7)	13,203 (78.4)	
Yes	8044 (15.9)	1648 (9.8)	2752 (16.3)	3644 (21.6)	
CVD, n (%)					< 0.01
No	44,892 (89.0)	15,484 (92.3)	14,923 (88.6)	14,485 (86)	
Yes	5570 (11.0)	1292 (7.7)	1916 (11.4)	2362 (14)	
All-cause death, n (%)					< 0.01
No	42,889 (85.0)	15,364 (91.6)	14,426 (85.7)	13,099 (77.8)	
Yes	7573 (15.0)	1412 (8.4)	2413 (14.3)	3748 (22.2)	
Cardiovascular death, n (%)					< 0.01
No	48,506 (96.1)	16,622 (99.1)	16,272 (96.6)	15,612 (92.7)	
Yes	1956 (3.9)	154 (0.9)	567 (3.4)	1235 (7.3)	

Notes: Data were expressed as mean ± SD, median (first quartile, third quartile), or n (%). Continuous and categorical data were compared using the *t*-test and χ^2 test as appropriate. The Mann-Whitney *U* test was used to compare continuous variables that exhibited skewed distributions. Two-sided *P*-values lower than 0.05 were deemed to be statistically significant.
For drinking status, participants were classified as alcohol drinkers if they had consumed at least 12 alcoholic beverages per year throughout their lifetime.
Abbreviations: GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; MAP, mean arterial pressure; ALT, alanine transaminase; AST, aspartate aminotransferase; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate.

were statistically significant based on the log-likelihood ratio test ($p < 0.01$). Similarly, a J-shaped curve was observed in the correlation between lnGGT/HDL-C and CVD mortality, as depicted in Fig. 3B. There was a notable increase in the risk of CVD mortality when lnGGT/HDL-C reached 2.5 (GGT/HDL-C was 12.2), with a 67.1 % increase (95 % CI = 1.42, 1.97) for every unit rise in the lnGGT/HDL-C level beyond this point (Table S1).

3.3. Subgroup analyses and sensitivity analyses

Multivariable regression analyses stratified by age, gender, BMI, smoking habits, hypertension, diabetes, as well as CVD were conducted to investigate whether participants' characteristics and comorbidities could account for the link between GGT/HDL-C levels and outcomes. The findings were consistent across subgroups for both overall mortality and CVD mortality (refer to Fig. 4). A stronger association was shown between GGT/HDL-C level and death among individuals younger than 65 (HR: 1.35 and 1.21 for all-cause death, and HR: 1.45 and 1.27 for CVD death, $p < 0.01$). In never smokers and current smokers, the association between GGT/HDL-C level and overall mortality was more pronounced than in former smokers (HR: 1.31 and 1.30 vs. 1.24, $p < 0.01$). Interestingly, this association did not have a significant effect on CVD mortality.

In the sensitivity analyses, the population distribution of missing variables remained consistent before and after imputation (Table S2). Prior to conducting multiple imputation, we analyzed the data and found that three models produced results comparable to those of the imputed data (Table S3). Furthermore, the exclusion of deaths occurring within the first 24 months of monitoring did not significantly alter the relationship between lnGGT/HDL-C and both overall as well as CVD mortality (see Table S4).

4. Discussion

This retrospective cohort study, based on a large population, observed a J-shaped relationship between the GGT/HDL-C level and the risk of death from both all-cause and CVD. Thresholds were identified at 10.0 for all-cause death and 12.2 for CVD death, indicating a significant increase in mortality correlation beyond these points. This finding was supported by a statistically significant *p*-value for nonlinearity (< 0.01). Subgroup analyses by gender, drinking status, smoking habits, and comorbidities (hypertension, diabetes, and CVD) did not reveal any significant interactions among the subgroups. The relationship between the GGT/HDL-C ratio and mortality risk is influenced by age, as an increase in the ratio is linked to a higher risk of all-cause and CVD death among individuals younger than 65 years of age.

The association between GGT concentrations and the risk of death has been validated by numerous studies. For instance, the Framingham Study established a clear association between log-GGT and the likelihood of developing new-onset CVD and mortality from any cause. With each incremental rise in log-GGT by one standard deviation, the risk of new-onset CVD increased by 15 %, and the likelihood of all-cause mortality rose by 26 % (Lee et al., 2007). Similarly, a cohort study involving diabetic patients from China found a significant correlation between GGT levels and overall mortality, CVD mortality, and cancer mortality. Those with GGT levels in the top quintile had a HR of 1.63 (95 % CI = 1.44, 1.84) for all-cause death compared to individuals in the lowest quintile (Guan et al., 2023a).

There is also a strong link between HDL-C and the risk of death. A prospective cohort study conducted among the South Korean population over a median monitoring period of 8.4 years showed a U-shaped connection between HDL-C levels and the risk of death, which was particularly pronounced among individuals younger than 65 years old (Yi et al., 2021). Furthermore, a recent large-scale cohort study with 3,397,547 individuals aged 35 to 75 demonstrated that HDL-C levels below 30 mg/dl or above 90 mg/dl were associated with significantly higher risks of death from any cause, CVD, and cancer compared to the intermediate group (Lu et al., 2023). Additionally, increased concentrations of HDL-C have been correlated with higher mortality rates from conditions such as alcoholic liver disease, oropharyngeal cancer, and chronic liver disease, while lower concentrations are more strongly linked to higher death rates in ischemic heart disease and other CVD (Mørland et al., 2023).

Limited research exists on the association between GGT/HDL-C

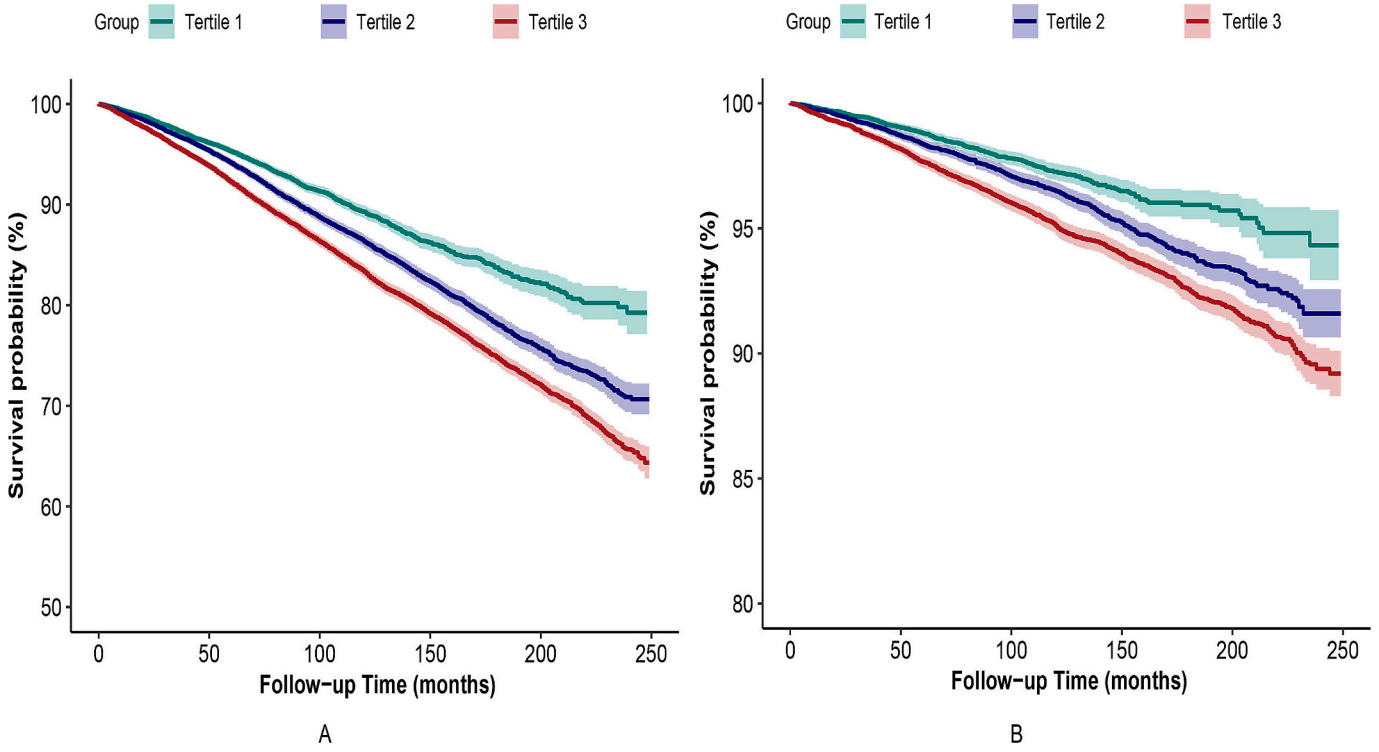

Fig. 2. Title: Kaplan-Meier survival analysis curves for all-cause and cardiovascular mortality by the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio among U.S. adults from the National Health and Nutrition Examination Survey (1999–2018). Footnotes: A, all-cause mortality; B, cardiovascular mortality. Tertile 1: lnGGT/HDL-C < 1.9; Tertile 2: 1.9 ≤ lnGGT/HDL-C < 2.6; Tertile 3: lnGGT/HDL-C ≥ 2.6. Abbreviations: GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol.

Table 2
Multivariate Cox regression analysis of the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio with all-cause death and cardiovascular death among U.S. adults from the National Health and Nutrition Examination Survey (1999–2018).

Variable	n	Crude Model		Model 1		Model 2	
		HR	95 % CI	HR	95 % CI	HR	95 % CI
All-cause death							
lnGGT/ HDL-C	50,462	1.28	1.24, 1.31	1.28	1.24, 1.32	1.23	1.19, 1.28
Subgroups							
Tertile 1	16,776	Reference					
Tertile 2	16,839	1.32	1.24, 1.42	1.08	1.01, 1.16	1.07	0.96, 1.19
Tertile 3	16,847	1.62	1.52, 1.72	1.34	1.26, 1.43	1.29	1.10, 1.51
Cardiovascular death							
lnGGT/ HDL-C	50,462	1.31	1.25, 1.38	1.42	1.35, 1.5	1.47	1.39, 1.55
Subgroups							
Tertile 1	16,776	Reference					
Tertile 2	16,839	1.39	1.22, 1.59	1.24	1.13, 1.37	1.08	0.98, 1.18
Tertile 3	16,847	1.81	1.60, 2.05	1.61	1.47, 1.77	1.25	1.14, 1.37

Crude Model: not adjusted for any variables.
Model 1: adjusted for gender, age, and race/ethnicity.
Model 2: adjusted for gender, age, race/ethnicity, drinking status, smoking status, BMI, MAP, ALT, AST, total cholesterol, fasting triglycerides, hypertension, diabetes, and cardiovascular disease.
Tertile 1: lnGGT/HDL-C < 1.9; Tertile 2: 1.9 ≤ lnGGT/HDL-C < 2.6; Tertile 3: lnGGT/HDL-C ≥ 2.6.
Abbreviations: GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; MAP, mean arterial pressure; ALT, alanine transaminase; AST, aspartate transaminase.

levels and mortality risk. Our study integrated GGT and HDL-C as predictive indicators, resulting in enhanced predictive accuracy. Despite controlling for all variables, the independent association between GGT/HDL-C levels and CVD mortality, as well as overall mortality, persisted. Subgroup analyses revealed that, apart from age, the link between the GGT/HDL-C level and mortality remained consistent regardless of gender, BMI, smoking status, or comorbidities such as hypertension, diabetes, and CVD.

Previous research consistently demonstrated that GGT/HDL-C was associated with the development of new-onset diabetes, metabolic syndrome, and CVD (Feng et al., 2020a; Zhao et al., 2023; Xie et al., 2022b; Jung et al., 2023), all of which are linked to an unfavorable prognosis. Our study's findings further support this relationship. For instance, a study conducted in South Korea (Jung et al., 2023) revealed gender disparities in the correlation between GGT/HDL-C and new CVD, with a significant association observed among females but not males. Conversely, our research demonstrated that males faced an increased risk of CVD fatality, with a more robust link compared to females [(HR = 1.39, 95 % CI = 1.25, 1.56) vs (HR = 1.27, 95 % CI = 1.10, 1.46)]. The reasons for this inconsistency are not fully understood and may stem from variations among study populations.

In a study involving adult diabetes patients in China, it was found that the influence of GGT on overall mortality varies depending on BMI and abnormal blood lipid levels. Notably, a more significant correlation was noted among those with a BMI below 25 or individuals with optimal blood lipid levels (Guan et al., 2023b). Our study delved into the combined impact of GGT and HDL-C, a blood lipid component, yielding more significant results. Subgroup analyses showed no significant interactions between BMI and GGT/HDL-C ratio and total or CVD mortality (p -values for interaction were 0.67 and 0.93, respectively). The lack of interaction in the BMI-stratified analysis may be attributed to the correlation between participants' dyslipidemia and their BMI levels. Individuals with hyperlipidemia often exhibit higher BMIs, and

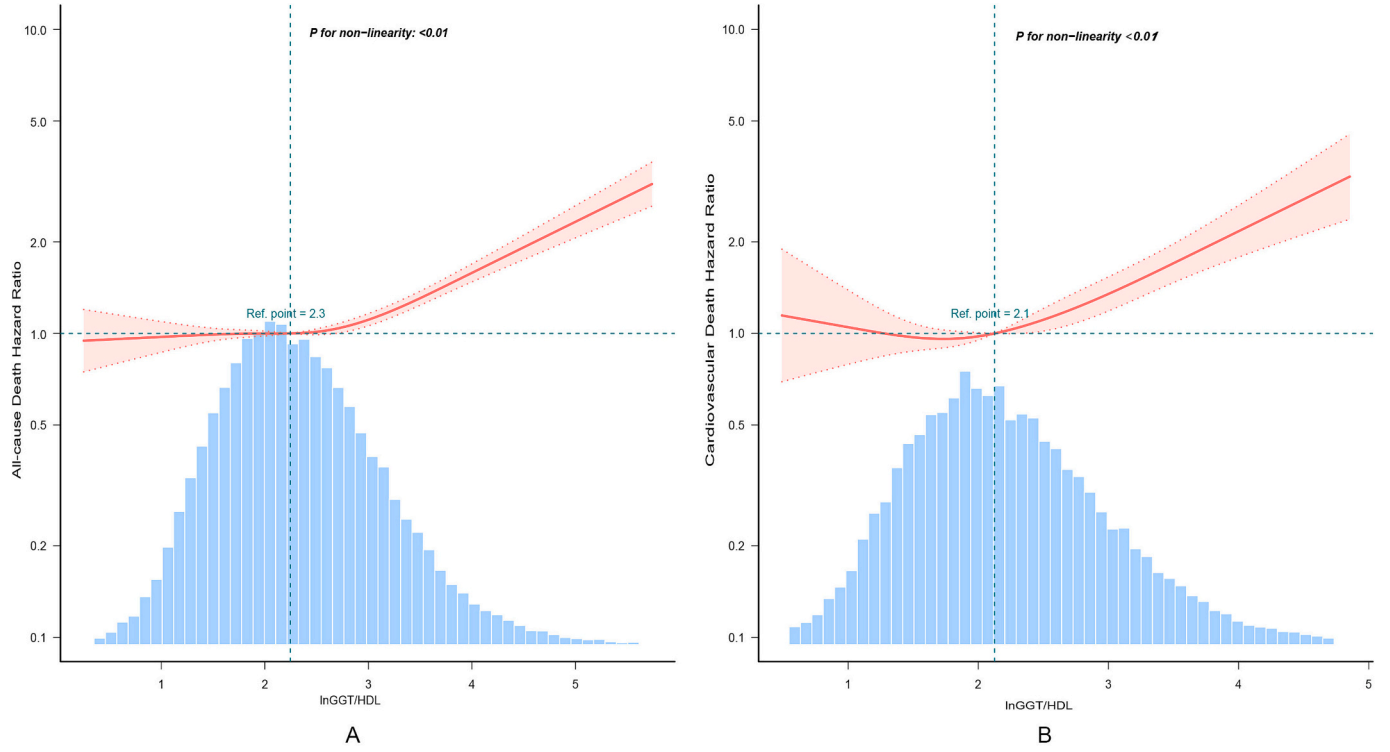

Fig. 3. Title: Association between the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio and all-cause and cardiovascular mortality among U. S. adults from the National Health and Nutrition Examination Survey (1999–2018). Footnotes: A, all-cause mortality; B, cardiovascular mortality. Each hazard ratio was computed with a GGT/HDL-C ratio of A 2.3 and B 2.1 as the reference. Adjusted for gender, age, race/ethnicity, drinking status, smoking status, BMI, MAP, ALT, AST, total cholesterol, fasting triglycerides, hypertension, diabetes, and cardiovascular disease. Abbreviations: GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; MAP, mean arterial pressure; ALT, alanine transaminase; AST, aspartate transaminase; HR, hazard ratio.

incorporating blood lipid levels into the analysis may reduce the impact of BMI.

The results of our study indicate that the relationship between GGT/HDL-C ratios and death, whether from CVD or all causes, is stronger among participants under the age of 65 compared to older individuals. Previous studies have emphasized how age affects the connection between HDL-C and mortality (Yi et al., 2021; Yi et al., 2022). For instance, one study found that a 39 mg/dl increase in HDL-C levels (below 60 mg/dl) was associated with a 1.47 risk of CVD mortality (95 % CI = 1.23, 1.76) among individuals aged 18–44 years and a 1.03 risk (95 % CI = 0.97, 1.08) in those aged 65–99 years (Yi et al., 2022). These studies suggest that maintaining optimal GGT/HDL-C ratios or HDL-C levels is more crucial for enhancing prognosis in individuals under 65 years of age compared to older adults.

This study marks the inaugural comprehensive exploration into the association of GGT/HDL-C levels with mortality from all causes and CVD, leveraging data from NHANES (1999–2018) and NDI. A thorough examination of potential confounders and biases, alongside a population-based design and substantial sample sizes, enhances the credibility of our findings.

However, this study has limitations. The observational cohort design prevents definitive causal inferences. Despite meticulous adjustment for foreseeable influences and subgroup analyses on various factors, residual confounding effects may persist. Moreover, the focus solely on the GGT/HDL-C ratio at baseline neglects potential associations with changes during follow-up, warranting further investigation. Additionally, the exclusively U.S.-based cohort underscores the necessity for studies in diverse populations to validate our findings. Nevertheless, robust data from well-designed trials with extensive nationwide samples and prolonged monitoring periods enhance the validity of our results.

5. Conclusion

Our findings provide evidence that the GGT/HDL-C ratio can predict both all-cause and cardiovascular mortality within the broader U.S. adult population, particularly demonstrating stronger correlations in participants under 65 years of age. These findings advocate for the utilization of this ratio as a potential prognostic indicator for adverse health outcomes, especially in younger individuals. Further research is imperative to validate these results, elucidate underlying mechanisms, and ascertain the clinical significance of GGT/HDL-C levels in predicting overall and CVD mortality.

Ethics approval and consent to participate

The survey conducted by the National Center for Health Statistics (NCHS) obtained approval from the NCHS Institutional Review Board. Before the commencement of NHANES health examinations, all eligible participants provided informed consent.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Shujuan Qiu: Writing – review & editing, Writing – original draft, Software, Resources, Data curation, Conceptualization. **Chunlei Li:**

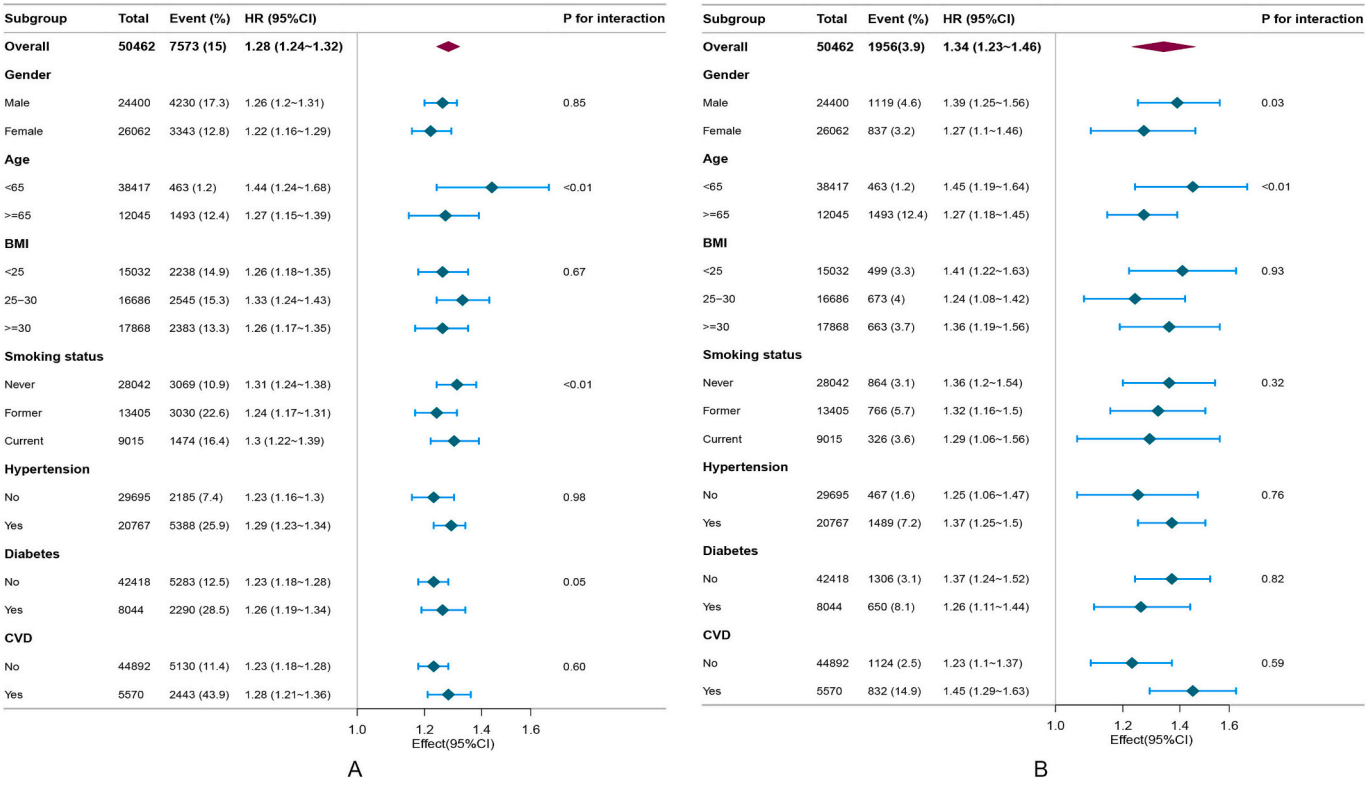

Fig. 4. Title: Subgroup analysis of the association between the gamma-glutamyltransferase to high-density lipoprotein cholesterol ratio and all-cause and cardiovascular mortality among U.S. adults from the National Health and Nutrition Examination Survey (1999–2018). Footnotes: A, all-cause mortality; B, cardiovascular mortality. Adjusted for gender, age, race/ethnicity, drinking status, smoking status, BMI, MAP, ALT, AST, total cholesterol, fasting triglycerides, hypertension, diabetes, and cardiovascular disease, except for the subgroup factors themselves. Abbreviations: BMI, body mass index; MAP, mean arterial pressure; ALT, alanine transaminase; AST, aspartate transaminase.

Software, Project administration, Investigation, Data curation. **Zhentao Guo:** Writing – review & editing, Writing – original draft, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102958.

Data availability

The dataset is accessible on the NHANES website: https://www.cdc.gov/nchs/nhanes/index.htm.

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