RESEARCH

Associations between TG/HDL ratio and insulin resistance in the US population: a cross-sectional study

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Abstract

Background: Clinical data on the relationship between triglycerides (TG)/HDL ratio and insulin resistance (IR) suggest that TG/HDL ratio may be a risk factor for IR. However, there is evidence that different races have different risk of developing IR. The relationship on TG/HDL ratio and IR in various populations needs to be improved. Therefore, we investigated whether TG/HDL ratio was linked to IR in different groups in the United States after controlling for other covariates.

Methods: The current research was conducted in a cross-sectional manner. From 2009 to 2018, the National Health and Nutrition Examination Survey (NHANES) had a total of 49,696 participants, all of whom were Americans. The target-independent variable was TG/HDL ratio measured at baseline, and the dependent variable was IR. Additionally, the BMI, waist circumference, education, race, smoking, alcohol use, alanine transaminase, aspartate transaminase, and other covariates were also included in this analysis.

Results: The average age of the 10,132 participants was 48.6 ± 18.4 years, and approximately 4936 (48.7%) were males. After correcting for confounders, fully adjusted logistic regression revealed that TG/HDL ratio was correlated with IR (odds ratio = 1.51, 95% CI 1.42–1.59). A nonlinear interaction between TG/HDL ratio and IR was discovered, with a point of 1.06. The impact sizes and CIs on the left and right sides of the inflection point were 6.28 (4.66–8.45) and 1.69 (1.45–1.97), respectively. According to subgroup analysis, the correlation was strong in females, alcohol users, and diabetes patients. Meanwhile, the inverse pattern was observed in the aged, obese, high-income, and smoking populations.

Conclusion: In the American population, the TG/HDL ratio is positively associated with IR in a nonlinear interaction pattern.

Key Words
- TG/HDL ratio
- insulin resistance
- association
- logistic regression
- subgroup analysis

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Background

Insulin resistance (IR) is the insensitivity to insulin in insulin-dependent organs and tissues (1). The clinical manifestation of IR is the failure to respond to increase in blood sugar, which is associated with metabolic disorders of fat, protein, and carbohydrate storage in the body (2). The development of obesity usually accompanies IR (3). Moreover, IR is a key pathological driver of the development of type 2 diabetes and cardiovascular disease (4, 5, 6, 7, 8), and the presence of IR has been linked to metabolic disturbances in several studies (9).

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Furthermore, IR is most likely to intensify those conditions and increase death rate from all causes (10, 11, 12). Welsh *et al*. found that older adults without IR had a much lower incidence of diabetes than those with IR (13). Another 13-year follow-up study showed that patients with IR also had a considerably increased risk of cardiovascular disease (14). Perseghin *et al*. conducted a 15-year cohort study and concluded a 5.6% higher mortality rate of cancer patients with IR relative to non-IR cancer cases (15). Therefore, it is highly desirable to prevent the occurrence of IR for patient survival and public health (16).

Many causes, such as smoking, alcohol, hyperlipidemia, and hypertension, have been identified as risk factors for developing IR. Since these causes are common in modern life, we expect IR to become increasingly common in the general population unless public awareness is increased (17).

There are currently a variety of approaches for making a primary diagnosis of IR, either directly or indirectly (18). The gold standard for diagnosing IR is the hyperinsulinemic-euglycemic clamp test, which was initially developed by DeFronzo *et al*. (19). Unfortunately, this strategy has a number of drawbacks due to its high cost, time requirements, and invasiveness. As a result, this procedure is unsuitable for clinical use, especially when assessing a large number of samples (20). It is necessary to study the effective method in clinical prediction of IR, and correlative factors need to be found.

Triglycerides (TG) and HDL have been shown to be important factors in the formation of IR (21, 22). An increase in TG was shown to be a risk factor for the development of IR, while an increase in HDL was considered a protective factor. Many scholars have used the ratio of the two to investigate the relationship of both factors with IR. The TG/HDL ratio was found to be more closely linked to the development of IR than either TG or HDL alone. Notably, studies indicate that the TG/HDL ratio is a straightforward quantifiable measurement of IR and a marker of diabetes and coronary heart disease (23, 24).

However, results from previous studies on the relationship between TG/HDL ratio and IR suggest that more investigation is needed, especially since the sample sizes were small (25, 26). It should be noted that the conditions for the development of IR vary among populations. Therefore, more research is needed to understand the differences in study design, target population, and data processing. In this study, we used data from the National Health and Nutrition Examination Survey (NHANES) to investigate whether the TG/HDL ratio was linked to IR in adults in the United States.

Participants and methods

Study design

This was a cross-sectional study. The target-independent and outcome variable was the TG/HDL ratio and IR, respectively. All indicators of each sample were detected at the same time and collected by the NHANES database. The total population was divided into two groups according to the outcome, IR positive and IR negative group.

Study population

The data for this study were derived from the NHANES cross-sectional study by the Centers for Disease Control (CDC) and Prevention National Center for Health Statistics (NCHS; http://www.cdc.gov/nchs/nhanes/). The sample source of NHANES was based on a complex, stratified, multi-stage design with a resident sample derived from a nationally representative population sample (17, 27). The NHANES program began in the early 1960s as a series of surveys of different populations or health topics. The NHANES study program is described in detail at the website of CDC. The NHANES protocol has been revised and approved by the NCHS Research Ethics Committee. All participants provided written informed consent before participation. The survey consists of a combination of interviews and medical examinations.

The study ensured that the results were representative of the American population, and we selected data from five NHANES cycles over 10 years (2009–2018). A total of 49,696 participants were enrolled in the survey over five cycles. The inclusion criteria were as follows: (1) at least 18 years old; (2) fasting blood glucose and insulin were measured; and (3) biochemical indexes such as TG and HDL were measured. Exclusion criteria included were (1) acute complications (diabetic ketoacidosis, diabetic hypersomnic coma, or lactic acidosis); (2) combined liver, biliary, and renal diseases or diseases affecting calcium and phosphorus metabolism; (3) patients taking any drugs for blood lipid metabolism and patients with abnormal secretion of thyroid and parathyroid hormones; (4) patients with infectious diseases, immune diseases, and malignant tumors; (5) history of osteoporosis or other diseases characterized by abnormal bone metabolism; (6) recent history of surgery, trauma, severe infection, or other severe stress; and (7) patients with mental illness. Finally, a total of 10,132 participants were enrolled in the study. There is no significant statistical difference of sample sensitivity between the selected and excluded groups.

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Variables

The TG/HDL ratio was measured at the start of the study and followed as a constant variable. Blood samples from the patients were frozen at −30°C and sent to the University of Minnesota for processing. In all tests, each stage of specimen reception, transport, and examination was defined. The tests were on a random subset comprising 2% of the sample, and NHANES used a lot of approaches to ensure that the results were accurate. Detailed analysis methods can be accessed on the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

According to the published guidelines, HOMA-IR was calculated as the fasting glucose-insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (28). In a study of HOMA-IR in American adults, IR was considered to have occurred when the HOMA-IR index was higher than or equal to 2.73 (29), and no IR was thought to have occurred when the HOMA-IR index was lower than 2.73 (29, 30, 31). Accordingly, IR was defined as HOMA-IR ≥ 2.73 in this study.

In this study, we selected potential covariates as follows: (1) demographic data, (2) variables that were previously reported to affect TG/HDL ratio or IR, (3) introducing covariance resulted in a change of more than 10% in the regression coefficient of the basic model, and (4) other variables based on our clinical experience. Therefore, the following variables were used to construct the fully adjusted model: (1) continuous variables: age, BMI, waist circumference (WC), alanine transaminase (ALT), aspartate transaminase (AST), urea nitrogen (BUN), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), and vitamin D3 (VD3) (obtained at baseline); (2) categorical variables: gender, race, education, income, smoking, alcohol use, diabetes, hypertension, and hyperuricemia.

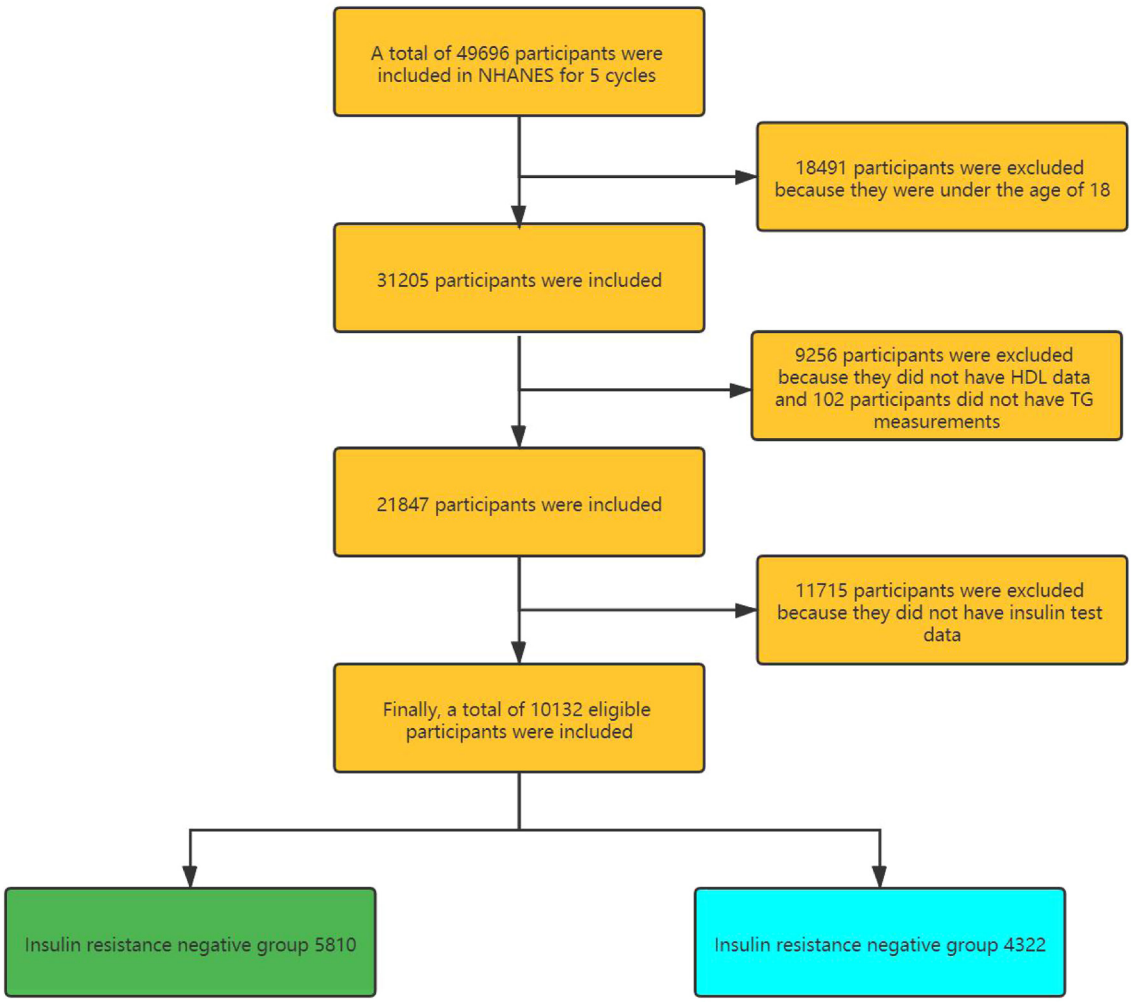

Figure 1
Flowchart of participant selection.

Table 1 Descriptive characteristics of the study participants.

Variables	Total (n = 10,132)	IR-negative (n = 5810)	IR-positive (n = 4322)	*P* value
Sex, *n* (%)				0.02
Male	4936 (48.7)	2772 (47.7)	2164 (50.1)	
Female	5196 (51.3)	3038 (52.3)	2158 (49.9)	
Age, mean ± SD	48.6 ± 18.4	47.0 ± 18.7	50.7 ± 17.9	<0.001
Race, *n* (%)				<0.001
Mexican American	1407 (13.9)	673 (11.6)	734 (17)	
Other Hispanics	1077 (10.6)	558 (9.6)	519 (12)	
Non-Hispanic White	3809 (37.6)	2296 (39.5)	1513 (35)	
Non-Hispanic Black	2172 (21.4)	1228 (21.1)	944 (21.8)	
Other race	1667 (16.5)	1055 (18.2)	612 (14.2)	
BMI, mean ± SD	29.1 ± 7.1	26.2 ± 5.3	33.0 ± 7.4	<0.001
WC, mean ± SD	99.1 ± 17.0	91.8 ± 13.4	109.0 ± 16.2	<0.001
Smoking, *n* (%)				0.116
No	5896 (58.2)	3420 (58.9)	2476 (57.3)	
Yes	4236 (41.8)	2390 (41.1)	1846 (42.7)	
Alcohol use, *n* (ng%)				<0.001
No	6591 (65.1)	3737 (67.3)	2854 (62.3)	
Yes	3541 (34.9)	1814 (32.7)	1727 (37.7)	
Diabetes, *n* (%)				<0.001
No	8519 (84.1)	5392 (92.8)	3127 (72.4)	
Yes	1613 (15.9)	418 (7.2)	1195 (27.6)	
Education, *n* (%)	1615 (15.9)	390 (7)	1225 (26.7)	<0.001
No higher education	4488 (44.3)	2428 (41.8)	2060 (47.7)	
Received higher education	5644 (55.7)	3382 (58.2)	2262 (52.3)	
Income, *n* (%)				<0.001
No more than $100,000	6557 (64.7)	3621 (62.3)	2936 (67.9)	
More than $100,000	3575 (35.3)	2189 (37.7)	1386 (32.1)	
Hypertension, *n* (%)				<0.001
No	4809 (47.5)	3268 (56.2)	1541 (35.7)	
Yes	5323 (52.5)	2542 (43.8)	2781 (64.3)	
ALT, median (IQR)	20.0 (15.0, 27.0)	18.0 (14.0, 24.0)	23.0 (17.0, 32.0)	<0.001
AST, median (IQR)	22.0 (18.0, 26.0)	21.0 (18.0, 26.0)	22.0 (18.0, 28.0)	<0.001
BUN, median (IQR)	4.6 (3.6, 5.7)	4.6 (3.6, 5.7)	4.6 (3.6, 6.1)	<0.001
GGT, median (IQR)	19.0 (14.0, 29.0)	17.0 (12.0, 25.0)	23.0 (17.0, 35.0)	<0.001
LDH, median (IQR)	130.0 (113.0, 150.0)	128.0 (112.0, 149.0)	131.0 (115.0, 152.0)	<0.001
VD3, median (IQR)	48.0 (29.1, 64.6)	50.5 (31.2, 68.3)	44.8 (26.6, 60.2)	<0.001
TG, median (IQR)	1.2 (0.8, 1.7)	1.0 (0.7, 1.4)	1.5 (1.0, 2.1)	<0.001
HDL, median (IQR)	1.3 (1.1, 1.6)	1.4 (1.2, 1.8)	1.2 (1.0, 1.4)	<0.001
TG/HDL, median (IQR)	0.9 (0.5, 1.4)	0.7 (0.4, 1.1)	1.2 (0.8, 2.0)	<0.001

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, urea nitrogen; GGT, γ-glutamyl transpeptidase; FPG, fasting plasma glucose; IR, insulin resistance; LDH, lactate dehydrogenase; TG, triacylglycerol; UA, uric acid; WC, waist circumference; VD3, vitamin D3 (cholecalciferol).

Covariate definitions

Education

The study population was divided into (1) participants who received a college education or above and (2) participants who have not received a junior college degree or above.

Income

Based on the American Average Income Report, we defined participants in this study as high income with a household income of more than $100,000 per year and low income with less than $100,000 per year.

Smoking

We divided the participants into three groups depending on their smoking status: (1) current smokers: smoked more than one cigarette per day within the past 30 days; (2) current nonsmokers: smoked less than one cigarette per day on average within the past 30 days or smoked more than 100 cigarettes in total over their lifetime; and (3) nonsmokers: smoked less than 100 cigarettes in total over their lifetime or never smoked. In this study, because the number of nonsmokers was too small, we finally defined the population as current nonsmokers as nonsmokers (27).

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Alcohol use

We looked at the classification of alcohol consumption in previous studies and classified alcohol consumption into drinkers, those who consume more than 12 drinks a year; and nondrinkers, those who do not drink more than 12 drinks a year (32, 33).

Diabetes mellitus

The 2015 American Diabetes Association criteria were used as the basis for the definition of diabetes. In this study, we defined diabetic patients as a population of participants with self-reported diabetes, those taking medication for diabetes, HbAlc ≥ 6.5, fasting glucose ≥ 7.0, based on questionnaires and laboratory tests (34).

Hypertension

In this study, we averaged the blood pressure values based on the participants' three measurements in the resting state and used the mean to determine whether the participants had hypertension. Hypertension was diagnosed based on systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or those who self-reported having hypertension or were taking antihypertensive drugs (33, 35). This definition is consistent with the 2017 American Heart Association blood pressure guidelines.

Hyperuricemia

Through multiplying the measured value by 59.48, the unit was converted from mg/dL to μmol/L. According to the literature, the hyperuricemia is diagnosed as a level of uric acid higher than 420 μmol/L in men or higher than 360 μmol/L in women.

Statistical analyses

Categorical variables were expressed as frequencies or percentages. We used the χ^2 test (categorical variables), means, and 95% CIs (normal distribution), or median and Q1–Q3 (skewed distribution) to test for differences between distinct IR-positive and IR-negative groups. Based on previous studies, participants with HOMA-IR ≥ 2.73 (30) were defined as the IR-positive group, while those with HOMA-IR < 2.73 were defined as the IR-negative group. Step 1: Univariate and multivariate logistics regression was employed. We constructed four models: model 1, no covariates were adjusted; model 2, only adjusted for sociodemographic factors; model 3, model 2+ BMI, WC, smoking, alcohol use, education, and income; model 4, model 3+ other covariates. Step 2: To address the nonlinearity of TG/HDL ratio and IR, logistic regression and smoothed curve fitting (penalized spline method) were conducted. If nonlinearity was detected, we first calculated the inflection point using a recursive algorithm and then constructed a two-part logistic regression on both sides of the inflection point of the logistic regression. Step 3: Subgroup analyses were performed using stratified logistic regression models. Continuous variables were first converted into categorical variables according to

Table 2 Univariate analysis for IR.

Variables	OR (95% CI)	*P* value
Age	1.01 (1.01–1.01)	<0.001
Gender		
Male	1	0.019
Female	0.92 (0.85–0.99)	
Race		
Mexican American	1	
Other Hispanics	0.85 (0.73–1)	0.049
Non-Hispanic White	0.6 (0.53–0.68)	<0.001
Non-Hispanic Black	0.7 (0.62–0.81)	<0.001
Other race	0.53 (0.46–0.61)	<0.001
BMI	1.20 (1.19–1.21)	<0.001
WC	1.08 (1.08–1.09)	<0.001
TG	2.15 (2.03–2.27)	<0.001
HDL	0.13 (0.12–0.15)	<0.001
TG/HDL	2.12 (2.01–2.24)	<0.001
ALT	1.03 (1.02–1.03)	<0.001
AST	1.00 (1.00–1.01)	0.002
BUN	1.06 (1.04–1.08)	<0.001
VD3	0.99 (0.99–0.99)	<0.001
Hypertension		
No	1	
Yes	2.32 (2.14–2.52)	<0.001
Smoking		
No	1	
Yes	1.07 (0.99–1.16)	0.112
Alcohol use		
No	1	
Yes	1.25 (1.15–1.35)	<0.001
Diabetes		
No	1	
Yes	4.93 (4.37–5.56)	<0.001
Education		
No higher education	1	
Received higher education	0.79 (0.73–0.85)	<0.001
Income		
No more than $100,000	1	
More than $100,000	0.78 (0.72–0.85)	<0.001

ALT, alanine transaminase; AST, aspartate transaminase; BUN, urea nitrogen; FPG, fasting plasma glucose; GGT, γ-glutamyl transpeptidase; IR, insulin resistance; TG, triglyceride; UA, uric acid; VD3, vitamin D3 (cholecalciferol).

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Table 3 The association between the TG/HDL ratio and IR in multiple logistic regression models. The data represent ORs and 95% CIs. Model 1, non-adjusted; model 2, adjusted for age, gender, and race; model 3, adjusted for model 2 + BMI, WC, education, income, diabetes, and hypertension; model 4, adjusted for model 3 + ALT, AST, BUN, LDH, GGT, and VD3.

Variable	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
TG/HDL	2.12 (2.01–2.24)	<0.001	2.18 (2.06–2.31)	<0.001	1.56 (1.48–1.65)	<0.001	1.51 (1.42–1.59)	<0.001
TG/HDL group								
TG/HDL < 1.10	1		1		1		1	
TG/HDL ≥ 1.10	4.16 (3.82–4.53)	<0.001	4.39 (4.01–4.8)	<0.001	2.69 (2.43–2.98)	<0.001	2.50 (2.25–2.77)	<0.001

the clinical cutoff, followed by an interactive test. The likelihood ratio test followed tests for effect modification for subgroup indicators. To ensure the robustness of the data analysis, we did a sensitivity analysis. We converted the TG/HDL ratio into a categorical variable and calculated the *P* value for trend. The purpose was to test the results of TG/HDL ratio as a continuous variable and observe the possibility of nonlinearity. All the analyses were conducted using the statistical software package R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed test was performed, and differences with $P < 0.05$ (two-sided) were considered statistically significant.

Results

Base characteristics of enrolled participants

A total of 10,132 participants were selected for final data analysis (see flow chart in Fig. 1). The characteristics of the selected participants are listed in Table 1. The IR-positive and IR-negative groups were divided according to HOMA-IR 2.73 as the cutoff value (30).

The average age of the 10,132 selected participants was 48.6 ± 18.4 years, and 48.7% were male. The variables we selected were statistically significant in both groups (all $P < 0.05$). Participants from the IR-positive group had higher values of age, BMI, WC, TG, ALT, AST, GGT, and LDH than those in the IR-negative group. Additionally, the IR-positive group contained more participants who were smoking, use alcohol, or had hypertension and hyperuricemia than the IR-negative group. The opposite patterns were observed for VD3, HDL, education, and income.

Univariate analyses

The results of univariate analysis are presented in Table 2. Univariate logistic regression indicated that race, BMI, TG, HDL, hypertension, smoking, alcohol use, VD3, diabetes, education, and income were significantly associated with IR. We also concluded that education, income, VD3, and HDL were negatively associated with IR. By contrast, the univariate logistic regression showed that BMI, TG, hypertension, smoking, alcohol use, and diabetes were positively correlated with IR.

Results of unadjusted and adjusted regression model

In this study, we constructed four logistic models to analyze the independent effects of TG/HDL ratio on IR (univariate and multivariate logistic regression). The effect sizes of odds ratios (ORs) and 95% CIs are shown in Table 3. The model-based effect value indicated the probability of IR increased for each addition of TG/HDL ratio. For example, the effect size of 2.12 for IR in the unadjusted model means a 112% increased risk of IR (OR 2.12; 95% CI 2.01–2.24) with each 0.1 increased TG/HDL ratio. In the model only adjusted for sociodemographic data (model 2), with each 0.1 TG/HDL ratio increase, the risk of IR increased 118% (OR 2.18; 95% CI 2.06–2.31). In model 3, with each 0.1 TG/HDL ratio increase, the risk of IR increased 56% (OR 1.56; 95% CI 1.48–1.65). In the fully adjusted model (model 4), with each 0.1 TG/HDL ratio increase, the risk of IR increased 51% (OR 1.51; 95% CI 1.42–1.59).

Meanwhile, four linear regression models were constructed to analyze the association between TG/HDL

Table 4 The association between the TG/HDL ratio and IR in multiple linear regression models. The data represent ORs and 95% CIs. model 1, non-adjusted; model 2, adjusted for age, gender, and race; model 3, adjusted for model 2 + BMI, WC, education, income, diabetes, hypertension, and hypercholesterolemia; model 4, adjusted for model 3 + ALT, AST, BUN, LDH, GGT, and VD3.

Variable	Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	P value	β (95% CI)	*P* value
TG/HDL	0.81 (0.72–0.89)	<0.001	0.81 (0.72–0.9)	<0.001	0.47 (0.39–0.56)	<0.001	0.43 (0.35–0.52)	<0.001

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ratio and IR when IR was regarded as a continuous variable (Table 4). The effect sizes of βs and 95% CIs showed that with each TG/HDL ratio increase, the β value of HOMA-IR increased. For fully adjusted model (Model 4), the value of HOMA-IR increased 0.43 as TG/HDL ratio increased each 0.1.

For sensitivity analysis, we converted TG/HDL ratio from a continuous variable to a categorical variable. The *P* value for the trend of TG/HDL ratio with a categorical variable in a fully adjusted model was consistent with the result obtained using TG/HDL ratio as a continuous variable. Additionally, we also found that the tendency of the effect size in different TG/HDL ratio groups was isometric.

Nonlinearity of TG/HDL ratio and IR

In this study, we analyzed the nonlinear relationship between the TG/HDL ratio and IR (Fig. 2). Curve analysis and the results of logistic regression showed that the relationship between the TG/HDL ratio and IR was nonlinear after adjusting for age, race, BMI, WC, TC, ALT, AST, education, income, smoking, alcohol use, and hypertension. We used both logistic regression and two-part logistic regression to fit the association and select the best-fitting model based on the log-likelihood ratio test.

Table 5 Threshold effect analysis of TG/HDL ratio on incidence of IR in the NHANES study, 2009–2018. Adjusted for age, gender, race, BMI, WC, smoking, alcohol use, diabetes, hypertension, hypercholesterolemia, education, income, ALT, AST, BUN, GGT, LDH, and VD3.

Outcome	OR (95% CI)	*P* value
Break point	1.06 (1.04–1.08)	<0.001
Two-part logistic regression model		
TG/HDL < 1.06	6.278 (4.663–8.452)	<0.001
TG/HDL ≥ 1.06	1.69 (1.448–1.973)	<0.001
Likelihood ratio test	<0.001	
Nonlinearity test	<0.001	

Because the *P* value of the log-likelihood ratio test was less than 0.05, we chose two-part logistic regression to fit the association between TG/HDL ratio and IR because it can accurately represent the relationship. The two-part logistic regression and recursive algorithm indicated that the inflection point was 1.06. On the left side of the

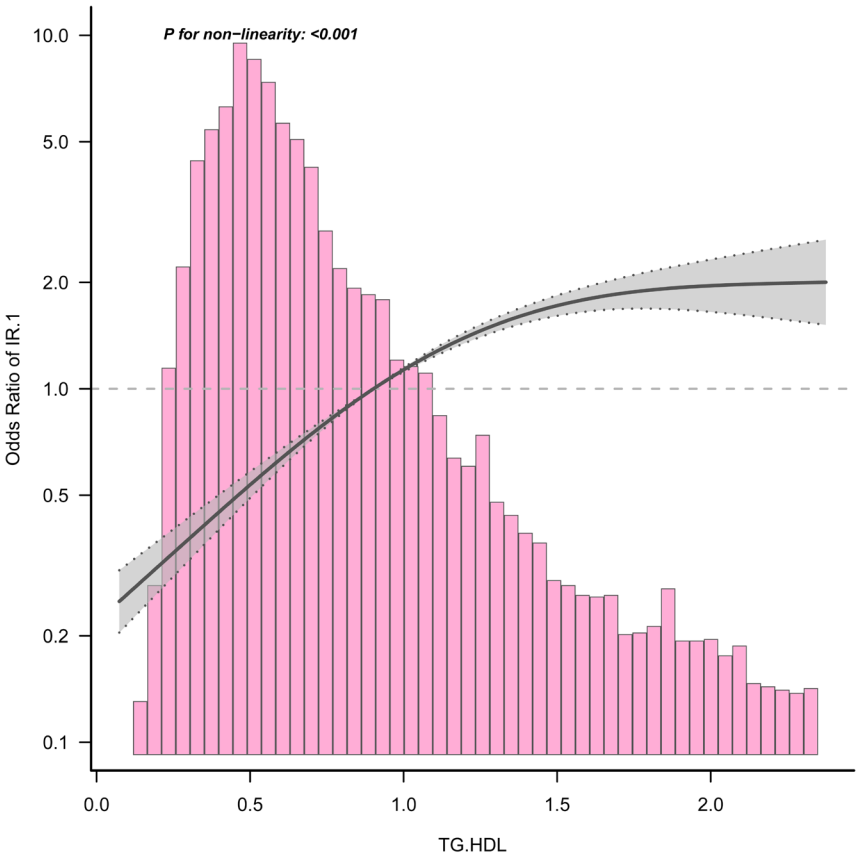

Figure 2
Multifactor logistic regression analysis of the association between the TG/HDL ratio and IR.

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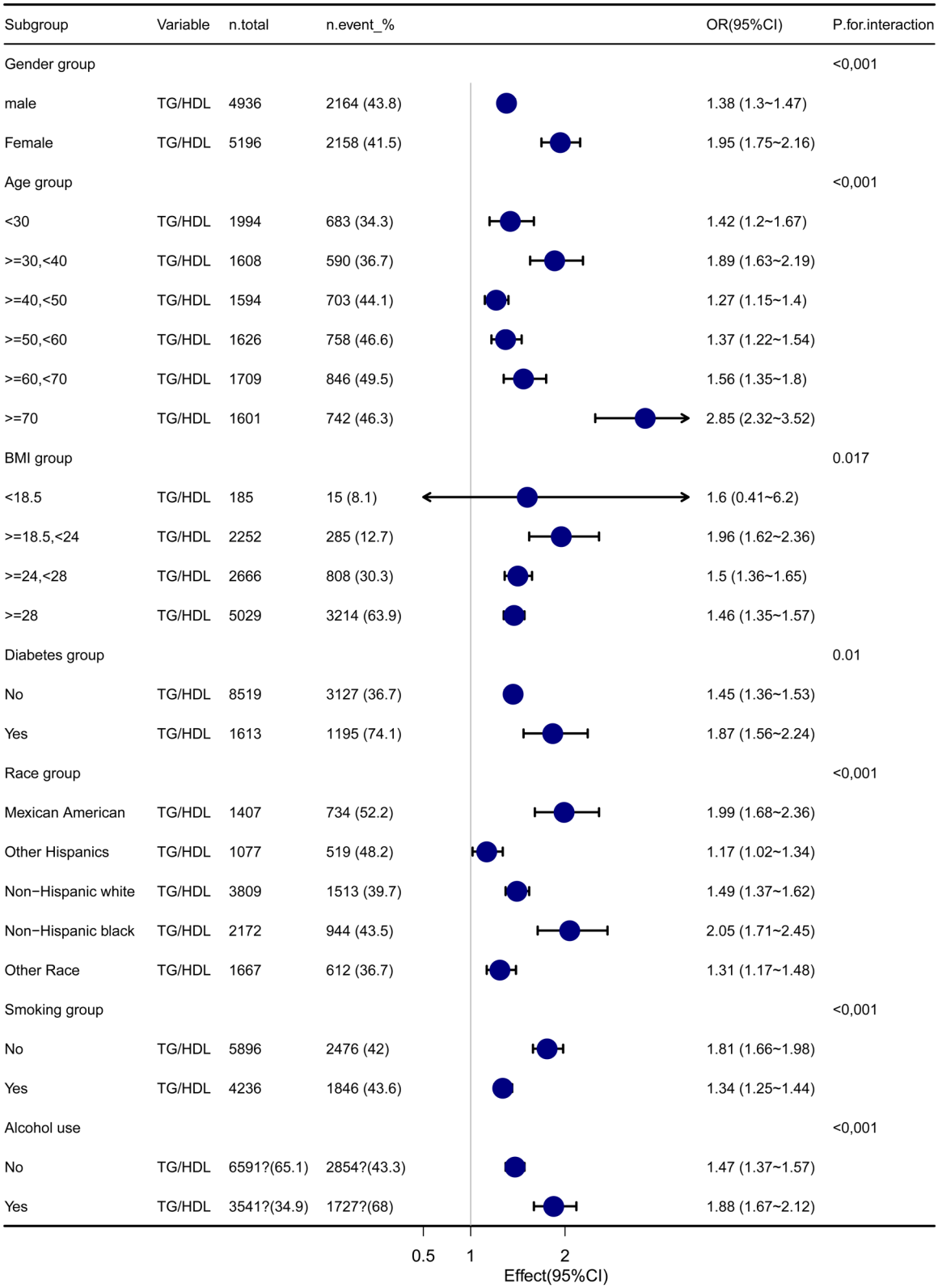

Figure 3
Subgroup analysis based on the analysis of multi-factor logistic regression for the association between the TG/HDL ratio and IR.

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inflection point, the effect size and 95% CI were 6.28 and 4.66–8.45, respectively. On the right side of the inflection point, the effect size and 95% CI were 1.69 and 1.45–1.97, respectively (Table 5).

Subgroup analyses

We used age, gender, race, BMI, smoking, and diabetes as the stratification variables to study the trend of effect sizes in these variables (Fig. 3). Interactions were observed based on our *a priori* specification, including age, gender, BMI, smoking, and diabetes (all with *P* values for interaction < 0.05). In this study, a stronger association was detected for women, alcohol user, and diabetes patients compared with male and non-diabetes cases. In the age groups, the highest association was observed in group of older than 70s, the second strong level of the association was in the group of 30–40 years old, and the weakest association was in the 40–60 groups. Meanwhile, a weaker association was observed in the obese and smokers. It should also be noted that compared with Mexican and non-Hispanic Black Americans, other American races have a relatively weaker association between TG / HDL ratio and IR.

Discussion

Our results indicate that the TG/HDL ratio is positively associated with IR after adjusting for covariates. Notably, a nonlinear interaction between TG/HDL ratio and IR was discovered. The trend of the effect sizes for the left and right sides of the inflection point is not consistent (left: OR 6.28, 95% CI 4.66–8.45; right: OR 1.69, 95% CI 1.45–1.97). These results suggest an L curve for the independent association between the TG/HDL ratio and IR. Subgroup analysis will help us better understand the trend of the TG/HDL ratio and IR in atypical populations. This study found a stronger association in women, patients with diabetes, and those who consume alcohol. By contrast, a weaker association was detected in obese and smokers. In the age groups, the highest association was in old group (≥70 years) and the second relationship was in the middle age group (Fig. 3). Compared with Mexican and non-Hispanic Black Americans, other American races have a relatively weaker association between TG/HDL ratio and IR.

Moriyama suggested that the TG/HDL-C ratio is linked to IR, components of metabolic syndrome (MetS), exercise, physical activity, and smoking, but lack of alcohol intake, in a sample of 1068 healthy Japanese subjects (36). Similar findings were also reported by Sánchez-Escudero *et al.* (37) Rodríguez-Gutiérrez *et al.* (38), and He *et al.* (39) and consistent with the result of this study.

However, there are still important differences between the studies. Here, we elaborated the association between TG/HDL ratio and IR from different perspectives and in different subpopulations. We concluded that the association between TG/HDL ratio and IR gradually decreased with BMI, and the association was strongest in people with a BMI of 18.5–24. Moreover, we found the previous studies did not show a two-stage effect. The different results may be due to the following reasons: (1) the targeted population is different; (2) their studies did not analyze the relationship between the TG/HDL ratio and IR by curve fitting; and (3) these studies did not consider the effects of VD3, LDH, GGT, income, and education on the relationship between the TG/HDL ratio and IR when adjusting for covariates. However, these previous studies have confirmed the relationship of TG/HDL ratio and IR.

According to experimental studies, high TG/HDL ratio will lead to less retention of fatty acids, resulting in more fatty acids to be transported to the liver for TG synthesis, which become a vicious circle (40). TG-rich lipoproteins may accelerate the synthesis of factors including leptin, angiotensinogen, tumor necrosis factor α, interleukin 6, plasminogen activator inhibitor 1, transforming growth factor B, adiponectin, adiponectin and resistin. These factors, at least in experimental level, are risk factors for insulin resistance or diabetes (41, 42, 43, 44).

The clinical value of this study can be summarized in the following two aspects: (1) to our best knowledge, this is the first report of an independent association between the TG/HDL ratio and IR in US adults, as well as the first report that shows age, BMI, and VD3 influence the relationship between TG/HDL ratio and IR in American adults; (2) the findings of this study will aid future research on the establishment of diagnostic or predictive models of IR.

The clinical value of this study can be summarized as follows: (1) as far as we know, our study sample is larger than previous samples; (2) we performed logistic regression curve fitting to analyze the relationship between the TG/HDL ratio and IR; (3) the adjustment strategies in our study are better suited than those used in previous ones, and the results were more reliable after including VD3, LDH, and GGT as the adjusted variables; (4) we conducted a sensitivity analysis in this study; and (5) we conducted a subgroup analysis and discovered an interaction among gender, age, BMI, diabetes, race, smoking, and drinking.

Finally, there are also some limitations in the present study. (1) This study is based on American adults, which is

a definite limitation for the universality and extrapolation of this research. (2) This study did not consider pregnant women, children, or people with specific medical conditions, so it is difficult to know whether the results of this study would apply to these populations. These limitations mainly come from the characteristics of NHANES database and do not affect the applicability of our results to the US adults. In this study, we have controlled the confounding factors to minimize the bias so as to make the results more credible.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethics approval and consent to participate

All data from the NHANES database have undergone ethical review, for details please see the NHANES website (https://www.cdc.gov/nchs/nhanes/index.htm).

Availability of data and materials

Data can be downloaded from the 'NHANES' database (https://www.cdc.gov/nchs/nhanes/index.htm).

Author contribution statement

Rongpeng Gong and Gang Luo conceived the study; Rongpeng Gong wrote the manuscript; Mingxiang Wang, Shengnan Sun, and Lingbo Ma collected the data; Xiaoxing Wei read and revised the manuscript. All authors read and approved the final manuscript. Rongpeng Gong is the first author, Gang Luo is co-first author, Shengnan Sun and Xiaoxing Wei are the corresponding authors.

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