

Association of the triglyceride-high-density lipoprotein-glucose-body index (TyHGB) with depression in US adults: A population-based cross-sectional study

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Abstract

Background

The triglyceride-high-density lipoprotein-glucose-body index (TyHGB) is a novel composite metabolic marker integrating atherogenic dyslipidemia, hyperglycemia, and adiposity. Although insulin resistance is implicated in depression pathophysiology, the association between TyHGB and depressive symptoms remains unexplored.

Methods

This cross-sectional study analyzed data from 13,769 adults in the National Health and Nutrition Examination Survey (NHANES) 2005–2018. Depressive symptoms were defined as a Patient Health Questionnaire-9 (PHQ-9) score ≥ 10 . TyHGB was calculated as $[\text{TG (mmol/L)}/\text{HDL-C (mmol/L)}] + 0.7 \times \text{FBG (mmol/L)} + 0.1 \times \text{BMI (kg/m}^2\text{)}$. Weighted multivariable logistic regression, restricted cubic splines, two-piecewise linear regression, and subgroup analyses were used to examine the association. Four machine learning models (Random Forest, XGBoost, Support Vector Machine, and LightGBM) were additionally applied to evaluate predictive performance.

Results

Among 13,769 participants, higher TyHGB levels were independently associated with increased odds of depressive symptoms after full adjustment (OR per unit increase = 1.02, 95% CI: 1.01–1.04, $P = 0.003$). Participants in the highest TyHGB quartile had 60% higher odds compared to the lowest quartile (OR = 1.60, 95% CI: 1.25–2.06, P for trend = 0.003). A significant J-shaped nonlinear relationship was identified (P for nonlinearity < 0.001), with an inflection point at TyHGB = 7.56. Above this threshold, each unit increase was associated with an 8.3% higher odds of depressive symptoms (OR = 1.08, 95% CI: 1.03–1.14). Machine learning analyses confirmed TyHGB as an important predictor, with Random Forest achieving the highest discriminative ability (AUC = 0.705).

Conclusions

TyHGB is significantly and nonlinearly associated with depressive symptoms in U.S. adults, exhibiting a J-shaped dose-response pattern. As a simple, low-cost marker derived from routine clinical parameters, TyHGB may serve as a practical screening tool for early identification of individuals at elevated depression risk. Prospective studies are needed to establish causality.

1.Introduction

Depression is a highly prevalent and debilitating psychiatric disorder that has emerged as a leading cause of global disability, affecting over 300 million individuals worldwide[1]. It is characterized by persistent low mood, anhedonia, and significant functional impairment, severely compromising quality of life. The World

Health Organization projects that by 2030, depression will become the foremost contributor to the global disease burden[2]. In addition to its psychological effects, depression is associated with an increased risk of suicide, disability, and all-cause mortality[3] [4]. Despite substantial advancements in therapeutic approaches, the pathogenesis of depression remains incompletely understood[5, 6], and diagnosis continues to rely primarily on subjective clinical interviews and self-report scales[7]. The absence of objective, accessible biomarkers for early risk identification constitutes a critical barrier to effective prevention. Consequently, the identification of straightforward and routinely measurable metabolic markers for early detection is of paramount importance. [8].

A growing body of evidence suggests that metabolic dysfunction, particularly insulin resistance (IR), plays a pivotal role in the pathophysiology of depression[9, 10]. Insulin resistance may exacerbate depression through several interrelated mechanisms, including chronic low-grade inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis, oxidative stress, and impaired central dopamine signaling, which disrupts reward processing[11]. Numerous large-scale population studies have established that elevated levels of insulin resistance, even among non-diabetic individuals, are independently associated with increased severity of depression and a heightened risk of developing depression over time[12–14]. Collectively, these findings highlight the significance of metabolic health in mood regulation. Consequently, it is imperative to conduct further research into the development of an integrated metabolic marker that effectively encapsulates the multifaceted characteristics of IR-related disturbances and evaluates its potential utility in the screening of depression.

A newly developed composite index, the TyHGB, has recently been introduced as a promising tool for the comprehensive evaluation of metabolic risk. The TyHGB distinctively integrates three essential and interrelated aspects of metabolic dysfunction—atherogenic dyslipidemia, hyperglycemic status, and general adiposity—into a singular, easily accessible metric[15, 16]. Each component parameter is regularly collected during standard clinical assessments, making the TyHGB a practical and cost-effective instrument that necessitates no supplementary testing. The index was originally developed and validated as a robust predictor of insulin resistance during pregnancy[17]. Subsequent research has demonstrated its strong associations with various cardiometabolic conditions, including non-alcoholic fatty liver disease and incident stroke across diverse populations. Notably, these studies have consistently found that the TyHGB index outperforms the traditional triglyceride-glucose (TyG) index in predicting these outcomes[18, 19]. This suggests that the inclusion of HDL cholesterol and BMI in the TyHGB index provides a more comprehensive assessment of metabolic risk. The biological efficacy of the TyHGB index is attributed to its ability to simultaneously capture the synergistic pathological pathways that drive systemic inflammation and neuroendocrine dysregulation, mechanisms that are also centrally implicated in depression. Given that each core component of the TyHGB index has been independently associated with the pathophysiology of depression, it is biologically plausible that this integrated index may serve as a sensitive indicator of the cumulative metabolic burden that predisposes individuals to depression[20–22].

Despite the compelling biological rationale, no research has yet explored the association between TyHGB and depression. Previous studies at the intersection of metabolic health and psychiatry have largely concentrated on isolated lipid or glycemic parameters, neglecting to simultaneously address the comprehensive spectrum of insulin resistance-related metabolic burden that TyHGB represents. This oversight signifies a significant

gap in the literature, particularly given the potential of this multidimensional marker to offer new insights into the metabolic underpinnings of depression. This study is the first to examine the relationship between the TyHGB index and depression, utilizing a nationally representative sample of U.S. adults from the National Health and Nutrition Examination Survey.

2. Methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, comprehensive health assessment initiative that systematically evaluates the health and nutritional status of the non-institutionalized U.S. population through meticulously designed interviews and comprehensive physical examinations. The NHANES protocol received approval from the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all participants prior to their enrollment. Given that all NHANES data are publicly accessible and free to use, no additional institutional ethics approval was necessary for this secondary analysis. Further information regarding NHANES data is available on the CDC website (<https://www.cdc.gov/nchs/nhanes/>).

This study conducted an analysis of data derived from seven consecutive two-year cycles of the National Health and Nutrition Examination Survey (NHANES) spanning 2005 to 2018, initially encompassing a cohort of 70,190 participants. To ensure the reliability of the data, the following exclusion criteria were implemented: (1) participants lacking information on the PHQ-9 (N = 33,931); (2) participants without TyHGB values (N = 19,919); and (3) participants with incomplete data on essential covariates (N = 2,571). Following the application of these exclusion criteria, the final analytical sample consisted of 13,769 participants. The selection process is illustrated in (Fig. 1).

2.2. Assessment of TyHGB

The TyHGB index was calculated using the formula: $\text{TyHGB} = \text{TG (mmol/L)} / \text{HDL-C (mmol/L)} + 0.7 \times \text{FBG (mmol/L)} + 0.1 \times \text{BMI (kg/m}^2\text{)}$.

2.3. Assessment of depression

The Patient Health Questionnaire-9 (PHQ-9) is a well-validated instrument for screening depression among adults in the United States, demonstrating high sensitivity and specificity, particularly in large-scale survey contexts[23]. Within the National Health and Nutrition Examination Survey (NHANES), depression were evaluated using the PHQ-9, which comprises nine items, each rated on a scale from 0 to 3, with higher scores reflecting increased symptom severity. Consequently, the total score ranges from 0 to 27. Based on substantial evidence supporting the PHQ-9's accuracy, a score of 10 or above was employed to identify potentially clinically significant depression.

2.4. Covariates

Covariates adjusted for in the analysis included age, gender, race, education level, marital status, poverty-to-income ratio (PIR), hypertension, diabetes, cardiovascular disease (CVD), smoking status and alcohol status.

Race was categorized as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other races. Educational level was classified into three categories: below high school, high school graduate, and above high school. Marital status was classified into three groups: Married/Living with a partner, Widowed/Divorced/Separated, or never married. Poverty status was defined using the PIR and categorized into three levels: ≤ 1.0 , $1.0-3.0$, and > 3.0 . Smoking status was classified into three categories based on lifetime tobacco use: never users, former users, and current users. Drinking history was used to categorize alcohol status into three groups: never users, former users, and current users.

Hypertension was defined as meeting any of the following: (1) systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, recorded on three non-consecutive measurement occasions; (2) a physician's diagnosis of hypertension; or (3) current use of antihypertensive medication. Diabetes mellitus was defined as meeting any of the following criteria: (1) an HbA1c level $\geq 6.5\%$; (2) a fasting blood glucose level ≥ 126 mg/dL; (3) a physician's diagnosis of diabetes; or (4) current use of insulin or other glucose-lowering medications. CVD was defined as the presence of any of the following conditions: stroke, myocardial infarction, angina, coronary heart disease, or congestive heart failure.

2.5. Statistical analysis

In accordance with NHANES analytical guidelines, appropriate sampling weights were applied to account for the complex multistage survey design. The two-year fasting subsample weights (WTSAF2YR) from the 2005–2018 cycles were used for all weighted analyses. All models accounted for the complex sampling design by incorporating NHANES-provided strata and primary sampling units (PSUs).

Continuous variables were summarized as medians (Q1, Q3) and compared using the Kruskal-Wallis test. Categorical variables were presented as weighted percentages (95% CI) and compared using the Rao-Scott adjusted χ^2 test. Three multivariable logistic regression models were fitted. Model 1 was unadjusted. Model 2 adjusted for age, gender, and race. Model 3 additionally adjusted for marital status, education level, PIR, smoking status, alcohol use, cardiovascular disease, hypertension, and diabetes. The P for trend was obtained by incorporating the quartile categories as a continuous variable in the regression model. Potential non-linear associations between the TyHGB index and depression were examined using restricted cubic splines with five knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. Stratified and interaction analyses were performed across prespecified subgroups, including gender, age, race, marital status, educational attainment, PIR, BMI, diabetes, hypertension, cardiovascular disease, smoking status, and alcohol status. Additionally, we developed and evaluated four machine learning models—Random Forest (RF), XGBoost (XGB), Support Vector Machine (SVM), and LightGBM (LGBM)—using the relevant covariates from the fully adjusted model to predict depression. The discriminative performance of each model was assessed by plotting receiver operating characteristic (ROC) curves and calculating the corresponding area under the curve (AUC) values. Sensitivity analyses were performed using mode imputation for missing categorical covariates to assess the robustness of the primary findings. All statistical analyses were performed using R version 4.4.2, and a two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the participants

As displayed in Table 1, a total of 13,769 participants (unweighted) were included, weighted to represent 189 million US adults. The median age was 47.00 years (IQR, 33.00–60.00), and 49.0% (95% CI, 48.2%–49.9%) were male. All characteristics—age, gender, race, education level, marital status, PIR, BMI, hypertension, diabetes, and CVD—differed significantly across TyHGB quartiles (all $P < 0.001$). Compared to those with lower TyHGB, individuals with higher TyHGB were generally older, more likely to be male, Mexican American, married or living with a partner, to have lower educational attainment and PIR, to have a higher BMI, and to have a greater prevalence of hypertension, diabetes, and CVD.

Table 1
Demographics and characteristics of participants by TyHGB Index Quartiles.

Characteristic	Overall N = 13769	Q1 N = 3443	Q2 N = 3442	Q3 N = 3442	Q4 N = 3442	P-value
Age(years)	47.00 (33.00, 60.00)	40.00 (28.00, 54.00)	47.00 (33.00, 61.00)	49.00 (35.00, 62.00)	50.00 (39.00, 62.00)	< 0.001
Gender(%)						< 0.001
Male	49.0(48.2, 49.9)	34.7(32.6, 36.8)	48.9(46.8, 51.1)	53.7(51.6, 55.7)	61.0(59.0, 62.9)	
Female	51.0(50.1, 51.8)	65.3(63.2, 67.4)	51.1(48.9, 53.2)	46.3(44.3, 48.4)	39.0(37.1, 41.0)	
Race(%)						< 0.001
Mexican American	8.0(6.9, 9.4)	5.5(4.5, 6.7)	7.6(6.2, 9.3)	8.9(7.6, 10.5)	10.5(8.8, 12.4)	
Other Hispanic	5.0(4.2, 5.9)	4.2(3.3, 5.4)	4.7(3.8, 5.7)	6.3(5.3, 7.6)	4.9(3.9, 6.2)	
Non-Hispanic White	69.4(66.9, 71.8)	68.9(65.9, 71.7)	70.5(67.5, 73.4)	67.3(64.3, 70.1)	71.0(68.1, 73.7)	
Non-Hispanic Black	10.6(9.3, 12.0)	12.8(11.1, 14.7)	11.3(9.7, 13.1)	10.4(8.9, 12.0)	7.4(6.3, 8.8)	
Other Race	7.0(6.3, 7.8)	8.6(7.3, 10.1)	5.9(5.0, 6.9)	7.1(6.0, 8.5)	6.1(5.2, 7.3)	
Education level(%)						< 0.001
Below high school	15.0(13.8, 16.3)	11.0(9.6, 12.6)	14.0(12.3, 15.8)	17.0(15.3, 18.9)	18.9(17.2, 20.6)	
High school graduate	23.2(21.9, 24.6)	18.6(16.9, 20.5)	23.1(20.9, 25.4)	25.1(23.2, 27.1)	26.6(23.9, 29.5)	
Above high school	61.8(59.7, 63.8)	70.4(67.7, 73.0)	62.9(60.0, 65.7)	57.9(55.1, 60.7)	54.5(51.4, 57.6)	
Note: Median (IQR) for continuous variables: the P value was calculated by the Design-based Kruskal Wallis test						
Weighted%(95%confidence interval) for categorical variables: the P value was calculated by the Rao-Scott chi-square test.						
Abbreviations: BMI, Body Mass Index; CVD, Cardiovascular Disease; FBG, Fasting Blood Glucose; HDL, High-density Lipoprotein; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty-to-Income Ratio;						

Characteristic	Overall N = 13769	Q1 N = 3443	Q2 N = 3442	Q3 N = 3442	Q4 N = 3442	P-value
Marital status(%)						< 0.001
Married/Living with a partner	64.5(63.0, 66.0)	61.1(58.4, 63.7)	64.1(61.5, 66.6)	65.2(62.9, 67.5)	68.2(65.7, 70.6)	
Widowed/Divorced/Separated	17.9(16.9, 18.9)	14.2(12.7, 15.8)	19.6(17.8, 21.5)	18.6(17.0, 20.2)	19.5(17.8, 21.3)	
Never Married	17.6(16.4, 18.9)	24.7(22.5, 27.1)	16.3(14.5, 18.3)	16.2(14.4, 18.3)	12.3(10.8, 14.0)	
PIR(%)						< 0.001
≤ 1	13.7(12.6, 14.9)	13.2(11.8, 14.8)	12.2(11.0, 13.6)	14.4(12.5, 16.5)	15.2(13.7, 17.0)	
1.1-3	36.2(34.6, 37.8)	31.6(29.3, 33.9)	36.8(34.5, 39.1)	37.7(35.1, 40.4)	39.2(37.1, 41.4)	
>3	50.1(48.0, 52.2)	55.2(52.4, 58.0)	51.0(48.3, 53.7)	47.9(44.7, 51.1)	45.5(42.7, 48.4)	
BMI(%)						< 0.001
< 25	29.9(28.6, 31.1)	70.4(68.3, 72.4)	26.0(24.1, 28.1)	11.6(10.3, 13.2)	6.0(5.0, 7.2)	
25–30	32.8(31.8, 33.9)	26(24.1, 28.0)	45.1(43.0, 47.2)	33.6(31.6, 35.6)	26.6(24.7, 28.6)	
≥ 30	37.3(36.0, 38.6)	3.6(3.0, 4.3)	28.9(27.1, 30.8)	54.8(52.5, 57.0)	67.4(65.1, 69.6)	
Smoking status(%)						< 0.001
Never	54.2(24.5, 27.2)	60.7(18.8, 22.7)	56.1(22.4, 27.6)	50.9(25.7, 29.7)	48.0(28.7, 32.9)	
Ever	25.8(18.8, 21.3)	20.7(16.6, 20.7)	24.9(17.2, 20.9)	27.7(19.5, 23.5)	30.8(19.6, 22.9)	
Note: Median (IQR) for continuous variables: the P value was calculated by the Design-based Kruskal Wallis test						
Weighted%(95%confidence interval) for categorical variables: the P value was calculated by the Rao-Scott chi-square test.						
Abbreviations: BMI, Body Mass Index; CVD, Cardiovascular Disease; FBG, Fasting Blood Glucose; HDL, High-density Lipoprotein; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty-to-Income Ratio;						

Characteristic	Overall N = 13769	Q1 N = 3443	Q2 N = 3442	Q3 N = 3442	Q4 N = 3442	P-value
Current	20.0(52.6, 55.8)	18.6(58.2, 63.2)	19.0(53.4, 58.8)	21.4(48.7, 53.1)	21.2(45.9, 50.2)	
Alcohol status(%)						< 0.001
Never	10.0(14.3, 16.2)	10.3(8.6, 11.5)	10.5(12.8, 15.8)	9.0(16.0, 19.4)	10.2(18.0, 22.2)	
Ever	15.3(73.3, 76.1)	10(77.5, 81.7)	14.2(73.1, 77.2)	17.7(71.2, 75.3)	20.0(67.3, 72.1)	
Current	74.7(9.1, 11.0)	79.7(8.9, 11.9)	75.2(9.3, 12.0)	73.3(8.0, 10.1)	69.8(8.7, 11.8)	
Hypertension(%)						< 0.001
No	62.2(36.3, 39.2)	79.9(18.0, 22.3)	66.0(31.8, 36.2)	54.9(43.1, 47.1)	45.1(52.1, 57.6)	
Yes	37.8(60.8, 63.7)	20.1(77.7, 82.0)	34.0(63.8, 68.2)	45.1(52.9, 56.9)	54.9(42.4, 47.9)	
Diabetes(%)						< 0.001
No	86.2(12.9, 14.7)	98.5(1.1, 2.0)	95.4(3.9, 5.6)	85.3(13.2, 16.4)	62.8(34.7, 39.9)	
Yes	13.8(85.3, 87.1)	1.5(98.0, 98.9)	4.6(94.4, 96.1)	14.7(83.6, 86.8)	37.2(60.1, 65.3)	
CVD(%)						< 0.001
No	91.2(8.1, 9.5)	94.9(4.2, 6.2)	93.0(6.0, 8.1)	90.5(8.4, 10.6)	85.7(12.7, 16.1)	
Yes	8.8(90.5, 91.9)	5.1(93.8, 95.8)	7.0(91.9, 94.0)	9.5(89.4, 91.6)	14.3(83.9, 87.3)	
BMI(kg/m²)	27.90 (24.19, 32.60)	23.20 (21.10, 25.47)	27.50 (24.86, 30.69)	30.70 (27.29, 34.80)	32.80 (28.80, 37.92)	< 0.001
Note: Median (IQR) for continuous variables: the P value was calculated by the Design-based Kruskal Wallis test						
Weighted%(95%confidence interval) for categorical variables: the P value was calculated by the Rao-Scott chi-square test.						
Abbreviations: BMI, Body Mass Index; CVD, Cardiovascular Disease; FBG, Fasting Blood Glucose; HDL, High-density Lipoprotein; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty-to-Income Ratio;						

Characteristic	Overall N = 13769	Q1 N = 3443	Q2 N = 3442	Q3 N = 3442	Q4 N = 3442	P-value
FBG(mmol/L)	5.55 (5.16, 6.05)	5.16 (4.88, 5.44)	5.50 (5.16, 5.83)	5.72 (5.33, 6.16)	6.16 (5.61, 7.44)	< 0.001
HDL(mg/dL)	52.00 (43.00, 63.00)	66.00 (57.00, 77.00)	55.00 (48.00, 64.00)	48.00 (42.00, 54.00)	40.00 (35.00, 46.00)	< 0.001
TG(mg/dL)	102.00 (70.00, 151.00)	62.00 (48.00, 77.00)	91.00 (71.00, 111.00)	123.00 (99.00, 150.00)	198.00 (155.00, 262.00)	< 0.001
TG/HDL ratio	1.93 (1.17, 3.27)	0.95 (0.70, 1.24)	1.66 (1.29, 2.04)	2.63 (2.06, 3.22)	4.88 (3.75, 6.64)	< 0.001
Depression(%)						< 0.001
No	92.8(6.7, 7.8)	94.5(4.7, 6.5)	93.9(5.1, 7.1)	92.0(6.9, 9.4)	90.3(8.5, 11.1)	
Yes	7.2(92.2, 93.3)	5.5(93.5, 95.3)	6.1(92.9, 94.9)	8.0(90.6, 93.1)	9.7(88.9, 91.5)	
Note: Median (IQR) for continuous variables: the P value was calculated by the Design-based Kruskal Wallis test						
Weighted%(95%confidence interval) for categorical variables: the P value was calculated by the Rao-Scott chi-square test.						
Abbreviations: BMI, Body Mass Index; CVD, Cardiovascular Disease; FBG, Fasting Blood Glucose; HDL, High-density Lipoprotein; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty-to-Income Ratio;						

3.2. Association of TyHGB index with depression

The results of the multivariable logistic regression analysis examining the association between the TyHGB index and depression are presented in (Table 2). In all three models, a significant positive association was observed between the TyHGB index, as a continuous variable, and the prevalence of depression. In the crude, unadjusted Model 1, each unit increase in the TyHGB index was associated with a 3% higher odds of depression (OR = 1.03, 95% CI: 1.02–1.05, $P < 0.001$). This positive relationship remained robust after adjusting for demographic covariates in Model 2 (OR = 1.04, 95% CI: 1.03–1.06, $P < 0.001$). Further adjustment for a comprehensive set of socioeconomic, lifestyle, and clinical factors in Model 3 only slightly attenuated the association, which remained statistically significant (OR = 1.02, 95% CI: 1.01–1.04, $P = 0.003$).

Table 2
Association between TyHGB index and depression.

TyHGB continuous	Model I	Model II	Model III
	OR (95%CI), <i>P</i>	OR (95%CI), <i>P</i>	OR (95%CI), <i>P</i>
	1.03(1.02,1.05),<0.001	1.04(1.03,1.06),<0.001	1.02(1.01,1.04),0.003
TyHGB quartile			
Q1	Ref	Ref	Ref
Q2	1.10(0.88,1.39),0.395	1.23(0.97,1.55),0.083	1.11(0.88,1.41),0.382
Q3	1.49(1.16,1.93),0.003	1.72(1.31,2.26),<0.001	1.37(1.04,1.81),0.026
Q4	1.84(1.51,2.24),<0.001	2.30(1.85,2.85),<0.001	1.60(1.25,2.06),<0.001
<i>P</i> for trend	< 0.001	< 0.001	0.003

To further investigate this relationship, the TyHGB index was analyzed as a categorical variable by dividing it into quartiles (Q1–Q4), with the lowest quartile (Q1) serving as the reference group. A clear dose-response trend was observed. In the fully adjusted Model III, participants in the highest quartile (Q4) of the TyHGB index had a 60% increased odds of depression compared to those in the lowest quartile (Q1) (OR = 1.60, 95% CI: 1.25–2.06, $P < 0.001$). The association was also significant for the third quartile (Q3) (OR = 1.37, 95% CI: 1.04–1.81, $P = 0.026$), while the second quartile (Q2) showed a positive but non-significant trend (OR = 1.11, 95% CI: 0.88–1.41, $P = 0.382$). The tests for linear trend were statistically significant across all three models (Model I: P for trend < 0.001 ; Model II: P for trend < 0.001 ; Model III: P for trend = 0.003), confirming that the odds of depression increases progressively with higher TyHGB index levels.

3.3. Non-linearity and threshold effect analysis between TyHGB and depression

To evaluate the potential nonlinear relationship between the TyHGB index and depression, restricted cubic spline (RCS) regression with five knots (placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the TyHGB distribution) was performed. The RCS analysis revealed a strongly significant nonlinear association (P for overall < 0.001 ; P for nonlinearity < 0.001), indicating that a simple linear model was inadequate to capture the relationship (Fig. 2).

To further characterize this nonlinear pattern and identify a potential threshold, a two-piecewise linear regression model was fitted. The optimal inflection point was determined at a TyHGB index value of 7.56 (Table 3). Below this threshold, each unit increase in the TyHGB index was associated with a reduced odds of depression, although the association did not reach statistical significance (OR = 0.88, 95% CI: 0.70–1.116, $P = 0.29$). Above the inflection point, each unit increase in the TyHGB index was significantly associated with an 8.3% higher odds of depression (OR = 1.08, 95% CI: 1.03–1.14, $P = 0.003$). The likelihood ratio test comparing the two-piecewise model with a standard linear model yielded a P value of 0.049, further supporting the presence of a threshold effect.

Table 3
Threshold effect analysis of TyHGB on depression using the two-piecewise regression model.

TyHGB	OR	95% CI	P value
threshold			
≤ 7.559	0.881	0.700,1.116	0.287
> 7.559	1.083	1.027,1.141	0.003
Likelihood ratio test			0.049

Collectively, these findings demonstrate a robust nonlinear relationship between the TyHGB index and depression risk, with a turning point identified at approximately 7.56. TyHGB levels exceeding this cutoff were significantly associated with an elevated risk of depression.

3.4. Subgroup analysis

To evaluate the consistency of the association between the TyHGB index and depression across different population strata, stratified analyses were performed by gender, age, race, education level, PIR, BMI, smoking status, alcohol consumption, hypertension, diabetes, and cardiovascular disease (Fig. 3). The positive association between the TyHGB index and depression remained largely consistent across all examined subgroups, with no statistically significant interactions detected for any of the stratifying variables (all *P* for interaction > 0.05). These findings indicate that the observed relationship between the TyHGB index and depression is robust and not materially modified by demographic, socioeconomic, lifestyle, or clinical characteristics.

3.5. Variable selection and machine-learning model performance

To ensure reproducibility, the original dataset was randomly split into a training set (70%) and a hold-out test set (30%) with random seed 1. To mitigate class imbalance, we applied random under-sampling exclusively to the training set (seed = 2), while the test set was kept intact to reflect real-world prevalence. On the balanced training data, we performed Lasso-penalized logistic regression with 10-fold cross-validation to select key predictors, followed by SHAP analysis for feature importance interpretation. Subsequently, four mainstream machine learning classifiers were constructed on the same training set, and all models were finally evaluated on the untouched test set.

As shown in Supplementary Figure S1, nine variables with non-zero coefficients were retained by Lasso, including RIAGENDR, Education, Marital status, PIR, BMI, HBP, CVD, smoking, and TyHGB. Variables with zero coefficients were excluded. Supplementary Figure S2 presents the mean absolute SHAP values, with PIR, smoking, BMXBMI, and TyHGB ranking as the top important features. The SHAP force plot (Supplementary Figure S3) further demonstrated that TyHGB had a positive contribution to the predicted risk of depression.

Based on the selected variables, we built four models – LGBM, random forest (RF), SVM, and XGB – to predict depression. The ROC curves and AUC values are shown in Supplementary Figure S4. The RF model achieved

the highest AUC (0.705), followed by LGBM (0.679), XGB (0.673), and SVM (0.569), indicating that the random forest model exhibited relatively better discriminative ability.

3.6. Sensitivity analyses

To address potential bias due to missing categorical covariate data (e.g., smoking status, alcohol use, education level, marital status, and PIR), we performed a sensitivity analysis using fixed-value imputation (missing values were assigned to the most frequent category or a prespecified reference level). The association between TyHGB and depression remained robust and materially unchanged compared with the primary complete-case analysis (Supplementary Table S1).

When TyHGB was analyzed as a continuous variable, each unit increase was associated with a 2% higher odds of depression (adjusted OR = 1.02, 95% CI: 1.01–1.03, $P = 0.002$). In quartile analysis (with Q1 as reference), participants in Q4 had a 52% increased odds of depression (adjusted OR = 1.52, 95% CI: 1.22–1.91, $P < 0.001$), and those in Q3 showed a 32% increased odds (adjusted OR = 1.32, 95% CI: 1.03–1.69, $P = 0.028$). Q1 and Q2 did not show statistically significant differences (Q2 vs. Q1: OR = 1.00, 95% CI: 0.80–1.25, $P = 0.995$). The dose–response trend across quartiles remained significant (P for trend < 0.001). These results are consistent with the primary analysis, confirming that our findings are not sensitive to the handling of missing covariate data.

4. Discussion

This nationally representative cross-sectional study examined the relationship between the novel TyHGB index and depression among adults in the United States. The principal finding indicated a significant positive correlation between the TyHGB index and the prevalence of depression, revealing a distinct dose-response trend. After full adjustment, participants in the highest TyHGB quartile (Q4) had a 60% higher odds of depression compared to those in the lowest quartile (Q1). A significant secondary finding of this study was the identification of a robust J-shaped nonlinear relationship, with a critical inflection point observed at a TyHGB value of 7.56. This indicates that the risk of depression does not increase in a linear fashion but rather accelerates once a specific metabolic threshold is surpassed. To the best of our knowledge, this is the first study to elucidate a J-shaped association between the TyHGB index and depression. To our knowledge, this study is among the first to examine TyHGB in relation to depressive symptoms in a national adult sample, extending prior evidence linking metabolic dysfunction to depression.

Our primary finding aligns with a growing body of evidence linking composite metabolic indices to depressive disorders. Studies have shown that related indices—such as the Metabolic Score for Insulin Resistance (METS-IR), the ZJU index, and the triglyceride-glucose (TyG) index—are positively associated with depression risk[24–26]. For instance, Yuan et al. found that higher TyG index was linked to poorer cognition in depressed patients, partially mediated by inflammation, while Zhou et al. observed a positive TyG-depression association in obese adults, where hypertension mediated about 10% of the effect[27, 28]. However, none of these indices fully capture the combined burden of atherogenic dyslipidemia (low HDL-C and high triglycerides), hyperglycemia, and adiposity in a single metric. The TyG index omits HDL C and BMI, the TyG-ABSI index requires waist circumference, and the ZJU index includes liver enzymes that are less routinely measured [25, 26, 29]. The TyHGB index uniquely integrates the TG/HDL-C ratio, fasting glucose, and BMI, all of which are

standard components of routine health checkups. Our study provides the first evidence that this integrated index is an independently associated maker for depression, offering a more holistic metabolic assessment. The persistence of the association after comprehensive adjustment for demographics, lifestyle, and comorbidities strengthens the assertion that TyHGB captures metabolic risk beyond established confounders.

The J-shaped relationship between TyHGB and depression, with a threshold at 7.56, suggests two distinct metabolic phases. Below the threshold, no significant risk increase was observed; in fact, a non-significant inverse trend was present. This may reflect a state of metabolic efficiency and preserved insulin sensitivity, where moderate levels of triglycerides, glucose, and BMI do not trigger pathogenic neuroinflammation [30, 31]. Above the threshold, each unit increase in TyHGB was associated with an 8.3% higher odds of depression. This phase likely represents a transition to pathological metabolic overload. Elevated TyHGB reflects a state of insulin resistance, dyslipidemia, and adiposity that promotes chronic low-grade systemic inflammation, characterized by increased IL-6, TNF- α , and CRP[32]. These peripheral inflammatory signals can compromise the blood-brain barrier, activate microglia, and trigger neuroinflammation, which in turn disrupts monoaminergic neurotransmission (serotonin, dopamine) and impairs neuroplasticity – key mechanisms in depression pathogenesis[33, 34]. Additionally, insulin resistance may directly affect central dopamine signaling and reward processing, contributing to anhedonia[35]. The presence of a clear inflection point supports the concept of a “metabolic tipping point” beyond which cumulative burden becomes clinically detrimental.

The positive association between TyHGB and depression was remarkably consistent across all examined subgroups, including gender, age, race, education, BMI, and comorbidities, with no significant interactions. This robustness suggests that the detrimental metabolic signal captured by TyHGB is a pervasive risk factor, transcending specific demographic or clinical characteristics. Our findings align with other large-scale NHANES analyses on the TyG and METS-IR indices, which also reported stable associations across diverse populations[24, 36]. Notably, while some studies have reported a stronger effect in females[37, 38], our interaction test did not support effect modification by gender. This discrepancy may stem from differences in sample composition, adjustment sets, or the specific metabolic construct measured. The observed discrepancy may arise from variations in sample composition, adjustment sets, or the particular metabolic construct assessed. Nonetheless, our finding of a consistent association across both sexes highlights the relevance of metabolic risk for the adult population as a whole.

This study possesses several notable strengths. Firstly, the utilization of a large, nationally representative sample, complemented by appropriate survey weights, ensures a high degree of generalizability to the non-institutionalized adult population in the United States. Secondly, the analytical approach employed was rigorous, incorporating multivariable logistic regression with comprehensive covariate adjustment, the application of restricted cubic splines for testing nonlinearity, and a two-piecewise linear regression model to identify and quantify threshold effects. Lastly, sensitivity analyses using fixed value imputation substantiated the robustness of the findings. Nevertheless, it is imperative to recognize several limitations inherent in this study. The cross-sectional design restricts the ability to draw causal inferences, thereby leaving open the possibility of reverse causality, wherein depression may contribute to poorer metabolic health. Additionally, the potential for residual confounding due to unmeasured variables—such as comprehensive dietary patterns, levels of physical activity, sleep quality, medication usage, and genetic predispositions—cannot be entirely

excluded. Furthermore, fasting insulin levels were not assessed, precluding direct comparison with the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Additionally, we did not distinguish between depression subtypes, such as atypical depression, which is characterized by increased appetite and weight gain and may have stronger metabolic associations. In conclusion, the threshold of 7.56, as determined from this U.S. sample, necessitates validation across diverse populations. Future prospective cohort studies are essential to elucidate the temporal sequence and causal direction of the observed associations. Mendelian randomization could be instrumental in clarifying causal relationships. Critically, interventional studies should investigate whether reducing TyHGB through lifestyle modifications or metabolic pharmacotherapy (such as GLP-1 receptor agonists and SGLT2 inhibitors) can enhance depression outcomes. Additionally, external validation of the 7.56 threshold in non-U.S. cohorts is imperative.

5. Conclusion

This study illustrates that the TyHGB index—a composite metabolic marker that integrates atherogenic dyslipidemia, hyperglycemia, and adiposity—exhibits a significant positive association with depression risk within a nationally representative sample of the U.S. adult population. By utilizing routinely measured clinical parameters such as triglycerides, HDL cholesterol, fasting glucose, and BMI, the TyHGB index may serve as a practical, cost-effective, and clinically feasible tool for identifying individuals at an elevated risk of depression in primary care settings. Although our findings position TyHGB as a novel indicator of depressive symptom risk, randomized controlled trials are necessary to establish causal relationships and to evaluate potential therapeutic interventions.

Declarations

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Authors' contributions

D.S.S.: Conceptualization and Methodology.

J.L.L. and Z.Q.W.: Methodology, Software and Writing-Original draft.

X.Y.C.,H,Z,W.N.W.,Y.B.L.: Methodology, Software, Writing-Reviewing and Editing. All authors: manuscript revision. All authors have reviewed the final manuscript.

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Availability of data and materials

The data used in this study are publicly available from the National Health and Nutrition Examination Survey (NHANES) website (<https://www.cdc.gov/nchs/nhanes/>). No additional data are available beyond what is provided by NHANES.

Ethics approval and consent to participate

The protocols of NHANES were approved by the institutional review board of the NCHS, CDC (<https://www.cdc.gov/nchs/nhanes/irba98.htm>). All participants have provided written informed consent.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Smith K. Mental health: a world of depression. *Nature*. 2014;515(7526):181.
2. McCarron RM, Shapiro B, Rawles J, Luo J. Depression. *Ann Intern Med*. 2021;174(5):ITC65–80.
3. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. *JAMA*. 2017;317(15):1517.
4. Petrak F, Baumeister H, Skinner TC, Brown A, Holt RIG. Depression and diabetes: treatment and health-care delivery. *Lancet Diabetes Endocrinol*. 2015;3(6):472–85.
5. Xu M, Zhang Z, Zhang Z, Liu D, Shang Y, Tang C, Wang W, Li H, You B, Ying H et al. The Pathogenesis and Medical Treatment of Depression: Opportunity and Challenge. *Neurol Int* 2025, 17(8).
6. Wu S, Yin Y, Du L. Blood-Brain Barrier Dysfunction in the Pathogenesis of Major Depressive Disorder. *Cell Mol Neurobiol*. 2022;42(8):2571–91.
7. Fang Y, Wu Z. Advance in Diagnosis of Depressive Disorder. *Adv Exp Med Biol*. 2019;1180:179–91.
8. Shi Y, Wang Q, Song R, Kong Y, Zhang Z. Non-coding RNAs in depression: Promising diagnostic and therapeutic biomarkers. *EBioMedicine*. 2021;71:103569.
9. Yao J, Zhu CQ, Sun Y, Huang YW, Li QH, Liao HM, Deng XJ, Li WM. Insulin resistance: The role in comorbid type 2 diabetes mellitus and depression. *Neurosci Biobehav Rev*. 2025;175:106218.
10. Krupa AJ, Dudek D, Siwek M. Consolidating evidence on the role of insulin resistance in major depressive disorder. *Curr Opin Psychiatry*. 2024;37(1):23–8.
11. Kontogianni A, Yang H, Chen W. Brain insulin resistance and neuropsychiatric symptoms in Alzheimer's disease: A role for dopamine signaling. *Neural Regen Res*. 2026;21(5):1995–6.

12. Li J, Chen S, Xian X, Xian Y. The relationship between depression and insulin resistance in the population without diabetes: Results from the 2005–2016 NHANES. *Psychiatry Res.* 2025;343:116311.
13. Oh DJ, Jeong C, Kim J, Kim ES, Oh KS, Shin YC, Shin DW, Jeon SW, Cho SJ. Insulin resistance and the risk of incident depression: the role of age, glycemic status, and adiposity in a prospective cohort study. *Lancet Reg Health West Pac.* 2025;62:101672.
14. Watson KT, Simard JF, Henderson VW, Nutkiewicz L, Lamers F, Nasca C, Rasgon N, Penninx B. Incident Major Depressive Disorder Predicted by Three Measures of Insulin Resistance: A Dutch Cohort Study. *Am J Psychiatry.* 2021;178(10):914–20.
15. Xu Z, Li C, Wang N, Song G. Association between the new TyG indicator-TyHGB and gestational diabetes mellitus: results from the case-control and prospective cohort studies. *J Transl Med.* 2025;23(1):190.
16. Song S, Zhang Y, Qiao X, Duo Y, Xu J, Peng Z, Zhang J, Chen Y, Nie X, Sun Q, et al. HOMA-IR as a risk factor of gestational diabetes mellitus and a novel simple surrogate index in early pregnancy. *Int J Gynaecol Obstet.* 2022;157(3):694–701.
17. Bai Y, Xi Y, Huang J, Wu K, Yin B, Zhang J. TyHGB as a predictive marker for preeclampsia: association with increased risk in pregnant women with normal glucose tolerance. *Lipids Health Dis* 2026.
18. Zhao E, Wang R, Chen Y, Xie H, Gao Y, Dong B, Zhang C. Evaluation of a new TyG indicator, TyHGB, in predicting non-alcoholic fatty liver disease: evidence from two independent populations. *Lipids Health Dis.* 2025;24(1):342.
19. Lu A, Xu Q. Association between the triglyceride-high-density lipoprotein-glucose-body index and new-onset stroke risk: a prospective cohort study. *Lipids Health Dis* 2026.
20. Wei YG, Cai DB, Liu J, Liu RX, Wang SB, Tang YQ, Zheng W, Wang F. Cholesterol and triglyceride levels in first-episode patients with major depressive disorder: A meta-analysis of case-control studies. *J Affect Disord.* 2020;266:465–72.
21. Wong S, Le GH, Guillen-Burgos HF, Ho R, Cao B, Lo HKY, Teopiz KM, McInyre RS. The association between depressive symptom severity and metabolic disturbances in major depressive and bipolar disorders: A systematic review and meta-analysis. *J Affect Disord* 2026, 395(Pt B):120783.
22. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry.* 2010;67(3):220–9.
23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16(9):606–13.
24. Huang Q, Wang D, Chen S, Tang L, Ma C. Association of METS-IR index with depressive symptoms in US adults: A cross-sectional study. *J Affect Disord.* 2024;355:355–62.
25. Cheng X, Fu S, Hu L, Zhang X, Liu F, Zhang Y, Zhong X, Guo J, Lin J, Wu J et al. Association between the ZJU index and depression in US adults: A cross-sectional NHANES analysis. *J Affect Disord* 2026, 395(Pt A):120747.
26. Sun Z, Bo Y, Sun L, Li Z, Xue M, Zhang C, Zhao Y, Zhuoma C, Yu Z, Han Z, et al. Association of the triglyceride-glucose index with risk of depression and anxiety: A prospective cohort study. *J Affect Disord.* 2025;391:119993.

27. Yuan Q, Wang L, Zhu X, Wu Z, He S, Zhang H, Lin D. Metabolic dysfunction and cognitive impairment in patients with depression: The role of the TyG index and peripheral inflammation. *J Affect Disord.* 2026;397:121026.
28. Zhou Y, Yu J, Qi L, Tan H, Xiao J. Association between triglyceride-glucose index and depression and the mediating role of hypertension: a cross-sectional study of obese adults. *J Affect Disord.* 2026;394(Pt A):120523.
29. Liu K, Zhang JY, Hu YQ, Zhang J. The association between the triglyceride-glucose-a body shape index (TyG-ABSI) and depressive symptoms in US adults: A population-based cross-sectional study. *J Affect Disord.* 2026;397:120916.
30. Ancelin ML, Carriere I, Boulenger JP, Malafosse A, Stewart R, Cristol JP, Ritchie K, Chaudieu I, Dupuy AM. Gender and genotype modulation of the association between lipid levels and depressive symptomatology in community-dwelling elderly (the ESPRIT study). *Biol Psychiatry.* 2010;68(2):125–32.
31. Karampela I, Chrysanthopoulou E, Christodoulatos GS, Dalamaga M. Is There an Obesity Paradox in Critical Illness? Epidemiologic and Metabolic Considerations. *Curr Obes Rep.* 2020;9(3):231–44.
32. Hamed-Shahraki S, Klisic A, Amirkhizi F, Mercantepe F. Association of the triglyceride-glucose index with inflammatory markers and dysregulation of adipokines in patients with metabolic syndrome. *BMC Endocr Disord.* 2026;26(1):44.
33. Jiao W, Lin J, Deng Y, Ji Y, Liang C, Wei S, Jing X, Yan F. The immunological perspective of major depressive disorder: unveiling the interactions between central and peripheral immune mechanisms. *J Neuroinflammation.* 2025;22(1):10.
34. Feng Q, Yuan Z, An Q, Wang K, Liu X. Serum inflammatory cytokines in the progression of depression. *Front Immunol.* 2026;17:1808989.
35. Gruber J, Hanssen R, Qubad M, Bouzouina A, Schack V, Sochor H, Schiweck C, Aichholzer M, Matura S, Slattery DA, et al. Impact of insulin and insulin resistance on brain dopamine signalling and reward processing - An underexplored mechanism in the pathophysiology of depression? *Neurosci Biobehav Rev.* 2023;149:105179.
36. Shi YY, Zheng R, Cai JJ, Qian SZ. The association between triglyceride glucose index and depression: data from NHANES 2005–2018. *BMC Psychiatry.* 2021;21(1):267.
37. Liu PL, Gao S, Zhang Y, Li J, Du J, Dong QL, Liu XR. Associations between the triglyceride-glucose index and its combined indices with sleep disorders and the mediating role of depressive symptoms: Results from two nationally representative population studies. *J Affect Disord.* 2025;386:119480.
38. Zhang L, Sun H, Yin J, Zhang Z, Yang J, Liu Y. Association between triglyceride glucose-body mass index and depression among US adults: A cross-sectional study. *Public Health.* 2024;237:410–7.

Figures

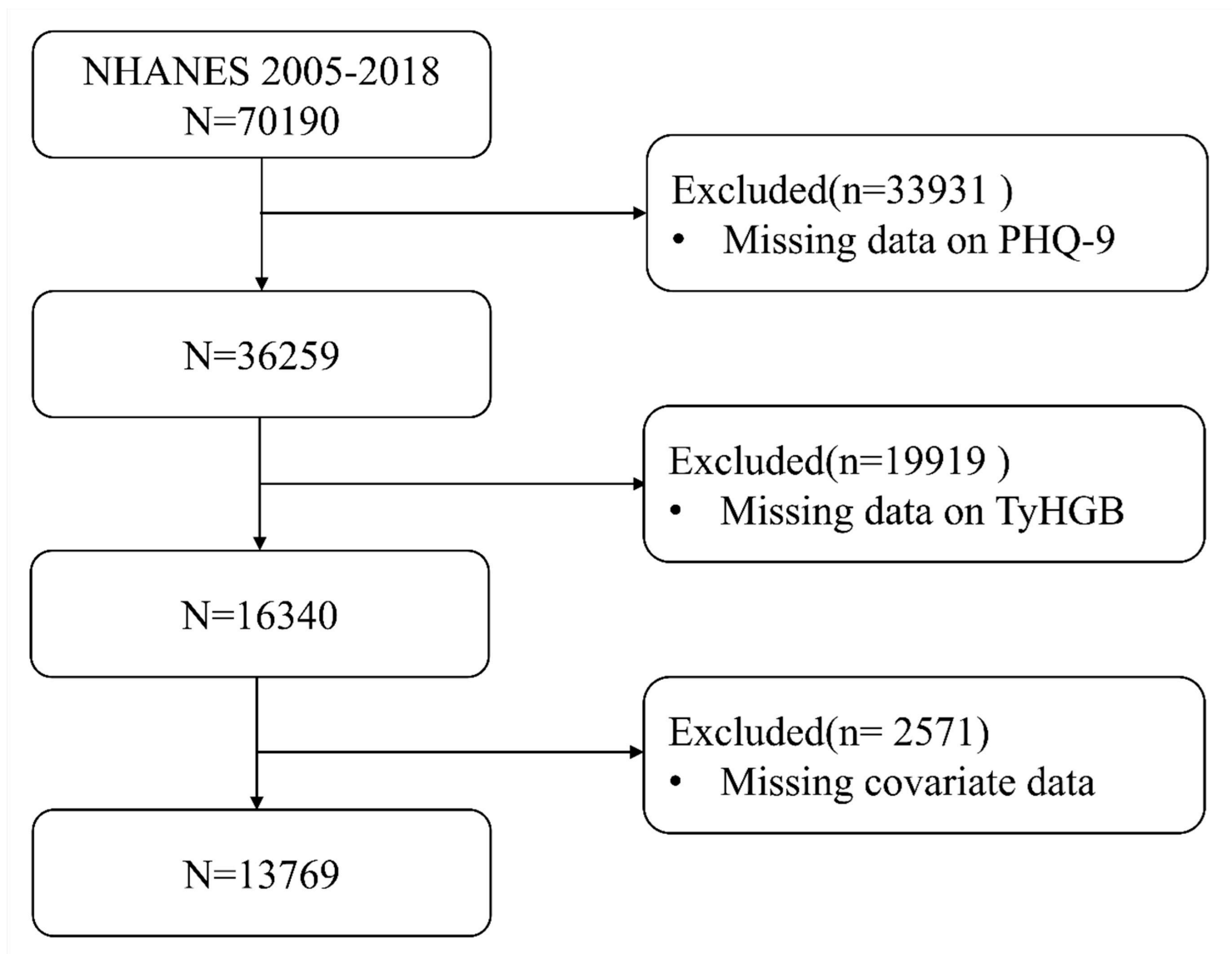


Figure 1

Flow chart of participant selection. Abbreviations: NHANES, National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9; TyHGB, Triglyceride High-density cholesterol-Glucose Body index.

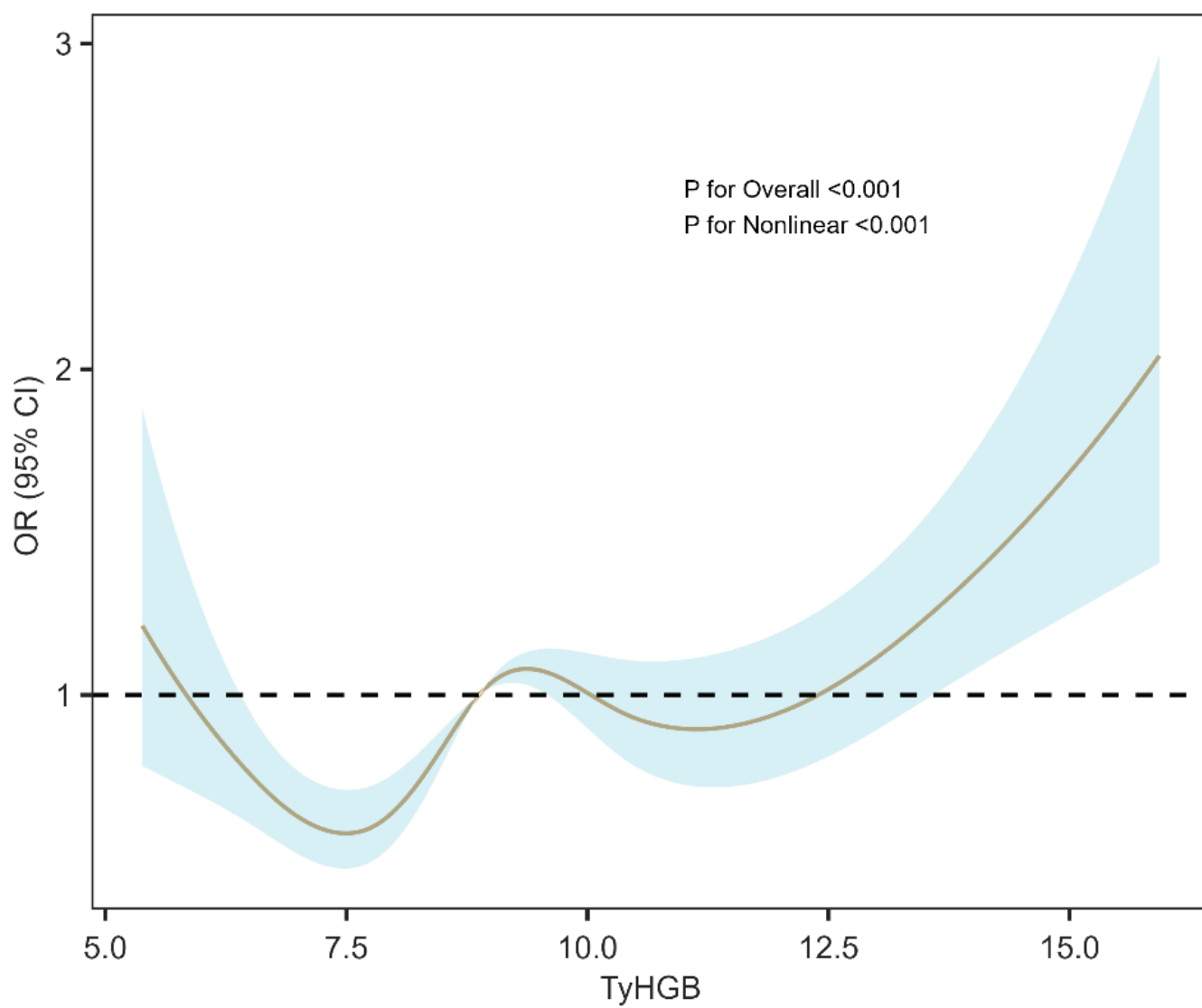


Figure 2

Nonlinear relationship between the TyHGB index and depression results from the restricted cubic spline (RCS) analysis.

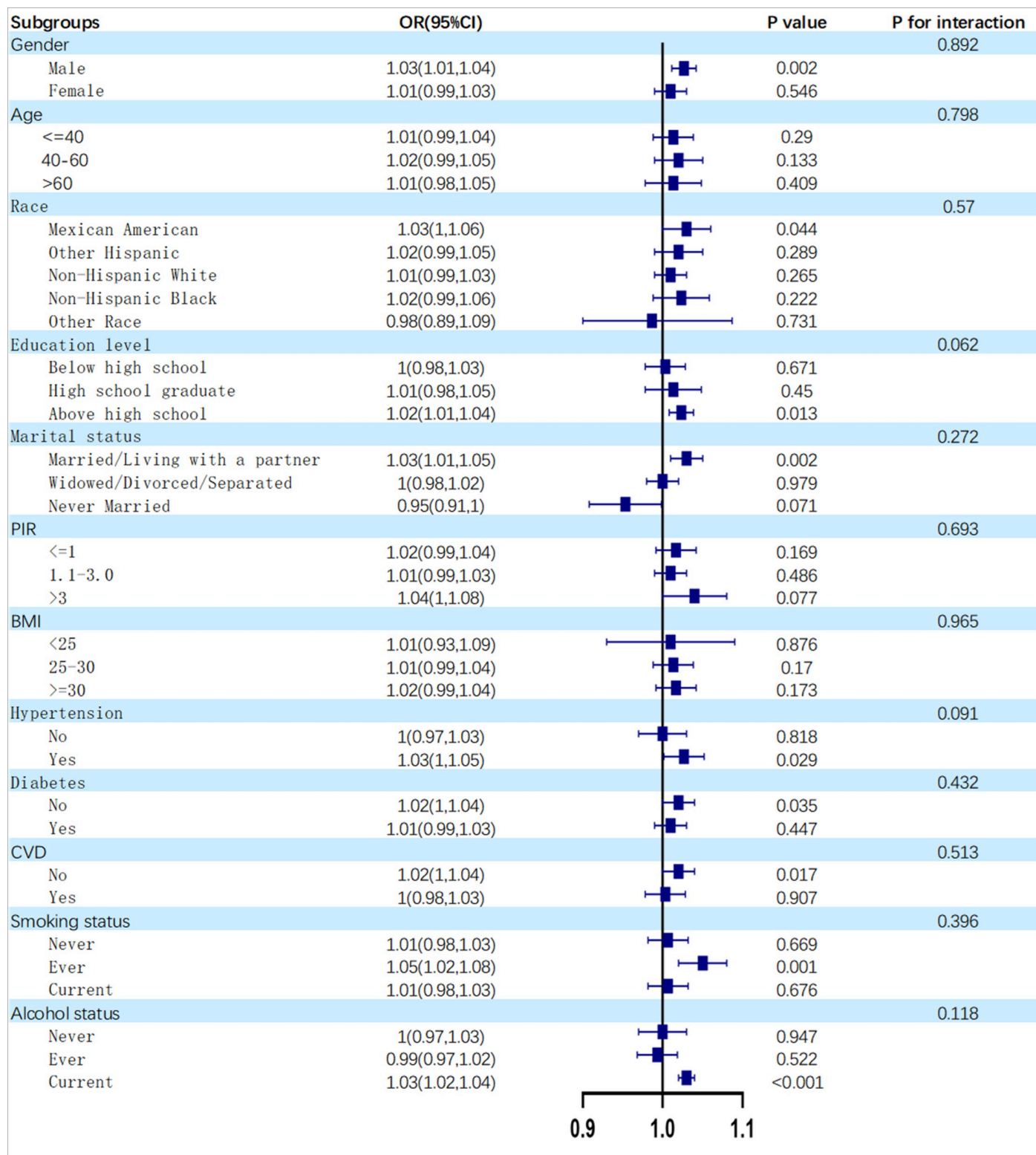


Figure 3

The association between TyHGB index and the risk of depression according to different subgroups.

Supplementary Files

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