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Mental Health

Gamma-Glutamyl Transferase to High-Density Lipoprotein Cholesterol Ratio as a Marker of Cognitive Dysfunction in Older Adults: A Cross-Sectional Study from NHANES 2011–2014

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Abstract

Background: The gamma-glutamyl transferase to high-density lipoprotein cholesterol (GGT/HDL-C) ratio has been reported to be associated with various metabolic diseases, but its relationship with cognitive dysfunction remains limited. This study aimed to investigate the relationship between the GGT/HDL-C ratio and cognitive dysfunction in older adults.
Methods and Results: This cross-sectional study included 2,769 participants and used data from the National Health and Nutrition Examination Survey (NHANES) database (2011~2014). Natural logarithmic (ln) transformation was performed on GGT/HDL-C before analysis. After adjusting for various covariates, logistic regression models showed that the association between ln(GGT/HDL-C) and cognitive dysfunction assessed by total-CF and AFT remained significant [OR (95% CI): 1.374 (1.126~1.676), 1.220 (1.030~1.444)], whereas no significant correlation was found with CERAD W-L or DSST (P>0.05). Then, restricted cubic spline (RCS) regression and threshold effect analyses were conducted, and we observed nonlinear associations between ln(GGT/HDL-C) and cognitive dysfunction measured by total-CF, CERAD W-L and DSST (all $P_{nonlinear}$<0.05). Subgroup analyses were performed based on multiple variables, including age, gender, BMI, race, education level, DM, sleep problems, hypertension, drinking, and smoking status. The results suggested that the association between ln(GGT/HDL-C) and cognitive dysfunction was comparable across most subgroups.
Conclusion: Our study suggested that higher levels of ln(GGT/HDL-C) might be associated with an increased risk of cognitive dysfunction in older adults.**(International Journal of Biomedicine. 2026;16(1):17-25.)**

Keywords: cognitive dysfunction • gamma-glutamyl transferase • high-density lipoprotein cholesterol • cross-sectional study

Abbreviations

AD, Alzheimer's disease; **AFT**, Animal Fluency Test; **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **BMI**, body mass index; **CERAD W-L**, Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest; **DSST**, Digit Symbol Substitution Test; **DM**, diabetes mellitus; **DRT**, delayed recall test; **GGT**, gamma-glutamyl transferase; **HDL-C**, high-density lipoprotein cholesterol; **IRT**, immediate recall test; **LDH**, lactate dehydrogenase; **NHANES**, National Health and Nutrition Examination Survey; **RCS**, restricted cubic spline; **total-CF**, total cognitive function; **TG**, triglyceride; **TC**, total cholesterol.

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Introduction

Cognitive dysfunction, particularly dementia, has become a major global public health concern due to increased life expectancy and population aging. Worldwide, nearly 57.4 million people are living with dementia. Alzheimer's Disease International (ADI) predicts that this number will increase to 152.8 million in 2050.[1] This increase may occur unless interventions are taken to prevent the occurrence and progression of Alzheimer's disease (AD) or other dementia-related disorders.[2] Despite extensive research efforts over recent decades, effective clinical treatments for dementia remain scarce. Hence, identifying modifiable factors that may lead to cognitive dysfunction is crucial for developing effective preventive strategies.

The pathogenesis of cognitive dysfunction is not fully understood. However, multiple investigations have demonstrated that oxidative stress and inflammation are crucial factors leading to cognitive dysfunction.[3,4] Glutathione is an important antioxidant in cells, and gamma-glutamyl transferase (GGT) is essential for glutathione metabolism. Serum GGT mainly originates from the liver and has been used clinically as an indicator of potential liver or biliary tract diseases.[5,6] Numerous studies have investigated the relationship between GGT levels and dementia. GGT levels, along with GGT variability, have been shown to be positively correlated with cognitive impairment.[7-9] Furthermore, elevated serum GGT levels are significantly linked to reduced total brain and gray matter volumes, as well as diminished cerebral blood flow and perfusion.[10] High-density lipoprotein cholesterol (HDL-C) is considered a beneficial lipoprotein due to its various protective roles, such as promoting atheroprotection, supporting endothelial health, regulating the immune system, inhibiting oxidative stress, reducing inflammation, and providing antithrombotic effects.[11] These functions are essential for preventing cognitive decline. Although the relationship between HDL-C and cognitive dysfunction is inconsistent, various studies have suggested that increased HDL-C levels are correlated with a decreased risk of dementia.[12-14]

Recent studies have highlighted the GGT/HDL-C ratio as a promising new biomarker. Evidence has indicated its utility in predicting nonalcoholic fatty liver disease (NAFLD), liver fibrosis, cardiovascular disease and diabetes mellitus.[15-17] Nonetheless, exploration of its correlation with cognitive function remains limited. Consequently, we employed the NHANES database to retrospectively examine the relationship between the GGT/HDL-C ratio and the risk of cognitive dysfunction.

Materials and Methods

Study Design and Participants

This cross-sectional study uses data from the NHANES database (https://www.cdc.gov/nchs/nhanes). It consists of five main parts: demographic data, dietary data, examination data, laboratory data, and questionnaire data, all updated every two years. Our analysis focused on the 2011-2012 and 2013-2014 surveys, as both cycles evaluated GGT, HDL-C and cognitive function. Approval of the NHANES procedures and protocols was granted by the NCHS Research Ethics Review Committee, and informed consent was secured from all participants.

In this study, we investigated 3,472 subjects from the NHANES 2011-2014 dataset. After excluding individuals with incomplete cognitive function data, missing GGT or HDL-C data, 2,769 participants were ultimately included. The screening process is illustrated in Figure 1.
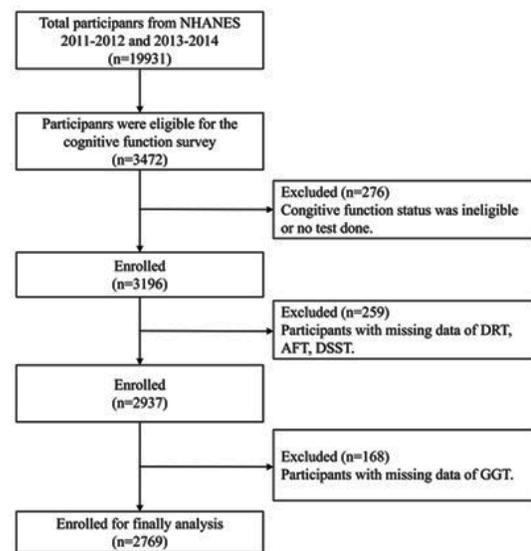

Figure 1. *Flow chart of the participants' selection from the National Health and Nutrition Examination Survey (NHANES) 2011-2014.*

GGT and HDL-C Measurement

The activity of GGT was measured via an enzymatic rate method with a Beckman Coulter UniCel DxC800 instrument. HDL-C levels were determined via polyethylene glycol-coupled cholesteryl esterase with a Roche modular P or Roche Cobas 6000 chemistry analyzer. Additional methodological details of the measurement can be found in the NHANES database.

Identification of Cognitive Dysfunction

This study assessed cognitive dysfunction through three tests: the Consortium to Establish a Registry for Alzheimer's Disease Word Learning subtest (CERAD W-L), the Animal Fluency Test (AFT), and the Digit Symbol Substitution Test (DSST). The CERAD W-L specifically measures both immediate and delayed learning capabilities concerning new verbal information. This assessment comprises three immediate recall tests (IRTs) and a delayed recall test (DRT). The IRT scores were processed as follows: for participants who completed two or three trials, the IRT score was determined by averaging the two highest scores, and for those who took only one test, that score was the IRT score. The sum of the IRT and DRT score was CERAD W-L score. The AFT evaluates verbal fluency, an aspect of executive function, while also assessing semantic memory and processing speed. The DSST, a subset of the Wechsler Adult Intelligence Scale III, assesses

processing speed, sustained attention, and working memory. The total cognitive function (total-CF) score is the aggregate of the CERAD W-L, AFT and DSST scores. As previously reported, the participants were divided into three age groups (60~69, 70~79, and ≥80 years). For each group, the lowest quartile of the cognitive function score (Supplementary Table 1) was set as the threshold for defining cognitive dysfunction.[18] Participants who scored below the cutoff values were classified as having cognitive dysfunction, whereas those who scored above the cutoff values were categorized as having normal cognitive performance.

Covariates

This analysis included a series of covariates. The demographic data included age, gender, BMI, race (divided into Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races), education level (below high school, high school and higher than high school), smoking status and drinking status. Medical conditions included hypertension, diabetes mellitus (DM) and sleep problems. The examination results included alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), triglyceride (TG) and total cholesterol (TC) levels. Smoking status was divided into two groups (yes or not) on the basis of self-reports to the question "Smoked at least 100 cigarettes in life." Participants were defined as alcohol drinkers if they had ever had at least 12 alcohol drinks lifetime. A history of hypertension and sleep problems was defined as self-reported or physician diagnosis. Diabetes mellitus was defined by any of the following criteria: a medical diagnosis of diabetes, HbA1c(%) ≥6.5, fasting glucose level ≥7.0 mmol/L, or 2h OGTT blood glucose ≥11.1 mmol/L.

Statistical analysis

Data processing and analysis were performed using SPSS software (version 21.0), R (version 4.3.3), and Zstats 1.0 (www.zstats.net). Normally distributed data were reported as mean ± standard deviation (SD), and the differences between groups were evaluated by One-Way ANOVA. Nonnormally distributed variables were presented as median (M) and interquartile range (IQR), and the Kruskal-Wallis test was used to detect the differences among groups. Categorical variables were expressed as case numbers (n) and frequencies (percentages), and χ^2-test was used for inter-group comparison. Because the GGT/HDL-C ratio was significantly skewed, a natural logarithm transformation (ln) was performed before analysis. $P<0.05$ was considered statistically significant.

Logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association between ln(GGT/HDL-C) and cognitive dysfunction. Model 1 was unadjusted. Model 2 was adjusted for age, gender, BMI, race, education level, DM, hypertension, sleep problems, ALT, AST, LDH, TG, TC, smoking and drinking status. Subsequently, ln(GGT/HDL-C) was processed from a continuous variable to a four-categorical variable to test for trends.

Furthermore, we employed restricted cubic spline (RCS) regression models to investigate the potential nonlinear relationship between ln(GGT/HDL-C) and cognitive dysfunction. P for nonlinearity <0.05 indicates a nonlinear relationship. Threshold effect analyses were performed to calculate the turning points within Model 2. Subgroup analyses and interaction tests were conducted to identify other relevant risk factors that may influence the association between ln(GGT/HDL-C) and cognitive dysfunction.

Results

ln(GGT/HDL-C) was divided into quartiles: Q1 (≤2.29), Q2 (2.29~2.69), Q3 (2.69~3.15), and Q4 (≥3.15) (Table 1). The analysis revealed that participants with higher ln(GGT/HDL-C) levels had lower scores in CERAD W-L, AFT, DSST, and total-CF. They also displayed higher body mass index (BMI), fasting glucose, HbA1c, ALT, AST, TG levels, history of DM, hypertension, sleep problems and smoking status. The four groups also differed in race, education level, gender and TC, and showed no significant difference in drinking status.

Table 2 illustrates the associations between ln(GGT/HDL-C) and cognitive dysfunction. Model 1 revealed significant correlations between ln(GGT/HDL-C) and cognitive dysfunction assessed by the CERAD W-L, AFT, DSST and total-CF ($P<0.05$). Specifically, the data indicated that for each unit increment in ln(GGT/HDL-C), the risk of cognitive dysfunction evaluated by the CERAD W-L, AFT, DSST or total-CF was increased 28.6%, 21.4%, 36.5% or 39.7% respectively [OR (95% CI): 1.286 (1.139~1.451), 1.214 (1.078~1.366), 1.365 (1.210~1.541) and 1.397 (1.236~1.578)]. After adjusting for various covariates, the associations between ln(GGT/HDL-C) and total-CF, as well as AFT, remained significant [OR (95% CI): 1.374 (1.126~1.676), 1.220 (1.030~1.444)], while no significant associations were found with CERAD W-L or DSST ($P>0.05$).

Furthermore, the ORs for cognitive dysfunction were computed for each ln(GGT/HDL-C) quartile using Q1 as the reference category. After multivariate adjustments, the OR for cognitive dysfunction assessed by total-CF was 1.540 (95% CI: 1.075~2.207, $P=0.019$, $P_{trend}= 0.012$). For AFT, the OR was 1.394 (95% CI: 1.024~1.897, $P=0.035$, $P_{trend}= 0.072$) for the highest quartile.

In Model 2, further exploration of the relationship between ln(GGT/HDL-C) and cognitive dysfunction evaluated by total-CF revealed a nonlinear relationship (Figure 2A). A two-piecewise logistic regression model was used to calculate the threshold effect. If the P value for the likelihood test is <0.05, it means the two-piecewise logistic regression model is superior to the single-line logistic regression model.[19] We observed that the inflection point was 3.055 (Table 3). Before reaching the inflection point, no correlation was identified [OR (95% CI): 1.044 (0.702~1.555), $P=0.830$], and above the inflection point, a significant association was identified with an OR of 2.091 (95% CI: 1.360~3.216). Similarly, a nonlinear relationship was observed between ln(GGT/HDL-C) and cognitive dysfunction assessed by CERAD W-L or DSST (Figure 2B, 2D), which was further supported by the threshold effect analysis (Table 3). However, there was no correlation observed between ln(GGT/HDL-C) and cognitive dysfunction evaluated by AFT in the RCS curve (Figure 2C).

Table 1.

Baseline characteristics of participants grouped according to ln(GGT/HDL-C) quartiles.

	Total	Q1	Q2	Q3	Q4	P-value
ln(GGT/HDL-C)	2.69 (2.29, 3.15)	2.05 (1.84, 2.17)	2.50 (2.39, 2.61)	2.90 (2.79, 3.02)	3.55 (3.33, 3.90)	-
Age (years)	69.46±6.79	70.54±6.97	70.03±6.78	69.03±6.61	68.20±6.54	<0.001
BMI (kg/m²)	29.06±6.32	26.99±6.05	29.09±6.59	29.95±6.08	30.26±6.03	<0.001
Gender						
Male	1357 (49.01)	205 (29.40)	307 (43.60)	426 (62.10)	419 (61.50)	<0.001
Female	1412 (50.99)	493 (70.60)	397 (56.40)	260 (37.90)	262 (38.50)	
CERAD W-L	13.5 (10.5, 16.0)	14.0 (10.5, 16.5)	13.5 (11.0, 16.0)	13.0 (10.5, 15.5)	13.0 (10.5, 15.5)	0.001
AFT	16.0 (13.0, 20.0)	17.0 (13.0, 20.0)	16.0 (13.0, 20.0)	16.0 (13.0, 20.0)	16.0 (12.0, 20.0)	0.027
DSST	46.0 (33.0, 59.0)	49.0 (36.0, 62.0)	46.0 (34.0, 59.0)	45.0 (33.0, 56.0)	43.0 (31.5, 56.0)	<0.001
total-CF	76.0 (59.0, 92.5)	80.0 (62.5, 97.5)	76.5 (60.5, 92.9)	75.0 (58.5, 89.5)	72.0 (56.5, 89.0)	<0.001
FG (mmol/L)	6.41±1.97	5.82±1.32	6.29±1.80	6.71±2.29	6.89±2.19	<0.001
HbA1c (%)	6.07±1.09	5.79±0.82	5.95±0.82	6.23±1.29	6.31±1.26	<0.001
ALT (U/L)	20 (16, 25)	17 (14, 21)	18 (15, 22)	20 (16, 26)	25 (19, 32)	<0.001
AST (U/L)	23 (20, 27)	22 (19, 26)	23 (20, 26)	23 (20, 27)	26 (22, 33)	<0.001
LDH (U/L)	131 (117, 148)	134 (119, 150)	131 (115, 147)	130 (116, 146)	131 (117, 152)	0.022
TG (mmol/L)	1.41 (0.95, 2.13)	1.04 (0.77, 1.46)	1.36 (0.98, 1.89)	1.61 (1.13, 2.38)	1.87 (1.24, 2.90)	<0.001
TC (mmol/L)	4.89 (4.16, 5.64)	5.12 (4.34, 5.87)	4.89 (4.19, 5.61)	4.80 (4.09, 5.59)	4.76 (3.98, 5.51)	<0.001
Race						
MA	244 (8.81)	46 (6.60)	63 (8.90)	56 (8.20)	79 (11.60)	
OH	278 (10.04)	52 (7.40)	74 (10.50)	77 (11.20)	75 (11.00)	
NHW	1352 (48.83)	403 (57.70)	355 (50.40)	309 (45.00)	285 (41.90)	<0.001
NHB	630 (22.75)	123 (17.60)	147 (20.90)	184 (26.80)	176 (25.80)	
OR	265 (9.57)	74 (10.60)	65 (9.20)	60 (8.70)	66 (9.70)	
Education level						
BHS	690 (24.94)	134 (19.20)	171 (24.30)	189 (27.60)	196 (28.80)	
HS	657 (23.74)	157 (22.50)	157 (22.30)	171 (24.90)	172 (25.30)	<0.001
AHS	1420 (51.32)	407 (58.30)	376 (53.40)	325 (47.40)	312 (45.90)	
DM						
No	1865 (69.75)	562 (82.80)	503 (74.00)	417 (63.50)	383 (58.20)	<0.001
Yes	809 (30.25)	117 (17.20)	177 (26.00)	240 (36.50)	275 (41.80)	
Hypertension						
No	1044 (37.77)	320 (45.90)	269 (38.40)	250 (36.40)	205 (30.10)	<0.001
Yes	1720 (62.23)	377 (54.10)	432 (61.60)	436 (63.60)	475 (69.90)	
High cholesterol						
No	1198 (43.56)	353 (50.90)	297 (42.30)	266 (39.00)	282 (42.00)	<0.001
Yes	1552 (56.44)	341 (49.10)	405 (57.70)	416 (61.00)	390 (58.00)	
Sleep problems						
No	1860 (67.17)	482 (69.10)	485 (68.90)	465 (67.80)	428 (62.80)	0.047
Yes	909 (32.83)	216 (30.90)	219 (31.10)	221 (32.20)	253 (37.20)	
Drinking status						
No	425 (15.61)	121 (17.60)	118 (17.10)	100 (14.80)	86 (12.90)	0.064
Yes	2298 (84.39)	567 (82.40)	574 (82.90)	575 (85.20)	582 (87.10)	
Smoking status						
No	1366 (49.37)	413 59.30)	368 (52.30)	314 (45.80)	271 (39.90)	<0.001
Yes	1401 (50.63)	284 (40.70)	336 (47.70)	372 (54.20)	409 (60.10)	

Abbreviations: *FG, fasting glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TG, triglycerides; TC, total cholesterol; DM, diabetes mellitus; MA, Mexican American; OH, other Hispanic; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHA, non-Hispanic Asian; OR, other races; BHS, below high school; HS, high school; AHS, above high school.*

Table 2.

Association between ln(GGT/HDL-C) and cognitive dysfunction.

	total-CF				
	Model 1	*P*-value	Model 2	*P*-value	
ln(GGT/HDL-C)	1.397 (1.236~1.578)	<0.001	1.374 (1.126~1.676)	0.002	
ln(GGT/HDL-C) quartile					
Q1 2.05 (≤2.29)	1(reference)		1(reference)		
Q2 2.50 (2.29-2.69)	1.180 (0.915~1.521)	0.203	1.033 (0.747~1.429)	0.846	
Q3 2.90 (2.69-3.15)	1.435 (1.118~1.843)	0.005	1.067 (0.763~1.492)	0.706	
Q4 3.55 (≥3.15)	1.782 (1.394~2.278)	<0.001	1.540 (1.075~2.207)	0.019	
P_{trend}		<0.001		0.012	
	CERAD W-L				
	Model 1	*P*-value	Model 2	*P*-value	
ln(GGT/HDL-C)	1.286 (1.139~1.451)	<0.001	1.187 (0.998~1.411)	0.053	
ln(GGT/HDL-C) quartile					
Q1 2.05 (≤2.29)	1(reference)		1(reference)		
Q2 2.50 (2.29-2.69)	1.021 (0.797~1.308)	0.869	0.896 (0.679~1.183)	0.440	
Q3 2.90 (2.69-3.15)	1.160 (0.907~1.483)	0.236	0.868 (0.648~1.163)	0.343	
Q4 3.55 (≥3.15)	1.570 (1.237~1.994)	<0.001	1.258 (0.921~1.717)	0.149	
P_{trend}		<0.001		0.095	
	AFT				
	Model 1	*P*-value	Model 2	*P*-value	
ln(GGT/HDL-C)	1.214 (1.078~1.366)	0.001	1.220 (1.030~1.444)	0.021	
ln(GGT/HDL-C) quartile					
Q1 2.05 (≤2.29)	1(reference)		1(reference)		
Q2 2.50 (2.29-2.69)	1.335 (1.052~1.693)	0.017	1.323 (1.010~1.734)	0.042	
Q3 2.90 (2.69-3.15)	1.338 (1.053~1.699)	0.017	1.236 (0.927~1.649)	0.148	
Q4 3.55 (≥3.15)	1.479 (1.165~1.875)	0.001	1.394 (1.024~1.897)	0.035	
P_{trend}		0.003		0.072	
	DSST				
	Model 1	*P*-value	Model 2	*P*-value	
ln(GGT/HDL-C)	1.365 (1.210~1.541)	<0.001	1.174 (0.965~1.428)	0.109	
ln(GGT/HDL-C) quartile					
Q1 2.05 (≤2.29)	1(reference)		1(reference)		
Q2 2.50 (2.29-2.69)	1.164 (0.906~1.495)	0.235	0.899 (0.652~1.241)	0.519	
Q3 2.90 (2.69-3.15)	1.432 (1.120~1.832)	0.004	0.955 (0.685~1.330)	0.785	
Q4 3.55 (≥3.15)	1.735 (1.362~2.210)	<0.001	1.239 (0.868~1.767)	0.238	
P_{trend}		<0.001		0.149	

Notes: Model 1: unadjusted; Model 2: adjusted for age, gender, BMI, race, education level, DM, hypertension, sleep problems, drinking status, smoking status, ALT, AST, LDH, TG and TC.

Table 3.

Threshold effect analysis of ln(GGT/HDL-C) on cognitive dysfunction.

	total-CF		CERAD W-L		AFT		DSST	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Model A	1.374 (1.126~1.677)	0.002	1.187 (0.999~1.412)	0.052	1.219 (1.030~1.444)	0.021	1.174 (0.965~1.428)	0.108
Model B Inflection point	3.055		3.019		2.361		2.848	
< Inflection point	1.044 (0.702~1.555)	0.830	1.008 (0.710~1.432)	0.962	1.297 (0.586~2.874)	0.521	0.806 (0.507~1.281)	0.361
≥ Inflection point	2.091 (1.360~3.216)	<0.001	1.697 (1.178~2.444)	0.004	1.173 (0.940~1.464)	0.159	1.625 (1.134~2.329)	0.008
P for likelihood test		0.013		0.020		0.371		0.021

Notes: Model A: Fitting model by single line regression; Model B: Fitting model by two piecewise linear regression. P for likelihood test <0.05, it means model B is superior to model A.
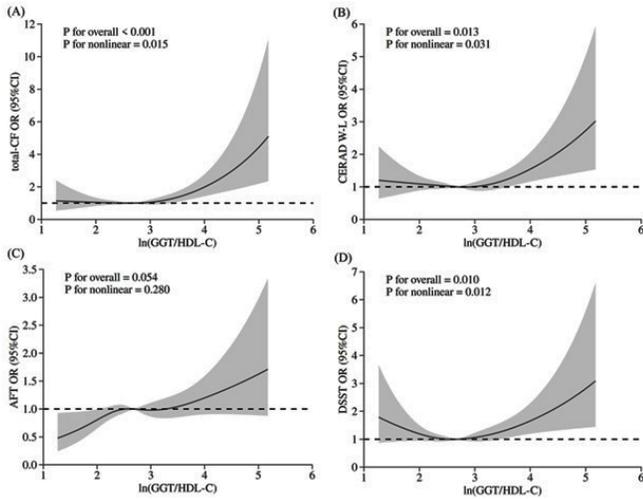
Figure 2. Restricted cubic spline (RCS) analysis between ln(GGT/HDL-C) and cognitive dysfunction assessed by total-CF (A), CERAD W-L (B), AFT (C), or DSST (D).
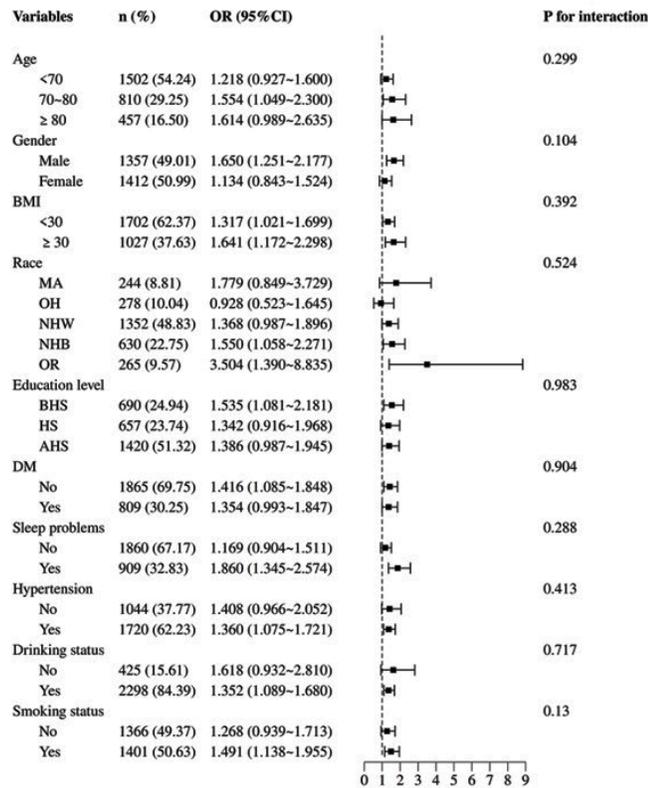

Figure 3. Forest map of ORs for the relationship between ln(GGT/HDL-C) and cognitive dysfunction stratified by different subgroups.

Subgroup analyses were performed based on multiple variables including age, gender, BMI, race, education level, DM, sleep problems, hypertension, drinking and smoking status. These analyses accounted for all confounding variables except the grouping variable itself. There were no significant interactions between subgroup variables and ln(GGT/HDL-C), with all $P_{interaction}$ >0.05 (Figure 3). The results suggested that the associations of ln(GGT/HDL-C) with cognitive dysfunction were comparable in most subpopulations.

Discussion

In this study, we evaluated the relationship between ln(GGT/HDL-C) and cognitive dysfunction in 2,769 participants aged 60 years and older from the NHANES 2011-2014 cycles. After adjusting for covariates, we discovered that ln(GGT/HDL-C) was positively associated with the risk of cognitive dysfunction assessed by total-CF.

Previous studies have established associations between GGT or HDL-C and cognitive function. In a large-scale population of middle-aged to older Finnish men, GGT was positively associated with the future risk of dementia.[8] Research conducted among Chinese female patients with mild cognitive impairment has shown similar results.[7] Additionally, Lee et al.[9] indicated that both baseline GGT and GGT variability are independent predictors of dementia. Zhang et al.[20] identified a nonlinear relationship wherein the risk of cognitive impairment escalated with increasing GGT levels in 25~94 U/L. Consistent with the above results, our study demonstrated that elevated GGT levels were associated with an increased risk of cognitive dysfunction and for every one unit increase in GGT, the risk increased by 0.7% (Supplementary Table 2). Although Kunutsor et al.[21] did not find a strong causal relationship between GGT and AD via the mendelian randomization method, the potential pro-inflammatory and pro-oxidative roles of GGT may significantly contribute to cognitive dysfunction. Moreover, GGT levels are directly implicated in atheromatous plaque formation, which is also considered as a fundamental pathological mechanism underlying cognitive impairment.[7]

The correlation between HDL-C and cognitive dysfunction is still controversial. Previous studies have suggested that higher levels of HDL-C are linked to improved cognitive function, while lower HDL-C levels are related to adverse outcomes.[14,22-25] These findings underscore the potential benefits of high HDL-C for preserving cognitive function during aging. However, our study did not identify a correlation between HDL-C and overall cognitive function (Supplementary Table 3), and similar results have been reported.[26,27] In addition, compared with that in women, the HDL-C level in men was negatively correlated with the risk of AFT injury (Supplementary Table 3), which is like the results reported by Boccardi et al.[28] The differences in the correlation between HDL-C and cognitive function may be influenced by multiple factors, including age, gender, stage of cognitive impairment, assessment criteria and the nonlinear relationship between them, and even by other lipid levels.[28-31]

Notably, a recent study conducted by Wang et al.[32] provided initial evidence of a negative correlation between the GGT/HDL-C ratio and cognitive performance (assessed by DSST score) in older adults, with diabetes mellitus serving as a mediator. In our study, we incorporated multiple indicators and constructed a composite cognitive score (total-CF), which could reduce measurement bias from single-indicator assessment and provide a more holistic representation of global cognitive capacity. Furthermore, unlike the data-analytical approach adopted by Wang et al., we focused on the relationship between ln(GGT/HDL-C) and the risk of cognitive

dysfunction and thus employed logistic regression analysis. Although no significant association was observed between ln(GGT/HDL-C) and cognitive dysfunction (assessed by DSST) in the adjusted model (Table 2), subsequent restricted cubic spline (RCS) and threshold effect analyses revealed a nonlinear association: for each 1-unit increase in ln(GGT/HDL-C) above the threshold of 2.848, the risk of cognitive dysfunction increased by 62.5%. In summary, the two studies are fundamentally consistent in confirming the association between the GGT/HDL-C ratio and cognitive function, albeit with differences in assessment methods and analytical depth.

The GGT/HDL-C ratio provides a comprehensive measure that reflects the interplay between liver enzyme and serum lipid concentrations in relation to cognitive dysfunction. The potential mechanisms underlying the association between an elevated GGT/HDL-C ratio, positively associated with the risk of cognitive dysfunction, may include the following: 1) The elevation of GGT levels potentially exacerbates oxidative damage within the brain by disrupting glutathione metabolism, while the anti-inflammatory and antioxidant functions of HDL-C are inhibited, which may weaken the protection of neurons and blood vessels; 2) abnormalities of GGT and HDL-C may reflect endothelial dysfunction or arteriosclerosis, resulting in reduced cerebral blood flow and microvascular lesions; 3) an increased GGT/HDL-C ratio acts as an indicator of metabolic disturbances that may indirectly impair cognitive function through mechanisms such as insulin resistance, obesity, or diabetes; and 4) impaired liver function (indicated by elevated GGT) potentially affects neurological health by crossing the blood-brain barrier via inflammatory mediators or toxins such as ammonia. However, the exact mechanism requires further investigation.

The main advantage of our study is that it used the NHANES database, allowing us to obtain a large sample size. Additionally, three standard tests were employed, and a comprehensive score was generated to assess cognitive performance. We used a different method from previous studies to calculate the IRT score. This approach reduces the impact of deviations among the three trials. Furthermore, as a new indicator, GGT/HDL-C may explain the impact of the interaction between oxidative stress and lipid metabolism on cognition.

However, it is imperative to recognize the potential limitations of our research. First, the study design precludes the establishment of causality. Second, the possibility of residual confounding variables remains elusive. Finally, it is important to note that our research did not include a clinical assessment that could diagnose and further stratify cognitive dysfunction. Therefore, further prospective studies or fundamental research are necessary to elucidate the causal relationships and mechanisms between GGT/HDL-C and cognitive dysfunction.

In conclusion, our study suggested that higher levels of ln(GGT/HDL-C) might be associated with an increased risk of cognitive dysfunction in older adults.

Data Availability

Publicly available datasets were analyzed in this study. The data can be found at: https://www.cdc.gov/nchs/nhanes.

Ethical Statement

Approval for the NHANES procedures and protocols was granted by the NCHS Research Ethics Review Committee, and informed consent was obtained from all participants. Under the premise of complying with data usage specifications, this study is exempt from obtaining secondary informed consent.

Competing Interests

The authors declare that they have no conflicts of interest.

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Supplementary Material

Supplementary Table 1.

Cutoff values for cognitive dysfunction across age groups.

Age (years)	total-CF	CERAD W-L	AFT	DSST
60-69	64.5	11.5	14.0	37.0
70-79	57.0	10.5	12.0	32.0
≥80	50.0	8.5	11.0	28.0

Supplementary Table 2.

Association between GGT and cognitive dysfunction.

	total-CF			
	Model 1	*P*-value	Model 2	*P*-value
ln(GGT)	1.360(1.185~1.562)	<0.001	1.361(1.103~1.679)	0.004
GGT	1.006(1.003~1.008)	<0.001	1.007(1.003~1.012)	0.001
Male	1.007(1.003~1.010)	<0.001	1.008(1.002~1.013)	0.008
Female	1.003(0.998~1.007)	0.224	1.010(1.002~1.017)	0.017
	CERAD W-L			
	Model 1	*P*-value	Model 2	*P*-value
ln(GGT)	1.182(1.029~1.357)	0.018	1.183(0.984~1.422)	0.074
GGT	1.004(1.001~1.006)	0.007	1.005(1.001~1.009)	0.006
Male	1.002(0.999~1.006)	0.168	1.003(0.998~1.007)	0.210
Female	1.004(0.999~1.008)	0.093	1.014(1.007~1.021)	<0.001
	AFT			
	Model 1	*P*-value	Model 2	*P*-value
ln(GGT)	1.152(1.007~1.319)	0.040	1.154(0.964~1.380)	0.119
GGT	1.002(0.999~1.004)	0.185	1.003(0.999~1.006)	0.129
Male	1.000(0.996~1.004)	0.991	1.002(0.998~1.007)	0.299
Female	1.005(1.000~1.009)	0.031	1.005(0.999~1.012)	0.103
	DSST			
	Model 1	*P*-value	Model 2	*P*-value
ln(GGT)	1.280(1.116~1.468)	<0.001	1.113(0.904~1.370)	0.314
GGT	1.005(1.002~1.007)	0.001	1.004(1.000~1.008)	0.079
Male	1.006(1.002~1.009)	0.001	1.005(1.000~1.010)	0.070
Female	1.001(0.997~1.006)	0.586	1.003(0.996~1.011)	0.388

Model 1: unadjusted; Model 2: adjusted for age, gender, BMI, race, education level, DM, hypertension, sleep problems, drinking status, smoking status, ALT, AST, LDH, TG, and TC. Male: association of GGT and cognitive dysfunction in male participants. Female: association of GGT and cognitive dysfunction in female participants.

Supplementary Table 3.

Association between HDL-C and cognitive dysfunction.

	total-CF			
	Model 1	*P*-value	Model 2	*P*-value
ln(HDL-C)	0.565(0.419~0.761)	<0.001	0.732(0.439~1.220)	0.231
HDL-C	0.720(0.583~0.890)	0.002	0.896(0.633~1.267)	0.534
Male	0.820(0.594~1.133)	0.229	0.686(0.420~1.120)	0.132
Female	0.781(0.577~1.056)	0.109	1.275(0.764~2.128)	0.352
	CERAD W-L			
	Model 1	*P*-value	Model 2	*P*-value
ln(HDL-C)	0.483(0.358~0.650)	<0.001	0.850(0.547~1.322)	0.471
HDL-C	0.637(0.514~0.788)	<0.001	0.941(0.697~1.270)	0.690
Male	0.832(0.611~1.133)	0.244	0.860(0.573~1.292)	0.468
Female	0.805(0.586~1.106)	0.181	1.109(0.702~1.754)	0.658
	AFT			
	Model 1	*P*-value	Model 2	*P*-value
ln(HDL-C)	0.610 (0.458~0.814	0.001	0.565(0.363~0.879)	0.011
HDL-C	0.715(0.583~0.876)	0.001	0.684(0.506~0.926)	0.014
Male	0.621(0.443~0.872)	0.006	0.589(0.374~0.930)	0.023
Female	0.708(0.535~0.936)	0.015	0.826(0.545~1.252)	0.367
	DSST			
	Model 1	*P*-value	Model 2	*P*-value
ln(HDL-C)	0.486(0.361~0.654)	<0.001	0.606(0.363~1.011)	0.055
HDL-C	0.646(0.523~0.799)	<0.001	0.805(0.569~1.139)	0.220
Male	0.750(0.544~1.034)	0.079	0.672(0.412~1.096)	0.111
Female	0.701(0.517~0.951)	0.022	0.980(0.586~1.637)	0.938

Model 1: unadjusted; Model 2: adjusted for age, gender, BMI, race, education level, DM, hypertension, sleep problems, drinking status, smoking status, ALT, AST, LDH, TG, and TC. Male: association of HDL-C and cognitive dysfunction in male participants. Female: association of HDL-C and cognitive dysfunction in female participants.