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The association between triglyceride-glucose index and its combination with post-stroke depression: NHANES 2005–2018

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Abstract

Background Growing evidence indicates a link between insulin resistance and post-stroke depression (PSD). This study employed the triglyceride glucose (TyG) index as a measure of insulin resistance to investigate its relationship with PSD.

Methods This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (2005–2018). PSD was assessed using data from patient health questionnaires, while the TyG index was calculated based on fasting venous blood glucose and fasting triglyceride levels. The formula used for the TyG index is ln[triglycerides (mg/dL) × fasting blood glucose (mg/dL)/2]. Participants were categorized into four groups according to the TyG index quartiles. A weighted multivariable logistic regression model was applied to examine the relationship between the TyG index and PSD.

Results A total of 1217 patients were included in the study, of which 232 were diagnosed with PSD. The TyG index was divided into quartiles (Q1-Q4) for analysis. After adjusting for potential confounders, we found a significant positive association between the highest quartile of the TyG index (Q4: ≥9.33) and PSD (OR = 2.51, 95% CI: 1.04–6.07, $p = 0.041$). This suggests that in the U.S. adult stroke population, individuals with higher TyG indices are more likely to experience depressive symptoms. Subgroup analysis further confirmed a stable and independent positive association between the TyG index and PSD (all trend $p > 0.05$).

Conclusion In this large cross-sectional study, our results suggest that among US adults who have experienced a stroke, those with higher TyG index levels are more likely to exhibit depressive symptoms. This provides a novel approach for the clinical prevention of PSD. Patients with higher TyG indices in the stroke population may require closer psychological health monitoring and timely intervention. Additionally, since the TyG index is calculated using only fasting blood glucose and triglyceride levels, it can help identify high-risk PSD patients, particularly in regions with limited healthcare resources.

Keywords PSD, Triglyceride glucose index, Insulin resistance, NHANES

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Introduction

Post-stroke depression (PSD) is one of the most prevalent complications following a stroke, marked by high incidence, mortality, and disability rates. A meta-analysis by Hackett et al., which included 51 studies, revealed that the comorbidity rate of PSD is approximately 33% [1]. Jianglong Guo summarized several representative studies and found that the incidence of PSD ranges from 11 to 41% [2]. Overall, about one-third of stroke patients experience depression. In recent years, the number of PSD patients has been gradually increasing due to the sharp rise in the number of stroke patients [1–3]. The occurrence of PSD significantly impacts the daily life and rehabilitation of stroke patients, increasing the burden on their families. Researches indicate that the development of PSD is closely related to various factors, including social factors and individual characteristics [4, 5].

Insulin resistance (IR) refers to the reduced sensitivity of insulin target cells to insulin concentration. It is not only associated with the occurrence of various metabolic-related diseases but also closely linked to the development of cardiovascular and cerebrovascular diseases [6, 7]. A longitudinal analysis of the Netherlands Study of Depression and Anxiety (NESDA) cohort by researchers from Stanford University revealed that individuals with insulin resistance exhibited a two-fold increased risk of developing major depressive disorder (MDD) compared to their insulin-sensitive counterparts. Notably, even among participants without baseline depressive symptoms, those with insulin resistance demonstrated a substantially elevated MDD incidence during follow-up [8]. Fernandes BS and colleagues have proposed that insulin resistance may serve as a biomarker for acute depressive states, with their meta-analysis demonstrating significant associations between IR and depression severity scores [9]. Studies have shown that for each unit increase in the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), the risk of PSD in stroke patients increases accordingly [10, 11]. This confirms the positive correlation between insulin resistance and the risk of PSD, suggesting that insulin resistance is an independent risk factor for PSD. The HOMA-IR is useful for the early prediction and assessment of PSD. However, the calculation of HOMA-IR requires fasting serum insulin, which is not a routine biochemical indicator and is thus limited in clinical application (it is not practical in clinical practice).

The triglyceride-glucose index (TyG index) is also an effective means of assessing insulin resistance [12]. Compared to the HOMA-IR, the TyG index offers distinct advantages in clinical applicability. Its calculation does not require fasting insulin measurements, relying solely on triglycerides and fasting glucose levels, thereby simplifying implementation and reducing costs in routine practice [13]. Furthermore, the TyG index exhibits high sensitivity and specificity for identifying insulin resistance, outperforming HOMA-IR in detecting individuals with reduced insulin sensitivity across diverse populations [14]. Critically, the TyG index demonstrates superior predictive performance for metabolic abnormalities compared to HOMA-IR, with consistent efficacy observed in key subgroups such as older adults and individuals with obesity [15]. To date, no studies have directly indicated a correlation between the TyG index and the risk of PSD. Therefore, our research team used a cross-sectional design based on data from the National Health and Nutrition Examination Survey (NHANES) to evaluate whether there is an association between the TyG index and the risk of PSD. The aim of this study is to provide a potential new method for clinically identifying PSD, which could be used for the early detection of high-risk groups, thereby guiding targeted interventions to mitigate the burden of PSD and improve patient outcomes.

Methods

Database and study population

The cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) database, covering the period from 2005 to 2018. All the data used in this study can be accessed from the official NHANES database website, which was visited on April 1, 2024. NHANES, developed by the Centers for Disease Control and Prevention (CDC), is a national health and nutrition survey program that gathers and analyzes data on various populations and health topics, including demographics, dietary information, laboratory data, and questionnaires. Before participation, all NHANES participants provided written informed consent, and the NHANES ethical protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board. The IRB approval numbers for the NHANES dataset from 2005 to 2018 are as follows: Protocol #2005-06 for the years 2005–2010,Protocol#2011-17for2011–2016,andProtocol#2018-01for2017–2018 (https://www.cdc.gov/nchs/nhanes/about/erb.html#print).

Out of the data collected from NHANES between 2005 and 2018, a total of 70,190 participants completed the interviews, with 39,749 being aged 20 years and above. We excluded participants without a history of stroke ($n = 38,158$), those with missing PHQ-9 scale data ($n = 294$), and those with missing serological data ($n = 80$). As a result, this cross-sectional study included 1,217 participants from NHANES (232 post-stroke depression patients and 985 non-post-stroke depression patients) for analysis. The detailed inclusion and exclusion process is illustrated in Fig. 1.

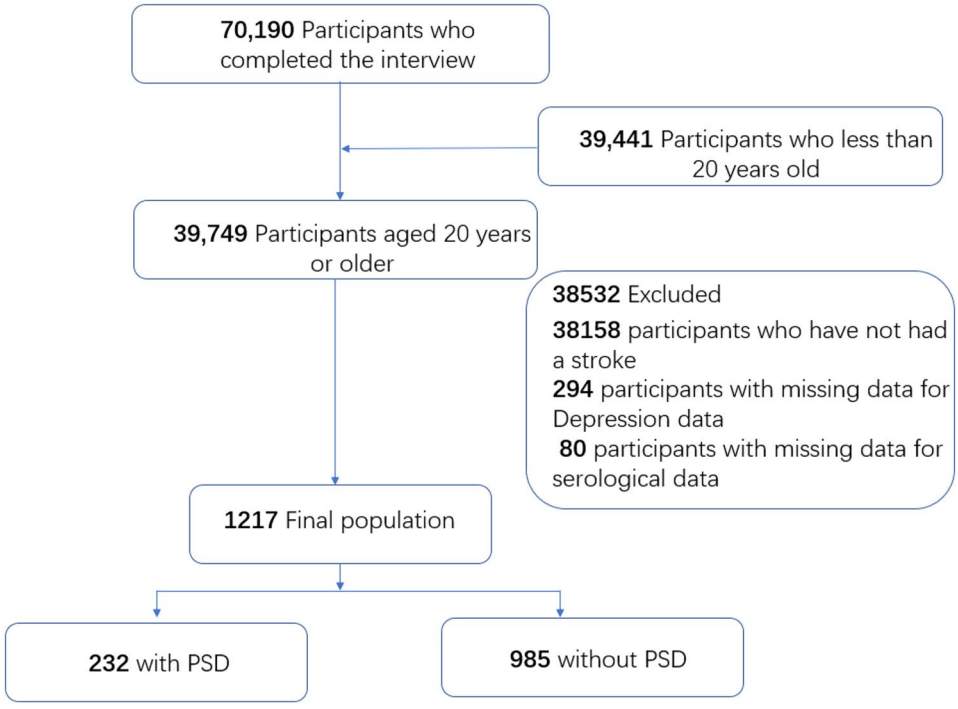

Fig. 1 Flow diagram of participants in the study. *Abbreviations: PSD, post-stroke depression

Exposure and outcomes

Venous blood was taken to measure fasting blood glucose and fasting triglyceride levels to calculate the TyG index. The formula for calculating the TyG index is as follows: TyG = ln [fasting triglycerides (mg/dL) × serum glucose (mg/dL)/2] [16]. Respondents' self-reported medical conditions were used to determine the presence of stroke: "Has a doctor or other health professional ever told you that you had a stroke?" If the participant's answer was "yes," they were classified as having had a stroke. The NHANES Patient Health Questionnaire (PHQ-9) was used to assess depressive status, consisting of 9 items with 4 response options: "not at all," "several days," "more than half the days," and "nearly every day." Each item was scored from 0 to 3, and the total score ranged from 0 to 27. A PHQ-9 score ≥ 10 was considered indicative of depression [17].

Covariates

Based on established or observed reasonable or relevant biological relationships and referencing relevant literature [18, 19], the following variables were selected as covariates for the analysis: age, gender, race, and education level, marital status, body mass index (BMI), smoking status, alcohol consumption, diabetes, coronary heart disease, and cancer. Race was categorized in this study as non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, and other, based on NHANES interviews. Education level was divided into less than 9 years (less than 9th-grade education), 9–12 years (① 9–11 years (including 12th grade without diploma), ② high school graduate/GED or equivalent), and 12 years or more (college graduate or higher, including some college or associate degree). Marital status was categorized as living with a partner (married or living with a partner) or never married or living alone (divorced, widowed, separated). BMI was calculated from standardized weight and height data from the NHANES physical examination. Smoking status was categorized based on whether the participant currently smoked or not. Alcohol consumption was based on daily alcohol intake (cups). The determination of past diseases (diabetes, cancer, and coronary heart disease) was based on responses to whether the participant had been previously diagnosed by a doctor.

Statistical analysis

According to NHANES analysis guidelines, all analyses included sample weights to account for complex survey designs. This study is a secondary analysis of publicly available datasets. Descriptive analysis was conducted on demographic characteristics and biochemical measurements, with participants classified into 4 groups based on TyG index quartiles (Q1<8.40, 8.40 ≤ Q2<8.85, 8.85 ≤ Q3<9.33, Q4 ≥ 9.33). Categorical variables were expressed as proportions (%), and continuous variables were presented as means (standard deviation, SD) or medians (interquartile range, IQR) based on the data distribution. One-way ANOVA (normal distribution),

Kruskal-Wallis test (skewed distribution), and chi-square test (categorical variables) were used to compare differences between groups. Logistic regression models were used to determine the odds ratio (OR) and 95% confidence interval (CI) between the TyG index and post-stroke depression (PSD). Three models were used in this analysis. Model 1 was adjusted for age, gender, race/ethnicity, marital status, education level, and BMI; Model 2 added smoking status and alcohol consumption to Model 1; and Model 3 was fully adjusted, including age, gender, race/ethnicity, marital status, education level, BMI, smoking status, alcohol consumption, diabetes, coronary heart disease, and cancer.

To assess whether there was potential modification in the relationship between the TyG index and PSD, subgroup analysis was conducted, including the following variables: gender, age (20–44 years,45-59years, ≥60 years), race(non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian, and other), education level (<9 years, 9–12 years,>12years), marital status (be married, spinster or living alone), BMI(<25 kg/m^2, ≥25 kg/m^2),smoking status (yes or no), diabetes (yes or no), coronary heart disease (yes or no), and cancer (yes or no). Multivariable logistic regression analysis was used to assess heterogeneity between subgroups, and likelihood ratio tests were conducted to assess the interaction between subgroups and the TyG index.

Since the sample size was determined solely by the provided data, no prior statistical power estimation was conducted. All analyses were performed using SPSS Statistics 26 and R software version 1.9.2. A two-tailed p-value of less than 0.05 was set as the threshold for statistical significance.

Results

Baseline characteristic

Based on the quartiles of the TyG index, the baseline characteristics of the study participants are shown in Table 1. A total of 1217 subjects were included in this study, and the results showed that 232 out of 1217 (19%) adults aged 20 and above had post-stroke depression (PSD). The average age of the study participants was 65.8 ± 13 years, with 615 (50.5%) being female and 602 (49.5%) being male. Compared to the group with the highest TyG index, the group with the lowest TyG index had significantly lower BMI, a higher percentage of non-Hispanic Black individuals, and a lower prevalence of diabetes. In our study, we did not find a significant correlation between the TyG index and gender, age, education level, marital status, smoking and drinking status, or comorbidities (coronary heart disease and cancer) ($p > 0.05$).

The association of TyG with PSD

The univariate analysis showed that age, gender, marital status, BMI, smoking status, alcohol consumption, coronary heart disease, and the TyG index were associated with PSD (Table 2). In the quartiles of the TyG index, the unadjusted OR values for the TyG index (Q1 (< 8.40), Q2 (≥ 8.40 and < 8.85), Q3 (≥ 8.85 and < 9.33), Q4 (≥ 9.33)) and PSD were: 1 (95% CI: 1–1), 0.92 (95% CI: 0.6–1.41, $p = 0.692$), 0.98 (95% CI: 0.64–1.5, $p = 0.913$), and 1.82 (95% CI: 1.23–2.7, $p = 0.003$, $p < 0.05$). After adjusting for all potential confounding factors, a significant positive correlation still existed between the fourth quartile of the TyG index and PSD, with an adjusted OR value of 2.51 (95% CI: 1.04–6.07, $p = 0.041$, $p < 0.05$) (Table 3). Compared to the first quartile of the TyG index, patients in the fourth quartile had a higher risk of developing PSD after multivariate adjustment.

Stratified subgroup analysis

Stratified analysis was conducted in several subgroups to assess the potential effect of the relationship between the TyG index and PSD. After stratification by gender, age, race, education level, marital status, smoking status, diabetes, coronary heart disease, and cancer, no significant interactions were found in any subgroup (Fig. 2).

Discussion

In this cross-sectional study, we utilized data from the NHANES database to evaluate the relationship between the TyG index and the risk of PSD in American adults. To our knowledge, this is the first study to explore the relationship between the TyG index and depression in stroke patients. The aim is to investigate whether the TyG index has practical value in the prevention and treatment of PSD in stroke patients.

Previous studies [20–22] have shown that insulin resistance is closely related to the occurrence of depressive states in the general population, young people, and obese adults. In addition, research has reported [10, 11] that the occurrence of depressive states in stroke patients is also closely related to insulin resistance. Consistent with these findings, our analysis found that in American adults, insulin resistance is associated with a high incidence of PSD. However, our study used the TyG index to represent the degree of insulin resistance, which is more convenient and practical than HOMA-IR.

Furthermore, compared with HOMA-IR, the TyG index demonstrates superior diagnostic performance in assessing insulin resistance (IR). When validated against the hyperinsulinemic-euglycemic clamp technique (the gold standard for IR detection), the TyG index achieves a sensitivity of 96.5% and specificity of 85.0%, with the added advantage of being unaffected by insulin therapy status [14]. Importantly, the TyG index exhibits stronger

Table 1 Characteristics of study participants by TyG index quartile

Characteristic	TyG					
	Total	Q1(<8.40)	Q2([8.40–8.85)	Q3([8.85–9.33)	Q4(≥ 9.33)	*p*-Value
NO.		302	312	296	307	
Sex, n (%)						0.465
Male	602 (49.5)	150 (49.7)	143 (45.8)	154 (52)	155 (50.5)	
Female	615 (50.5)	152 (50.3)	169 (54.2)	142 (48)	152 (49.5)	
Age(yaer), Mean (SD)	65.8 ± 13.0	64.6 ± 14.5	66.9 ± 13.0	65.8 ± 12.7	65.6 ± 11.6	0.184
Race, n (%)						< 0.001
Mexican-American	109 (9.0)	19 (6.3)	22 (7.1)	31 (10.5)	37 (12.1)	
Other Hispanics	70 (5.8)	10 (3.3)	19 (6.1)	17 (5.7)	24 (7.8)	
Non-Hispanic white	632 (51.9)	132 (43.7)	157 (50.3)	173 (58.4)	170 (55.4)	
Non-Hispanic blacks	325 (26.7)	121 (40.1)	90 (28.8)	63 (21.3)	51 (16.6)	
Other races	81 (6.7)	20 (6.6)	24 (7.7)	12 (4.1)	25 (8.1)	
Education level (year), n (%)						0.211
<9	407 (33.4)	94 (31.1)	104 (33.3)	94 (31.8)	115 (37.5)	
9 ~ 12	332 (27.3)	73 (24.2)	85 (27.2)	86 (29.1)	88 (28.7)	
>12	478 (39.3)	135 (44.7)	123 (39.4)	116 (39.2)	104 (33.9)	
Marital status, n (%)						0.552
Live alone	476 (39.1)	125 (41.4)	116 (37.3)	116 (39.2)	119 (38.8)	
Spinster	102 (8.4)	30 (9.9)	30 (9.6)	19 (6.4)	23 (7.5)	
Be married	638 (52.5)	147 (48.7)	165 (53.1)	161 (54.4)	165 (53.7)	
Body mass index (kg/m^2), Mean(SD)	30.1 ± 6.8	27.8 ± 6.3	29.5 ± 6.7	30.8 ± 6.7	32.1 ± 6.7	< 0.001
Alcohol(cup), Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 2.5)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	1.5 (1.0, 3.0)	0.622
Smoking status, n (%)						0.554
No	453 (60.1)	115 (59.9)	114 (58.8)	105 (57.4)	119 (64.3)	
Yes	301 (39.9)	77 (40.1)	80 (41.2)	78 (42.6)	66 (35.7)	
Diabetes, n (%)						< 0.001
No	753 (62.0)	236 (78.1)	219 (70.2)	188 (63.9)	110 (35.8)	
Yes	462 (38.0)	66 (21.9)	93 (29.8)	106 (36.1)	197 (64.2)	
Coronary heart disease, n (%)						0.141
No	983 (82.0)	245 (81.9)	261 (85.3)	242 (82.6)	235 (78.1)	
Yes	216 (18.0)	54 (18.1)	45 (14.7)	51 (17.4)	66 (21.9)	
Cancer, n (%)						0.509
No	952 (78.3)	234 (77.5)	240 (76.9)	229 (77.4)	249 (81.4)	
Yes	264 (21.7)	68 (22.5)	72 (23.1)	67 (22.6)	57 (18.6)	
Glucose(mg/dL), Mean(SD)	116.7 ± 50.8	92.3 ± 14.0	99.7 ± 17.8	111.1 ± 30.1	163.5 ± 76.0	< 0.001
Triglycerides(mg/dL), Mean(SD)	160.1 ± 115.0	71.4 ± 18.0	116.3 ± 24.7	166.2 ± 39.2	285.9 ± 156.4	< 0.001

Mean ± SD for continuous variables: P value was calculated by logistic regression model; % for Categorical variables: P value was calculated by chi-square test

predictive value than HOMA-IR for both cardiovascular diseases (CVD) and metabolic disorders. It shows more robust associations with atherosclerosis, myocardial infarction, and stroke events, while maintaining consistent predictive stability across diverse socioeconomic populations [23].The TyG index also outperforms HOMA-IR in identifying metabolic abnormalities in heterogeneous demographic subgroups, including older adults and individuals with obesity [15]. Our research confirmed that the TyG index may have potential clinical relevance in identifying the risk of depression in stroke patients, independent of established predictive factors.

The specific mechanism of the relationship between the TyG index and PSD is still unclear, but there are several possible explanations. Firstly, the TyG index is often used to represent the degree of insulin resistance. Currently, inflammation is considered to be the main pathophysiological link between PSD and type 2 diabetes [24]. Both diseases are characterized by increased pro-inflammatory cytokines, C-reactive protein (CRP), and insulin receptor resistance. Previous studies [24–26] have shown that elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a) are associated with the occurrence of PSD. Wang L [24] found that the levels of TNF-α and IL6 in post-stroke depression patients were significantly higher than in the stroke group. It was found that higher serum IL-6 levels were directly related to the worsening of PSD's physical manifestations [25], and the increase in TNF-α levels in the serum of PSD patients was positively correlated with

Table 2 Logistic univariate analysis

Variable	OR_95CI	P_value
Sex, n (%)		
Male	1 (reference)	
Female	1.5 (1.12 ~ 2)	0.006
Age(year),	0.96 (0.95 ~ 0.97)	< 0.001
Race, n (%)		
Mexican American	1 (reference)	
Other Hispanics	0.82 (0.38 ~ 1.78)	0.613
Non-Hispanic white	0.93 (0.56 ~ 1.54)	0.77
Non-Hispanic blacks	0.91 (0.53 ~ 1.57)	0.745
Other races	1.05 (0.52 ~ 2.14)	0.892
Education level (year), n (%)		
<9	1 (reference)	
9 ~ 12	0.9 (0.63 ~ 1.3)	0.588
>12	0.8 (0.57 ~ 1.11)	0.184
Marital status, n (%)		
Live alone	1 (reference)	
Spinster	2.03 (1.27 ~ 3.25)	0.003
Be married	0.78 (0.57 ~ 1.07)	0.119
Body mass index (kg/m2),	1.03 (1.01 ~ 1.05)	0.009
Diabetes, n (%)	1 (0.75 ~ 1.35)	0.98
Coronary heart disease, n (%)	1.7 (1.21 ~ 2.4)	0.002
Cancer, n (%)	1.22 (0.87 ~ 1.71)	0.241
Smoking status, n (%)	2.37 (1.66 ~ 3.39)	< 0.001
Alcohol(cup), Median (IQR)	1.12 (1.03 ~ 1.22)	0.011
TyG	1 (1 ~ 1)	0.003

the severity of depression [26], highlighting the potential role of the inflammatory response in the pathophysiology of PSD. These inflammatory factors can affect the synthesis and release of neurotransmitters, disrupt the synaptic activity of neurons, affect emotional regulation, and increase the risk of depression [27, 28].

Hotamisligil and others [29] observed that the pro-inflammatory cytokine TNFα was elevated in the adipose tissue of obese rodents, and inhibiting this cytokine could improve glucose tolerance and insulin sensitivity. This was the first demonstration that the pro-inflammatory cytokine TNF-α could induce insulin resistance. Studies [30, 31] have shown that macrophages secrete many different cytokines, such as TNFα and IL-1b, which can act on insulin target cells (i.e., hepatocytes, cardiomyocytes, and adipocytes) through a paracrine mechanism, directly inhibiting the action of insulin. These tissue cytokines may also block the conduction of insulin in the normal pathway by activating the inflammatory pathway, leading to insulin resistance [32]. Therefore, Leonard [27] and others proposed that chronic inflammation can lead to an increase in pro-inflammatory cytokines and insulin resistance, affecting the synthesis and release of neurotransmitters, thereby affecting emotional regulation and leading to the occurrence of emotional disorders. In addition, studies have pointed out that there is a strong correlation between the TyG index and WBC count/hs-CRP levels, indicating that the inflammatory response may be an important reason for the association between the TyG index and PSD [33].

Secondly, a possible common point between insulin resistance and PSD is chronic oxidative stress. Insulin plays an important role in the central nervous system (CNS), and both peripheral insulin and insulin produced in the brain can act through insulin receptors present in the brain, participating in neuroprotection, regulating neuronal survival, regulating synaptic plasticity, improving memory and cognitive functions, and other physiological activities [34, 35]. Related studies have shown that there is a strong correlation between the state of oxidative stress in the body and insulin resistance, which may be related to the insulin receptor signaling pathway [36]. According to literature reports, under conditions of insulin resistance, there is disorder of enzymatic and non-enzymatic antioxidants in serum/plasma, as well as in liver, adipose tissue, and brain tissue, and the level of reactive oxygen species (ROS) is increased [37–40]. Maciejczyk [38] and others found in their study that the content of oxidative stress biomarkers and the activity of pro-oxidant enzymes in the cerebral cortex and hypothalamic regions of IR rats were significantly higher than in the control group. Interestingly, they also observed a positive correlation between brain oxidative damage and the HOMA-IR (homeostasis model assessment of insulin

Table 3 Association between TyG and post-stroke depression

Quartiles		OR_95CI							
	NO.	Crude OR_95CI	*p*-Value	Model 1	*p*-Value	Model 2	*p*-Value	Model 3	*p*-Value
TyG									
Q1(<8.40)	302	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2([8.40–8.85)	312	0.92 (0.6 ~ 1.41)	0.692	1.04 (0.65 ~ 1.65)	0.871	0.47 (0.2 ~ 1.13)	0.092	0.45 (0.18 ~ 1.12)	0.086
Q3([8.85–9.33)	296	0.98 (0.64 ~ 1.5)	0.913	1.15 (0.72 ~ 1.83)	0.563	1.14 (0.52 ~ 2.47)	0.748	1.23 (0.54 ~ 2.8)	0.621
Q4(≥ 9.33)	307	1.82 (1.23 ~ 2.7)	0.003	2.07 (1.32 ~ 3.26)	0.002	2.16 (1.01 ~ 4.65)	0.048	2.51 (1.04 ~ 6.07)	0.041
Trend test	1217	1.23 (1.08 ~ 1.4)	0.002	1.28 (1.1 ~ 1.48)	0.001	1.38 (1.07 ~ 1.78)	0.014	1.44 (1.08 ~ 1.93)	0.014

*Model 1: age, sex, race, education level, and marital status were adjusted

Model 2: age, sex, race, education level, marital status, BMI, current smoking, and alcohol use were adjusted

Model 3: All covariates were adjusted

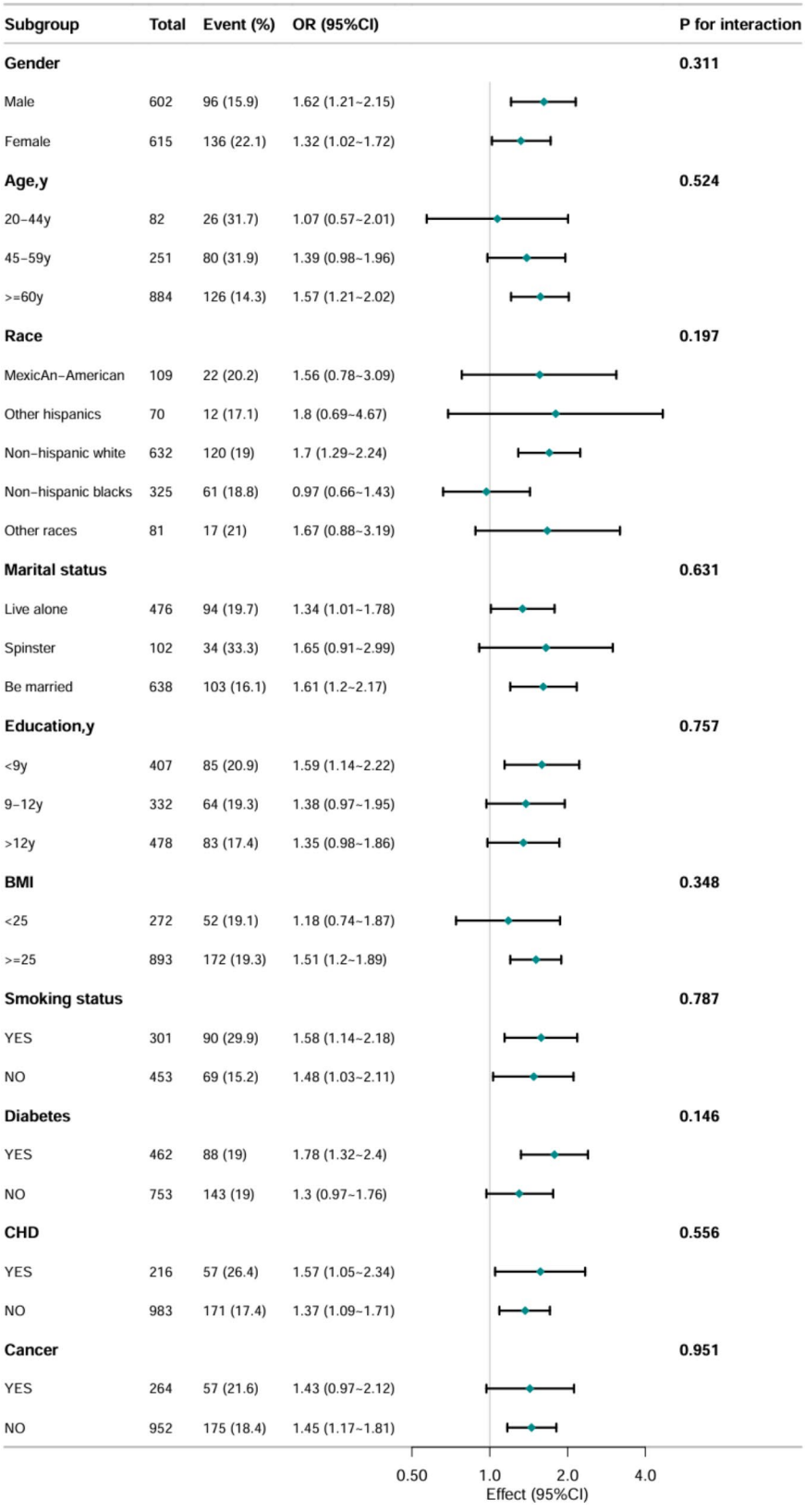

Fig. 2 Subgroup analysis

resistance) index, once again demonstrating that IR is involved in the development of brain oxidative stress.

Of all the organs in the body, the brain is particularly sensitive to attacks by free radicals and is easily affected by oxidative stress [38]. Therefore, it is not surprising that excessive production of ROS under IR conditions causes related brain oxidative damage. Recent studies [10, 39, 41] have shown that peripheral IR leads to brain dysfunction, which is closely related to the occurrence and development of various neurological diseases, such as cognitive impairment, depression, and Alzheimer's disease. Previous studies [38, 42] have shown that oxidative stress plays an important role in the pathophysiology of PSD. Animal experiments have confirmed that the SOD activity of hippocampal tissue in the PSD group is significantly higher than in the control group [43]. In one study [44], the SOD content was compared between the PSD group and the non-PSD group two weeks later, and it was found that although there was no statistical difference between the groups, the SOD in the PSD group showed a trend of increase at the prediction of 2 weeks, which also shows the role of oxidative stress in the occurrence and development of PSD. Liuzhihua [42] and colleagues found in their research that there is a positive correlation between the level of malondialdehyde (MDA), one of the oxidative stress biomarkers in the serum of stroke patients, and the HAMD score. They pointed out that an elevated MDA level (≥ 2.898 nmol/ml) can serve as an independent predictive indicator for post-stroke depression (PSD).

Thirdly, the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis may be one of the common mechanisms contributing to insulin resistance and the development of PSD. The occurrence of stroke triggers a series of complex events in the neuroendocrine system, including neuronal damage, leading to changes in the HPA axis [45]. Whether the dysfunction of the hypothalamic axis leads to PSD or is a consequence of PSD remains controversial. However, it is undeniable that the HPA axis is involved in the pathophysiological processes of PSD and depression. In patients with PSD and depression, overactivity of the hypothalamic-pituitary-adrenal (HPA) axis can be observed, including pituitary enlargement [46], blunted cortisol awakening response [47], and elevated levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids (GC) [46, 48–50]. This suggests that hyperactivity of the HPA axis is one of the pathogenic mechanisms of PSD and depression. Previous studies have shown a correlation between hyperactivity of the HPA axis and insulin resistance syndrome [51]. Hyperactivity of the HPA axis can lead to elevated levels of cortisol in the blood, and studies have shown that hypercortisolemia is closely related to the development of insulin resistance [52], and can induce peripheral insulin resistance [53]. Yokoyama K and others [54] found in their research that the HPA axis index (plasma cortisol concentration and cortisol peak) of elderly patients with depression is related to HOMA-IR (homeostasis model assessment of insulin resistance), and proposed that cortisol-induced insulin resistance is caused by a reduction in insulin sensitivity in the liver and extrahepatic tissues, further confirming the correlation between the HPA axis and insulin resistance.

In addition, a higher TyG index not only indicates insulin resistance but also suggests poor health status, which is related to cardiovascular diseases, obesity, diabetes, hypertension, atherosclerosis, etc [33, 55–57]. These disease states may also lead to elevated levels of triglycerides and blood glucose. Therefore, in model 1 corrected for age, gender, race, and education level, the association between a high TyG index and a higher prevalence of PSD is strongest. After adjusting for baseline comorbidities and smoking and drinking history, the association is somewhat reduced.

In this study, we acknowledge the potential for selection bias, but we have established three models by adjusting different variables. Despite certain flaws in sample selection, our conclusions remain reliable. This study lays a foundation for future multicenter cohort studies on PSD and TyG. However, this study also encountered some limitations. Firstly, it is unclear whether insulin resistance is involved in the development of PSD or is just a pathological response in the development of PSD. Due to the limitations of cross-sectional studies, this study cannot establish a causal relationship. Secondly, the database used in this study, NHANES, is a domestic database in the United States, so these results are mainly applicable to the United States, and it is unknown whether they have the same value in other regions. Thirdly, the database used only includes one-time participants who self-reported whether they had experienced depressive symptoms for at least two weeks in the previous year using the PHQ-9. As a self-reported scale, it may be influenced by cognitive impairments, fatigue, or somatic symptoms common after stroke, potentially inflating scores unrelated to mood (e.g., sleep disturbances attributed to neurological injury rather than depression).In addition, PSD can be classified into mild, moderate, and severe according to the severity of symptoms, and it is unknown whether the relationship with the TyG index varies.

Utilizing data from the National Health and Nutrition Examination Survey (NHANES), our findings provide novel perspectives for clinical prevention of post-stroke depression (PSD). These results highlight the importance of close monitoring of mental health status in stroke patients with elevated triglyceride-glucose (TyG) indices

by healthcare providers. Systematic assessment of TyG index in stroke populations may enable early identification of individuals at heightened risk for depression, thereby enhancing the potential for timely detection of PSD through routine clinical evaluations and guiding personalized care strategies to mitigate disease burden. The simplicity and efficiency of TyG index measurement render it particularly valuable for screening high-risk PSD patients in resource-limited clinical settings. Since the causal relationship between the TyG index and PSD remains unclear, further in-depth prospective cohort studies are necessary to confirm these findings. Additionally, comprehensive longitudinal studies should be conducted to explore and investigate the underlying biological mechanisms. As part of future research plans, we recommend integrating PHQ-9 screening with multidisciplinary clinical evaluations to improve diagnostic accuracy, particularly in distinguishing PSD from stroke-related symptom overlap. Furthermore, merging NHANES-derived insights with real-world clinical data will be critical to evaluate the practical utility of TyG index in PSD prevention and diagnostic applications within routine clinical practice.

Conclusion

In this large cross-sectional study, our results suggest that among US adults who have experienced a stroke, those with higher TyG index levels are more likely to exhibit depressive symptoms. This provides a novel approach for the clinical prevention of PSD. Patients with higher TyG indices in the stroke population may require closer psychological health monitoring and timely intervention. Additionally, since the TyG index is calculated using only fasting blood glucose and triglyceride levels, it can help identify high-risk PSD patients, particularly in regions with limited healthcare resources.

Supplementary Information

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Supplementary Material 1

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Author contributions
F.J.L wrote the main manuscript text and statistics of the data, B.H.Y was responsible for reviewing and revising it, and X.Q.S and X.C prepared Figs. 1 and 2. All authors reviewed the manuscript.

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Data availability
All the data used in this study can be accessed from the official NHANES database website, which was visited on April 1, 2024. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes/AnalyticGuidelines.aspx.

Declarations

Ethics approval and consent to participate
Before participation, all NHANES participants provided written informed consent, and the NHANES ethical protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board. US Department of Health & Human Services. Office of Extramural Research. Available online: http://grants.nih.gov/grants/policy/hs/hs_policies.htm (accessed on 2024.04.01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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