Clinical Interventions in Aging

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Four Non-Insulin-Based Insulin Resistance Indices and the Risk of Post-Stroke Depression

Ping Wang*, Mengchao Wang*, Zhe Xie*, Zhongwen Zhi, Yuqian Wang, Fan Liu, Yufeng Liu, Liandong Zhao

Department of Neurology, the Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yufeng Liu; Liandong Zhao, Department of Neurology, The Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, Jiangsu, People's Republic of China, Email lyf996226@163.com; zld202109@163.com

Purpose: Research suggests that insulin resistance (IR) is associated with acute ischemic stroke (AIS) and depression. The use of insulin-based IR assessments is complicated. Therefore, we explored the relationship between four non-insulin-based IR indices and post-stroke depression (PSD).

Patients and Methods: A total of 638 consecutive AIS patients were enrolled in this prospective cohort study. Clinical data were collected to compute indices such as the triglyceride glucose (TyG) index, triglyceride glucose-body mass index (TyG-BMI), insulin resistance metabolic score (METS-IR), and triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C). One month post-stroke, neuropsychological assessments were conducted using the 17-item Hamilton Depression Scale. Binary logistic regression analysis was performed to explore the relationship between the four non-insulin-based IR indices and PSD.

Results: Ultimately, 381 patients completed the 1-month follow-up, including 112 (29.4%) with PSD. The PSD group exhibited significantly higher levels of the four IR indices compared to the non-PSD group. Logistic regression analysis demonstrated that these indicators were independently associated with PSD occurrence, both before and after adjusting for potential confounders (all $P < 0.001$). Tertile analyses indicated that the highest tertile group had a greater risk of PSD occurrence than the lowest tertile group for four IR indicators, even after adjusting for potential confounders (all $P < 0.05$). Restricted cubic spline analysis revealed a linear dose-response relationship between the four IR indices and PSD. In the subgroup analysis, only the TyG index showed a significant interaction with diabetes (P for interaction = 0.014). The area under curve values for the TyG index, TyG-BMI, METS-IR, and TG/HDL-C were 0.700, 0.721, 0.711, and 0.690, respectively.

Conclusion: High TyG index, TyG-BMI, METS-IR, and TG/HDL-C at baseline were independent risk factors for PSD in AIS. Each of these indicators exhibits predictive value for PSD occurrence, aiding in the early identification of high-risk groups.

Keywords: acute ischemic stroke, post-stroke depression, insulin resistance, non-insulin-based insulin resistance indices

Introduction

Stroke is the leading global cause of death and disability in adults.[1] Post-stroke depression (PSD), a mood disorder linked to stroke events, affects approximately one-third of stroke survivors.[2] PSD is strongly associated with poor stroke prognosis. It prolongs hospitalization, impairs recovery of neurological function, reduces quality of life, and increases mortality. Therefore, it is clinically important to promptly identify, diagnose accurately, and treat depressive symptoms in stroke patients.

The pathogenesis of PSD is complex and potentially linked to biological, sociological, and psychological factors, including monoamine neurotransmitter imbalances, inflammatory responses, hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis disorders, neural network dysfunctions, daily living abilities, and social support.[3] Recent research indicates that insulin resistance (IR) is associated with neuropsychiatric disorders, including stroke,

Received: 17 October 2024
Accepted: 30 December 2024
Published: 9 January 2025

Alzheimer's disease, and depression.[4–6] Studies have recently shown a potential link between PSD and IR in patients with acute ischemic stroke (AIS). Furthermore, homeostasis model assessment of IR (HOMA-IR) is independently associated with PSD occurrence.[7,8] IR is typically defined as a reduced cellular response to insulin and decreased physiological effects of insulin in both peripheral tissues and the brain.[9] A growing body of research suggests that IR is linked to an increased risk of early neurological deterioration in AIS patients.[10] In a study with 3808 non-diabetic ischemic stroke patients, IR was associated with stroke recurrence[11] and linked to key mechanisms of brain damage in ischemic stroke, including inflammation, oxidative stress, and neuronal damage.[4] Insulin is secreted by the pancreas, travels through the bloodstream to reach the central nervous system, and crosses the blood-brain barrier via a saturable transport system.[12] Insulin functions as a crucial neuropeptide in the central nervous system, essential for neurotrophic, neuromodulatory, and neuroprotective processes, as well as cognitive functions.[13] Its biological effects are primarily mediated through the mitogen-activated protein kinase and phosphatidylinositol 3-kinase pathways.[14] Abnormalities in these pathways lead to IR in the brain,[15] potentially causing adverse effects like cognitive and mood disorders, alongside symptoms of anhedonia.[16] Anhedonia, a core symptom of major depression, is shown to be predicted by IR, which is also linked to a lack of response to selective serotonin and norepinephrine reuptake inhibitors.[17,18] IR in the dopamine pathway exacerbates depressive symptoms and anhedonia; conversely, glucagon-like peptide-1 receptor agonists may normalize IR, potentially modulating dopaminergic signaling to alleviate anhedonia.[19,20] This evidence suggests that IR correlates with depressive symptoms and affects medication efficacy. Potential mechanisms involve the regulation of neurotrophic factors, neurotransmitter secretion, synaptic plasticity, and the gut microbiota.[21] The high insulin-normal glucose clamp technique is the current gold standard for assessing IR; however, its clinical application is limited by its complexity and cost. As HOMA-IR is an insulin-based surrogate index, measuring serum insulin levels in the clinical setting can result in discrepancies due to measurement accuracy. Conversely, the non-insulin-based triglyceride glucose (TyG) index is more suitable for clinical use and has shown superior predictive ability for IR compared to HOMA-IR.[22,23] Additionally, the triglyceride glucose-body mass index (TyG-BMI),[24] insulin resistance metabolic score (METS-IR),[25] and triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C)[26] are methods for clinicians to assess IR.

Numerous studies demonstrate a strong correlation between the four non-insulin-based IR indices and stroke occurrence, progression, and prognosis, along with their association with depression. Nevertheless, the link between the four non-insulin-based IR indices and PSD remains undefined. This study investigates the relationship between the four non-insulin-based IR indices and depressive symptoms one month post-stroke in patients with AIS via a prospective cohort study, aiming to establish a basis for early PSD diagnosis and treatment.

Materials and Methods

Study Design and Population

This prospective study enrolled 638 patients with AIS who were hospitalized in the Department of Neurology, Affiliated Huai'an Hospital of Xuzhou Medical University, from November 2023 to August 2024. The study adhered to the Declaration of Helsinki and received approval from the Ethics Committee of Affiliated Huai'an Hospital of Xuzhou Medical University, with ethical approval number HEYLL202318. Informed consent was obtained from all participants or their immediate family members.

Inclusion criteria include age 18 to 80 years; admission within 7 days of stroke onset; confirmed diagnosis of ischemic stroke; all relevant examinations and clinical data completed; patients or their immediate family members consented to participate in the study by signing the informed consent form.

Exclusion criteria include transient ischemic attack or cerebral hemorrhage; impaired consciousness or severe cognitive dysfunction, aphasia, and dysarthria, which prevented them from taking relevant assessments; prior history of depression or other mental disorders before stroke, or usage of antidepressants, mood stabilizers, or antipsychotics two weeks before enrollment; history of other central nervous system disorders: Parkinson's disease, hydrocephalus, or trauma, and so on; comorbid serious physical illnesses: severe hepatic or renal insufficiency, severe infections, malignant tumors, blood disorders, autoimmune disorders; and major surgery history within the last 3 months.

Data Collection

Clinical data included demographic data: age, sex, body mass index (BMI) based on height and weight, education level (no formal education, primary school, or middle school and above), marital status (married or other), and hospitalization days; vascular risk factors: systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking, drinking, hypertension, diabetes, coronary artery disease, atrial fibrillation, and history of stroke; etiology and location: stroke etiologic subtypes (large-artery atherosclerosis, cardioembolic, small-vessel disease, and other or unknown cause) and lesion location (left/right side, brainstem, cerebellum, and other); laboratory investigations: venous blood was collected from all patients within 24 hours of admission to the hospital, and leukocytes, hemoglobin, fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin (ALB), and serum creatinine (Scr) were recorded.

Non-insulin-based IR indices and BMI formulae: TyG index = ln [TG (mg/dl) × FPG (mg/dl)/2];[22] BMI (kg/m^2) = body weight (kg) / height squared (m^2); TyG-BMI = TyG × BMI (kg/m^2);[27] METS-IR = Ln [(2 × FPG (mg/dl)) + TG (mg/dl)] × BMI (kg/m^2) ÷ Ln [HDL-C (mg/dl)];[25] HG/HDL-C = TG (mg/dl) / HDL-C (mg/dl).[26] Unit conversions: TG: 1 mg/dl = 0.011 mmol/L; FPG: 1 mg/dl = 0.056 mmol/L; HDL-C: 1 mg/dl = 0.026 mmol/L.

Assessment of Neurobehavioral and Psychological Scales

Stroke severity was evaluated upon admission by two neurologists using the National Institutes of Health Stroke Scale (NIHSS). Prior to discharge, the Barthel Index (BI) assessed patients' functional independence, while the modified Rankin Scale (mRS) evaluated their functional outcomes. Patients were followed up one month post-stroke onset, and their mental health status was assessed using the 17-item Hamilton Depression Scale (HAMD-17)[28] by a trained neurologist. The examiners were double-blinded during the analysis of results. PSD diagnosis conformed to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), with a HAMD-17 scale > 7.

Statistical Analysis

Data conforming to normal distribution were expressed as mean ± standard deviation (SD), and two independent sample t tests were used for inter-group comparison. Median and quartile [M (P25-P75)] descriptions were used for non-normal distribution data, and a non-parametric rank sum test (Mann–Whitney *U*-test) was used for inter-group comparison. Count data were represented as frequency and percentage (n, %), with the Pearson Chi-square test applied for group comparisons. Subjects in this study were stratified into tertiles based on sample size and continuous non-insulin-based IR indices (TyG index, TyG-BMI, METS-IR, and TG/HDL-C): TyG index: T1 (<8.506, n = 127), T2 (8.506–9.034, n = 126), T3 (≥9.034, n = 128); TyG-BMI: B1 (<204.154, n = 127), B2 (204.154–236.892, n = 127), B3 (≥236.892, n = 127); METS-IR: M1 (< 35.965, n = 127), M2 (35.965–41.140, n = 126), M3 (≥ 41.140, n = 128); TG/HDL-C: G1 (< 2.182, n = 126), G2 (2.182–3.746, n = 128), G3 (≥ 3.746, n = 127). In the binary logistic regression model, variables with $P < 0.05$ in the univariate logistic regression were adjusted to assess the four non-insulin IR indices in relation to PSD. We calculated odds ratios (OR), 95% confidence intervals (CI), P-values, and P-values for trend. Restricted cubic splines (RCS) were used within the logistic regression model to explore the dose-response relationship between the four non-insulin-based IR indices and PSD, fitting four restricted cubic spline functions with 4 knots (at the 5th, 35th, 65th, and 95th percentiles). The receiver operating characteristic (ROC) curve assessed the predictive value of the four non-insulin-based IR indices for predicting PSD occurrence. The area under curve (AUC), sensitivity, and specificity were calculated. The optimal threshold was determined using the Youden index. The DeLong test verifies the difference in the AUC of the four IR indices. Furthermore, participants were categorized into subgroups by sex, age (<65 years and ≥65 years), hypertension, and diabetes to assess the relationship between the four non-insulin-based IR indices and PSD across these subgroups. The likelihood ratio test of models with interaction terms was used to calculate the interaction between four non-insulin-based IR indices and potential effect modifiers.

SPSS 25.0 (IBM Corporation, IL, USA), MedCalc 22.0 (MedCalc Software LTD., Ostend, Belgium), and R Programming Language 4.4.1 (Vienna, Austria) were used for all study data analysis and image processing. All P values were two-tailed, and statistical significance was defined by the P value < 0.05.

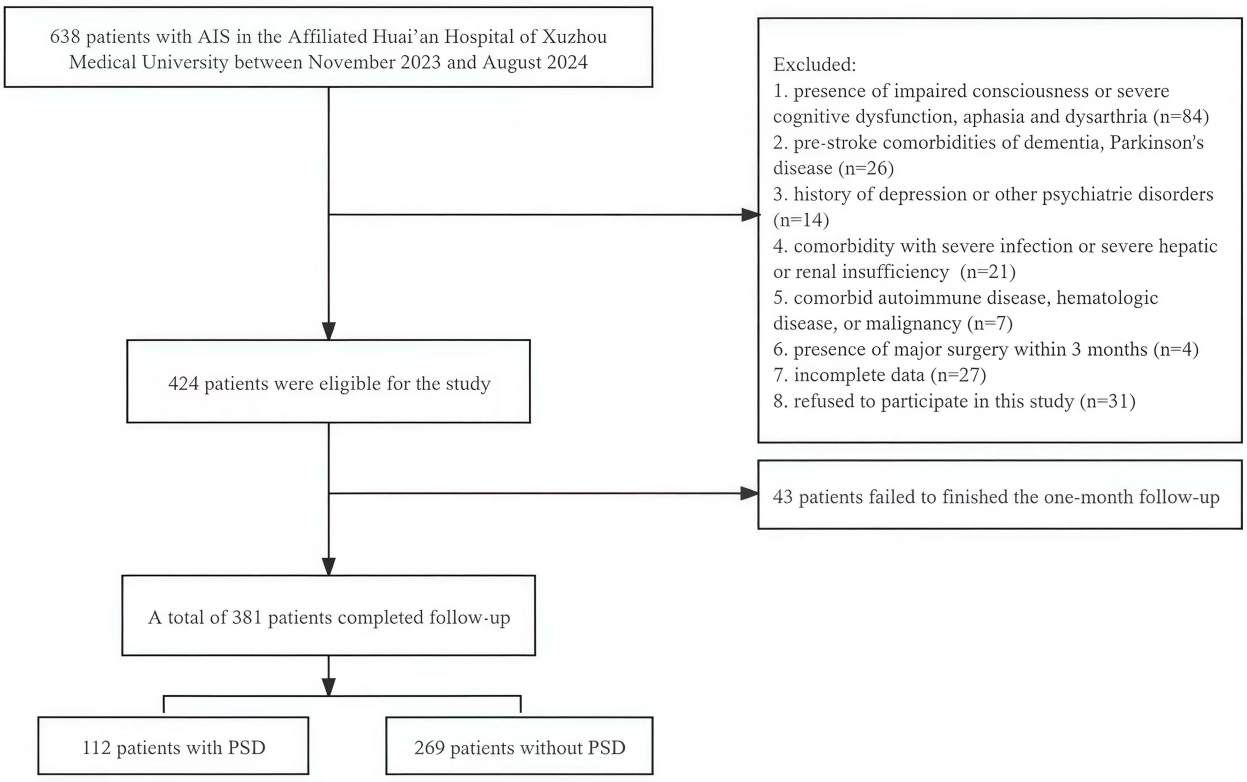

Figure 1 Patient flowchart. AIS, acute ischemic stroke; PSD, post-stroke depression.

Results

Flowchart

Initially, 638 patients with AIS were screened at the Department of Neurology, Affiliated Huai'an Hospital of Xuzhou Medical University, during the baseline period. Of these, 424 patients met the study's eligibility criteria. After one month of follow-up, 43 patients were lost to follow-up. Consequently, 381 AIS patients completed the follow-up and were included in the statistical analysis (Figure 1). After one month, 112 patients (29.4%) developed PSD.

Baseline Characteristics of Patients in the PSD and Non-PSD Groups

The median age of all patients was 65 (interquartile range, 56–71), with 162 (42.5%) being female. As shown in Table 1, patients in the PSD group were more frequently female and exhibited higher BMI, SBP, FPG, HbA1c, and TG levels,

Table 1 Comparison of Baseline Data Between PSD Group and Non-PSD Group

Variables	ALL (n=381)	PSD (n=112)	Non-PSD (n=269)	P value
Demographic data				
Female, n (%)	162 (42.5)	57 (50.9)	105 (39.0)	0.033
Age, years	65 (56,71)	64 (55,71)	65 (58,71)	0.450
BMI, kg/m^2	24.98 (22.49,26.90)	25.53 (24.20,28.04)	24.40 (22.05,26.67)	<0.001
Education level, n (%)				0.365
No formal education	79 (20.7)	24 (21.4)	55 (20.4)	
Primary school	246 (64.6)	76 (67.9)	170 (63.2)	
Middle school and above	56 (14.7)	12 (10.7)	44 (16.4)	
Marital status (Married), n (%)	359 (94.2)	106 (94.6)	253 (94.1)	0.822
Hospitalization days, days	13 (10,14)	13 (11,14)	13 (10,14)	0.251

(*Continued*)

 https://doi.org/10.2147/CIA.S501569

Table 1 (Continued).

Variables	ALL (n=381)	PSD (n=112)	Non-PSD (n=269)	P value
Vascular risk factors, n (%)				
SBP, mmHg	152.46 ± 17.41	155.31 ± 18.24	151.28 ± 16.94	0.039
DBP, mmHg	86.59 ± 12.09	87.03 ± 12.14	86.40 ± 12.09	0.646
Smoking	99 (26)	28 (25)	71 (26.4)	0.777
Drinking	66 (17.3)	20 (17.9)	46 (17.1)	0.859
Hypertension	275 (72.2)	90 (80.4)	185 (68.8)	0.022
Diabetes	127 (33.3)	58 (51.8)	69 (25.7)	<0.001
Atrial fibrillation	44 (11.5)	10 (8.9)	34 (12.6)	0.302
Coronary heart disease	33 (8.7)	8 (7.1)	25 (9.3)	0.497
History of stroke	48 (12.6)	18 (16.1)	30 (11.2)	0.187
Stroke etiologic subtypes, n (%)				0.126
Large-artery atherosclerosis	228 (59.8)	77 (68.8)	151 (56.1)	
Cardioembolic	45 (11.8)	10 (8.9)	35 (13.0)	
Small-vessel disease	100 (26.2)	24 (21.4)	76 (28.3)	
Other or unknown cause	8 (2.1)	1 (0.9)	7 (2.6)	
Lesion location, n (%)				
Left side	124 (32.5)	40 (35.7)	84 (31.2)	0.394
Right side	129 (33.9)	43 (38.4)	86 (32)	0.227
Brainstem	57 (15)	11 (9.8)	46 (17.1)	0.070
Cerebellum	35 (9.2)	7 (6.3)	28 (10.4)	0.200
Other	80 (21)	23 (20.5)	57 (21.2)	0.886
Neuropsychological function				
NIHSS on admission, score	3 (2,5)	4 (2,7)	2 (2,4)	<0.001
mRS at discharge	2 (1,2)	2 (2,3)	2 (1,2)	<0.001
BI at discharge	85 (70,90)	80 (60,85)	85 (80,95)	<0.001
Laboratory data				
Leucocyte, $\times 10^9$ /L	6.96 (5.72,8.33)	7.21 (5.79,8.44)	6.88 (5.66,8.33)	0.304
Hemoglobin, g/L	143.00 (132.00,154.50)	144.50 (136.00,155.75)	143.00 (131.00,154.00)	0.179
FPG, mmol/L	5.56 (4.91,6.96)	6.13 (5.17,8.29)	5.40 (4.77,6.69)	<0.001
HbA1c, %	6.10 (5.60,7.35)	6.4 (5.80,8.40)	6 (5.60,7.00)	<0.001
TC, mmol/L	4.43 (3.72,5.08)	4.49 (3.81,5.12)	4.41 (3.66,5.06)	0.568
TG, mmol/L	1.38 (1.01,1.99)	1.78 (1.21,2.59)	1.25 (0.95,1.71)	<0.001
HDL-C, mmol/L	1.13 (1.04,1.31)	1.09 (0.98,1.21)	1.14 (1.05,1.34)	0.002
LDL-C, mmol/L	2.71 (2.19,3.22)	2.68 (2.14,3.17)	2.71 (2.20,3.23)	0.565
ALB, g/L	40.10 (37.3,42.85)	40.45 (37.78,42.50)	39.60 (36.85,43.00)	0.287
Scr, μmol/L	63 (54,76.6)	64.30 (54.50,77.90)	62.50 (53.80,76.10)	0.271
TyG index	8.78 (8.38,9.21)	9.06 (8.69,9.84)	8.68 (8.27,9.08)	<0.001
TyG-BMI	220.33 (193.08,245.99)	237.95 (213.54,261.41)	213.41 (185.80,236.99)	<0.001
METS-IR	38.60 (34.03,42.79)	41.81 (37.63,45.85)	37.55 (32.22,41.14)	<0.001
TG/HDL-C	2.90 (1.85,4.32)	3.83 (2.57,6.20)	2.44 (1.71,3.83)	<0.001

Abbreviations: PSD, post-stroke depression; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; BI, Barthel Index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; ALB, Albumin; Scr, Serum creatinine; TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

along with lower HDL-C, compared to those in the non-PSD group (all $P < 0.05$). Furthermore, the PSD group exhibited a higher prevalence of hypertension and diabetes (all $P < 0.05$). Additionally, patients in this group demonstrated elevated NIHSS scores, increased mRS grades, and reduced BI scores. Each of the four non-insulin IR indices—TyG index, TyG-BMI, METS-IR, and TG/HDL-C—was significantly elevated in the PSD group compared to the non-PSD group (all $P < 0.001$) (Table 1).

Association Between Four Non-Insulin-Based IR Indices and PSD

Binary logistic regression was employed to develop Model 1 (crude model) and Model 2 (fully adjusted model) to evaluate the effects of four non-insulin IR indices on PSD. Model 2 was adjusted for covariates such as sex, BMI, SBP, hypertension, diabetes, FPG, HbA1c, HDL-C, admission NIHSS, discharge mRS, and discharge BI (of which the portion included with four non-insulin IR indices was not adjusted). Compared to tertile 1, the TyG index in tertile 3 (Odds Ratio [OR] = 2.163, 95% Confidence Interval [CI] = 1.043–4.486, P = 0.038), TyG-BMI in tertile 3 (OR = 2.928, 95% CI = 1.517–5.650, P = 0.001), METS-IR in tertile 3 (OR =3.852, 95% CI = 2.030–7.309, P < 0.001), and TG/HDL-C in tertile 3 (OR = 3.097, 95% CI = 1.575–6.088, P = 0.001) were significant risk factors for PSD, and when the four non-insulin IR indices were analyzed as continuous variables, and adjusted for identical confounders, the TyG index (OR=2.762, 95% CI=1.668–4.573, P < 0.001), TyG-BMI (OR = 1.022, 95% CI=1.013–1.031, P < 0.001), METS-IR (OR = 1.131, 95% CI=1.081–1.184, P<0.001), and TG/HDL-C (OR = 1.288, 95% CI = 1.142–1.452, P<0.001) also were found to be independently associated with the progression of PSD, as detailed in Table 2. The risk of PSD onset increased with higher levels of the four non-insulin IR indices (all P for trend <0.05). Additionally, the RCS analysis demonstrated a linear dose-response relationship between the four non-insulin IR indices and PSD risk, as illustrated in Figure 2.

Subgroup Analysis

We divided participants into subgroups by sex, age, hypertension, and diabetes to evaluate their effects on the relationship between four non-insulin IR indices and PSD. The adjustment factors included sex, BMI, SBP, hypertension, diabetes, FPG, HbA1c, HDL-C, admission NIHSS, discharge mRS, and discharge BI (adjustments were not made for risk factors treated as subgroups or included in the four non-insulin IR indices). Figure 3 shows an interaction between the

Table 2 Logistic Regression Analysis of Four Non-Insulin-Based Insulin Resistance Indices with PSD

Variables	PSD				
	Morbidity	Crude OR (95% CI)[a]	P value	Adjusted OR (95% CI)[b]	P value
TyG index	112 (29.4)	3.347 (2.304,4.863)	<0.001	2.762 (1.668,4.573)	<0.001
T1 (8.15[7.98–8.38])	20 (17.9)	Reference		Reference	
T2 (8.78[8.67–8.91])	34 (30.4)	1.977 (1.065,3.670)	0.031	1.662 (0.845,3.268)	0.141
T3 (9.43[9.20–9.93])	58 (51.8)	4.433 (2.455,8.003)	<0.001	2.163 (1.043,4.486)	0.038
P for trend			<0.001		0.040
TyG-BMI	112 (29.4)	1.028 (1.020,1.036)	<0.001	1.022 (1.013,1.031)	<0.001
B1 (184.06[174.81,193.22])	20 (17.9)	Reference		Reference	
B2 (220.33[212.47,226.98])	32 (28.6)	1.802 (0.966,3.361)	0.064	1.628 (0.842,3.149)	0.147
B3 (251.94[245.55,264.27])	60 (53.6)	4.791 (2.653,8.652)	<0.001	2.928 (1.517,5.650)	0.001
P for trend			<0.001		0.001
METS-IR	112 (29.4)	1.147 (1.101,1.196)	<0.001	1.131 (1.081,1.184)	<0.001
M1 (31.83[29.89,34.04])	20 (17.9)	Reference		Reference	
M2 (38.57[37.44,39.97])	31 (27.7)	1.746 (0.933,3.266)	0.081	1.708 (0.880,3.317)	0.114
M3 (44.57[42.73,47.61])	61 (54.5)	4.871 (2.700,8.788)	<0.001	3.852 (2.030,7.309)	<0.001
P for trend			<0.001		<0.001
TG/HDL-C	112 (29.4)	1.331 (1.197,1.479)	<0.001	1.288 (1.142,1.452)	<0.001
G1 (1.58[1.23,1.85])	21 (18.8)	Reference		Reference	
G2 (2.89[2.43,3.30])	34 (30.4)	1.809 (0.982,3.332)	0.057	1.828 (0.934,3.577)	0.078
G3 (5.01[4.30,6.99])	57 (50.9)	4.071 (2.269,7.305)	<0.001	3.097 (1.575,6.088)	0.001
P for trend			<0.001		0.001

Notes: a: unadjusted. b: adjusted for sex, BMI, SBP, hypertension, diabetes, FPG, HbA1c, HDL-C, admission NIHSS, discharge mRS, and discharge BI (of which the portion included with IR surrogates was not adjusted).

Abbreviations: PSD, post-stroke depression; OR, odds ratios; CI, confidence intervals; TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

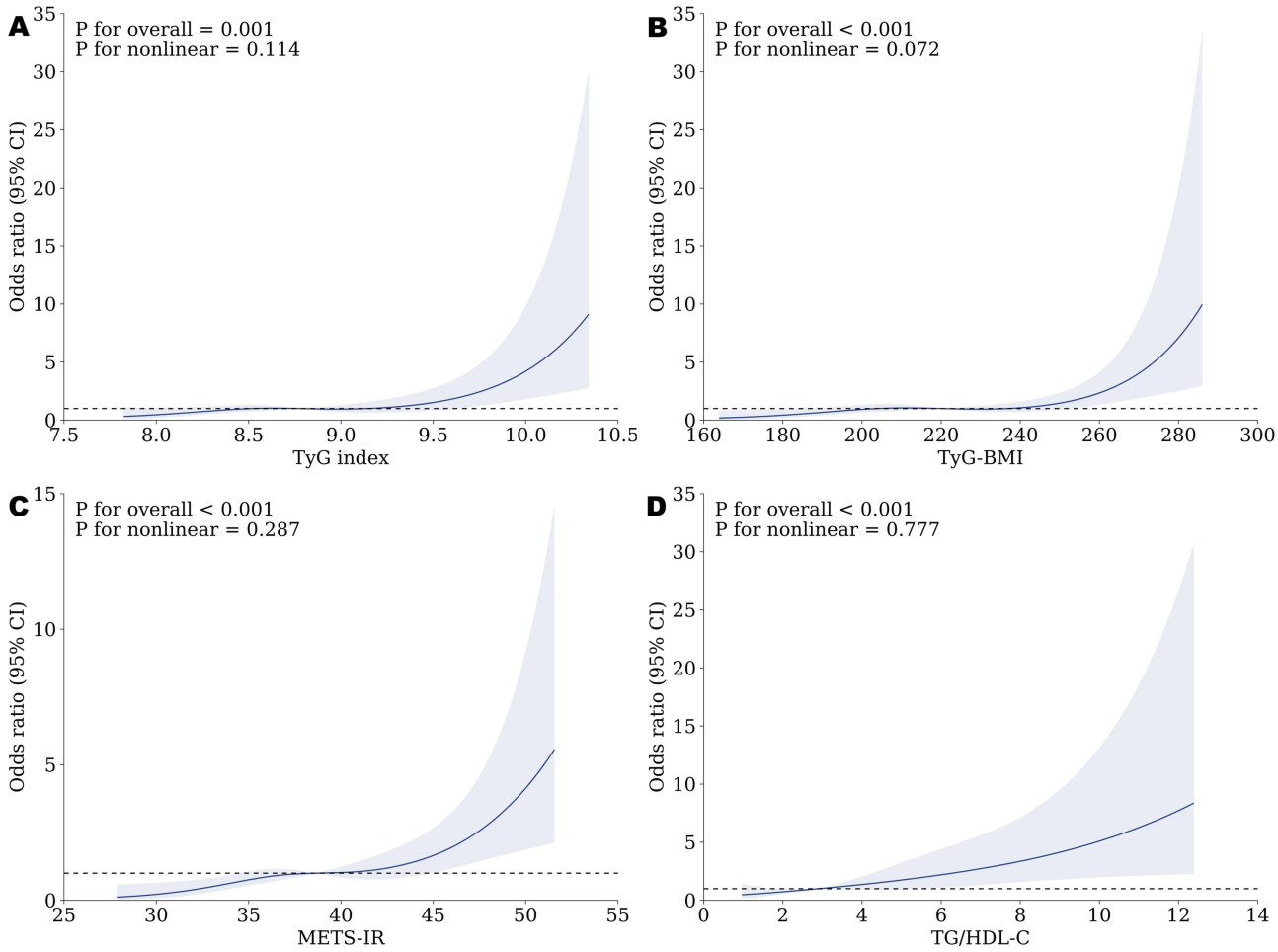

Figure 2 Restricted cubic spine showing the linear relationship between four non-insulin-based insulin resistance indices and PSD. (**A**) TyG index. (**B**)TyG-BMI. (**C**) METS-IR. (**D**) TG/HDL-C. Odds ratios and 95% confidence intervals derived from restricted cubic spline regression, with knots placed at the 5th, 35th, 65th, and 95th percentiles of the distribution of four non-insulin-based IR indices. The reference point is the median of four non-insulin-based IR indices. Odds ratios were adjusted for the same variables included in b in Table 2. TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

TyG index and diabetes within the diabetes subgroup (P for interaction = 0.014). No interaction was observed in the other subgroups with any of the four non-insulin IR indices (all P for interaction >0.05).

Predictive Value of the Four Non-Insulin-Based IR Indices in PSD Diagnosis

ROC curves were utilized to individually evaluate the predictive value of the four non-insulin-based IR indices for PSD (Figure 4). Table 3 displays the AUC, 95% CI, Youden index, cut-off value, and their associated sensitivity and specificity for the four non-insulin-based IR indices.

Discussion

This prospective cohort study is the first to systematically evaluate the relationship between four non-insulin-based IR indices—the TyG index, TyG-BMI, METS-IR, and TG/HDL-C—and the risk of developing PSD. The key findings are as follows: (1) The prevalence of PSD in the study was 29.4%, consistent with previously reported rates.[2,29] (2) The four non-insulin-based IR indices levels were elevated in the PSD group compared to the non-PSD group. Even after adjusting for confounders, logistic regression indicated an independent association with PSD occurrence. (3) The RCS analysis indicated a linear dose-response relationship between the four non-insulin-based IR indices and PSD occurrence.

https://doi.org/10.2147/CIA.S501569

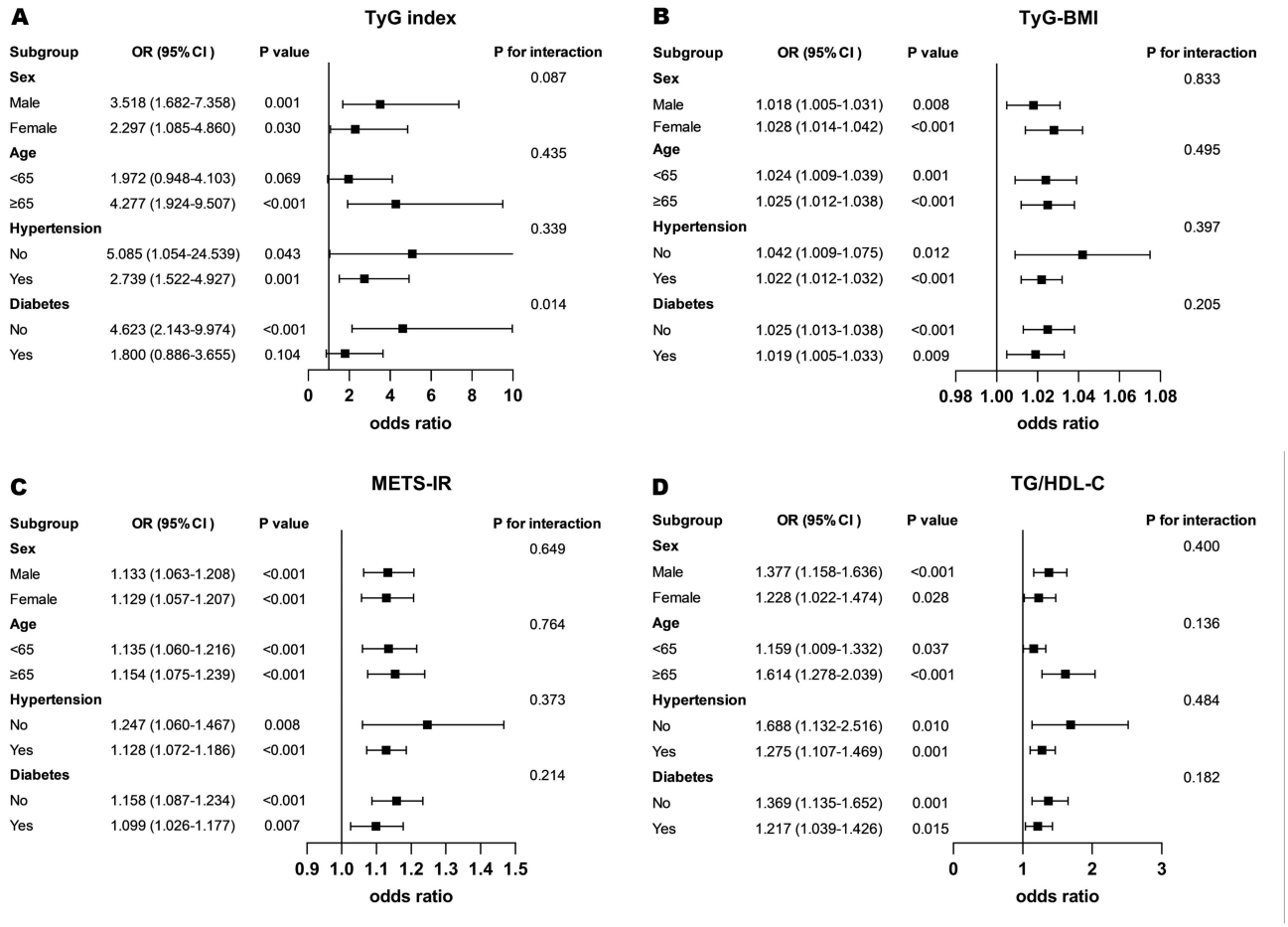

Figure 3 Subgroup analysis of four non-insulin-based insulin resistance indices with PSD. (**A**) TyG index. (**B**)TyG-BMI. (**C**) METS-IR. (**D**) TG/HDL-C. TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio; OR, odds ratios; CI, confidence intervals.

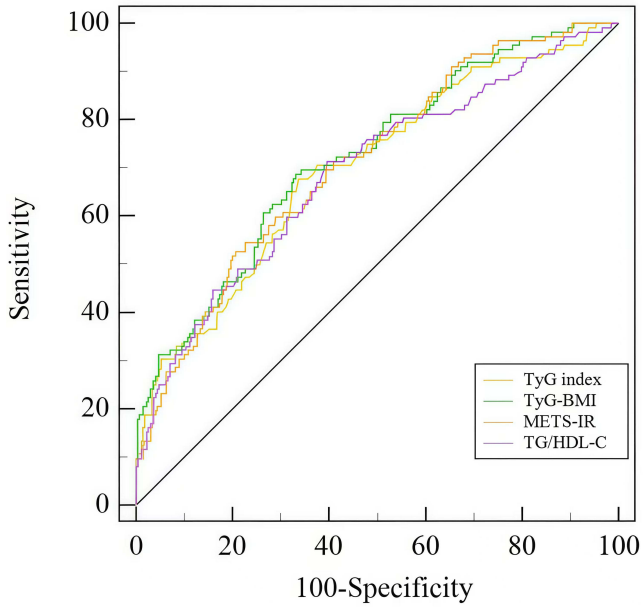

Figure 4 The receiver operating characteristic curve of four non-insulin-based insulin resistance indices to predict PSD. PSD, post-stroke depression; TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

https://doi.org/10.2147/CIA.S501569

Table 3 Performance of Four IR Surrogates for PSD Prediction

Variables	AUC	95% CI	Sensitivity	Specificity	P value	Cut-off value	Youden index
TyG index	0.700	0.652–0.746	67.86	66.17	<0.001	8.88	0.340
TyG-BMI	0.721	0.673–0.766	68.75	66.91	<0.001	225.36	0.357
METS-IR	0.711	0.663–0.756	52.68	79.18	<0.001	41.63	0.319
TG/HDL-C	0.690	0.641–0.736	71.43	60.22	<0.001	2.91	0.317

Abbreviations: PSD, post-stroke depression; IR, insulin resistance; AUC, area under curve; CI, confidence intervals; TyG index, triglyceride glucose index; TyG-BMI, triglyceride glucose-body mass index; METS-IR, insulin resistance metabolic score; TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio.

(4) Subgroup analysis revealed an interaction between diabetes and the TyG index but not with the other three IR surrogates. (5) The ROC curve demonstrated that the four non-insulin-based IR indices possess predictive value for PSD occurrence.

As medical technology advances and public awareness of stroke increases, the mortality rate of stroke patients has decreased. However, the disability rate among survivors has risen significantly,[30] PSD being a prevalent complication.[2] The World Health Organization forecasts that by 2030, major depression will become the leading cause of the global disease burden.[31] PSD diminishes patients' quality of life and may also elevate mortality rates.[32] Thus, early identification, diagnosis, and treatment of PSD patients are clinically significant. IR facilitates the progression of atherosclerotic plaques and enhances platelet adhesion, activation, and aggregation, which subsequently contribute to ischemic stroke.[33] Since measuring insulin in the brain is challenging and no clear definition or diagnostic criteria exist for brain IR, studies suggest that peripheral IR is closely linked to brain IR.[16] The current gold standard for IR assessment is complex, costly, and clinically limited. In contrast, HOMA-IR is susceptible to FPG measurement accuracy, resulting in variable outcomes. Consequently, non-insulin-based IR indices such as the TyG index, TyG-BMI, METS-IR, and TG/HDL-C have been developed. Prior studies have shown that the TyG index, TyG-BMI, METS-IR, and TG/HDL-C are linked to short-term prognosis in AIS.[10,34–36] However, research on the four non-insulin-based IR indices concerning PSD remains insufficient.

The TyG index, comprising TG and FPG, is a reliable surrogate of IR.[23] It is associated with stroke-related risk factors and is an independent predictor of stroke onset, as well as neurological deterioration and stroke recurrence in AIS patients.[37,38] The TyG index is also closely linked to depression. A high TyG index is associated with an increased likelihood of depression onset, suicidal ideation, and suicide attempts.[39] In the study, the TyG index was identified as an independent risk factor for PSD after adjusting for potential confounders via logistic regression modeling. The subgroup analyses examine the robustness of the findings. The analyses revealed an interaction between the TyG index and diabetes. However, there was a significant positive association in 3225 diabetes patients concerning depression occurrence and the TyG index.[40] The differences may be related to the small within-group differences in FPG in this study and the limited sample size, which limits further interpretation. Obesity is linked to depression,[41] and TyG-BMI is an IR marker derived from TyG in combination with the BMI.[24] Previous studies indicate that TyG-BMI is linked to increased stroke risk.[42] TyG-BMI demonstrated higher sensitivity and specificity than TyG alone in correlating with depressive symptoms.[43] This study identified TyG-BMI as an independent risk factor for PSD, exhibiting a linear dose-response relationship with no interactions in subgroup analysis. However, the DeLong test did not reveal a statistically significant difference between the AUC of TyG-BMI and TyG (P = 0.402). Abnormalities in lipid metabolism are linked to cardiovascular and cerebrovascular diseases. Reduced HDL-C is an independent risk factor for ischemic stroke and also independently associated with the development of PSD.[44] METS-IR is a novel IR surrogate incorporating four metabolic markers: FPG, TG, BMI, and HDL-C.[25] Previous studies indicate that, similar to TyG and TyG-BMI, elevated METS-IR is associated with an increased risk of ischemic stroke.[45] Recent studies have revealed a nonlinear relationship between METS-IR and depression risk in adults.[46] In this study, METS-IR was independently associated with the occurrence of PSD. The RCS indicated a linear dose-response relationship. ROC analysis demonstrated that METS-IR and TyG index had similar PSD predictive abilities. Although the AUC for METS-IR was slightly lower than TyG-BMI, the difference was not statistically significant (P = 0.341). The absence of a larger AUC for METS-IR may be due to

varying calculation methods. Owing to the small sample size, larger studies are necessary to further assess this correlation. TG/HDL-C serves as an indicator of abnormal lipid metabolism and can be used as a surrogate for IR.[47] A lower TG/HDL-C is strongly linked to the 3-month prognosis of stroke,[48] while a high TG/HDL-C during the acute phase of AIS is an independent risk factor for post-stroke cognitive impairment.[49] A study investigating the link between major depression and dyslipidemia in adolescents found that more severe depressive symptoms were associated with lower TG/HDL-C.[50] Variations exist in the effects of high and low TG/HDL-C on diseases. This study identified high TG/HDL-C levels as an independent risk factor for PSD; however, the AUC for TG/HDL-C was the smallest among the four non-insulin-based IR indices in the ROC analysis, with no statistically significant difference. The four non-insulin-based IR indices—TyG index, TyG-BMI, METS-IR, and TG/HDL-C—are independently associated with PSD. They offer simplicity, economy, and easy accessibility compared to the IR gold standard, making them more suitable for clinical adoption. Monitoring these IR surrogates can help identify high-risk groups for PSD early, allowing clinicians to make timely medical decisions for patients at high risk of depression following AIS.

The role of IR in the pathogenesis of PSD remains unclear. In humans, there are two subtypes of insulin receptor (IR): IR-A and IR-B. The IR-A subtype predominantly resides in the central nervous system. An imbalance in the IR-A to IR-B ratio is linked to IR, potentially leading to neurodegenerative disorders and depression, among other conditions.[51,52] In foundational experiments, insulin receptors were identified as being distributed throughout the brain, with the highest expression in areas regulating autonomic activity, appetite, olfaction, and emotional and cognitive functions.[53] Current research indicates several potential mechanisms: (1) Brain insulin and dopamine actions are interrelated. Brain IR results in hyperphagia, anxiety, depressive-like behaviors, and impairment of the dopaminergic system.[54] (2) IR is linked to abnormalities in the anterior cingulate cortex and hippocampal structures, affecting the functional connectivity of neural networks. IR causes atrophy in hippocampal and anterior cingulate cortex volumes and disrupts connectivity with the frontal-limbic reward network. High IR levels correlate negatively with depression severity, whereas low IR levels exhibit the opposite correlation.[55] (3) IR diminishes dendritic spine density, reduces brain-derived neurotrophic factor production, and impairs synaptic plasticity.[56,57] Conversely, increased dendritic spine numbers and elevated brain-derived neurotrophic factor levels ameliorate depressive symptoms.[58,59] Correcting synaptic plasticity dysregulation can also alleviate depression.[60] (4) IR in the brain triggers inflammation and mitochondrial damage in neurons,[6] which is closely linked to depression.[61]

Limitations

This study has several limitations: (1) Being a single-center prospective study, the conclusions may have limited generalizability, necessitating future validation through multicenter, large sample prospective studies. (2) The inclusion of patients with low baseline NIHSS scores and exclusion of those with severe aphasia or dysarthria may have introduced selection bias and led to an underestimation of PSD prevalence. (3) The analysis did not adjust for the use of glucose-lowering and lipid-modifying medications; it cannot be ruled out that these medications impact disease occurrence. (4) Measuring the four non-insulin-based IR indices in a metabolically stable state (after acute stress response) could provide better insights into IR's role in disease prognosis. (5) The study made baseline measurements of these IR indices, making it difficult to assess the impact of their dynamic changes on PSD occurrence.

Conclusion

In summary, despite certain limitations, our study confirmed that the TyG index, TyG-BMI, METS-IR, and TG/HDL-C are independent risk factors for PSD in AIS and effective predictors of PSD. By monitoring the four non-insulin-based IR indices, clinicians can identify individuals at high risk for PSD early, allowing for timely and effective interventions that may improve patient prognosis.

Acknowledgments

The authors thank the study participants and their relatives as well as the clinical staff for their support and contributions to this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Feigin VL, Stark BA, Johnson CO. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795–820. doi:10.1016/S1474-4422(21)00252-0
2. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9(8):1017–1025. doi:10.1111/ijs.12357
3. Wang Z, Shi Y, Liu F, et al. Diversiform etiologies for post-stroke depression. *Front Psychiatry*. 2018;9:761. doi:10.3389/fpsyt.2018.00761
4. Ding PF, Zhang HS, Wang J, et al. Insulin resistance in ischemic stroke: mechanisms and therapeutic approaches. *Front Endocrinol (Lausanne)*. 2022;13:1092431. doi:10.3389/fendo.2022.1092431
5. Fernandes BS, Salagre E, Enduru N, Grande I, Vieta E, Zhao Z. Insulin resistance in depression: a large meta-analysis of metabolic parameters and variation. *Neurosci Biobehav Rev*. 2022;139:104758. doi:10.1016/j.neubiorev.2022.104758
6. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol*. 2020;19(9):758–766. doi:10.1016/S1474-4422(20)30231-3
7. Yi X, Zhu X, Zhou Y, et al. The combination of insulin resistance and serum interleukin-1β correlates with post-stroke depression in patients with acute ischemic stroke. *Neuropsychiatr Dis Treat*. 2021;17:735–746. doi:10.2147/NDT.S291164
8. Qiu HC, Liu HZ, Li X, Zeng X, Zhao JZ. Insulin resistance as estimated by homeostasis model assessment predicts incident post-stroke depression in Chinese subjects from ischemic stroke. *J Affect Disord*. 2018;231:1–7. doi:10.1016/j.jad.2018.01.023
9. Shen J, Wang X, Wang M, Zhang H. Potential molecular mechanism of exercise reversing insulin resistance and improving neurodegenerative diseases. *Front Physiol*. 2024;15:1337442. doi:10.3389/fphys.2024.1337442
10. Wang J, Tang H, Tian J, Xie Y, Wu Y. Non-insulin-based insulin resistance indices predict early neurological deterioration in elderly and middle-aged acute ischemic stroke patients in Northeast China. *Sci Rep*. 2024;14(1):16138. doi:10.1038/s41598-024-66881-6
11. Jin A, Wang S, Li J, et al. Mediation of systemic inflammation on insulin resistance and prognosis of nondiabetic patients with ischemic stroke. *Stroke*. 2023;54(3):759–769. doi:10.1161/STROKEAHA.122.039542
12. Rhea EM, Rask-Madsen C, Banks WA. Insulin transport across the blood-brain barrier can occur independently of the insulin receptor. *J Physiol*. 2018;596(19):4753–4765. doi:10.1113/JP276149
13. Blázquez E, Velázquez E, Hurtado-Carneiro V, Ruiz-Albusac JM. Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. *Front Endocrinol (Lausanne)*. 2014;5:161. doi:10.3389/fendo.2014.00161
14. Zeng Y, Zhang L, Hu Z. Cerebral insulin, insulin signaling pathway, and brain angiogenesis. *Neurol Sci*. 2016;37(1):9–16. doi:10.1007/s10072-015-2386-8
15. Benedict C, Brooks SJ, Kullberg J, et al. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. *Diabetes Care*. 2012;35(3):488–494. doi:10.2337/dc11-2075
16. Sripetchwandee J, Chattipakorn N, Chattipakorn SC. Links between obesity-induced brain insulin resistance, brain mitochondrial dysfunction, and dementia. *Front Endocrinol (Lausanne)*. 2018;9:496. doi:10.3389/fendo.2018.00496
17. Siwek M, Chrobak AA, Sołtys Z, Dudek D, Krupa AJ. Insulin resistance, temperament and personality traits are associated with anhedonia in a transdiagnostic sample. *Brain Sci*. 2024;14(9):890. doi:10.3390/brainsci14090890
18. Krupa AJ, Chrobak AA, Sołtys Z, Dudek D, Szewczyk B, Siwek M. Insulin resistance, clinical presentation and resistance to selective serotonin and noradrenaline reuptake inhibitors in major depressive disorder. *Pharmacol Rep*. 2024;76(5):1100–1113. doi:10.1007/s43440-024-00621-5
19. Gruber J, Hanssen R, Qubad M, 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. doi:10.1016/j.neubiorev.2023.105179
20. Badulescu S, Tabassum A, Le GH, et al. Glucagon-like peptide 1 agonist and effects on reward behaviour: a systematic review. *Physiol Behav*. 2024;283:114622. doi:10.1016/j.physbeh.2024.114622
21. Zou XH, Sun LH, Yang W, Li BJ, Cui RJ. Potential role of insulin on the pathogenesis of depression. *Cell Prolif*. 2020;53(5):e12806. doi:10.1111/cpr.12806
22. Khan SH, Sobia F, Niazi NK, Manzoor SM, Fazal N, Ahmad F. Metabolic clustering of risk factors: evaluation of Triglyceride-glucose index (TyG index) for evaluation of insulin resistance. *Diabetol Metab Syndr*. 2018;10(1):74. doi:10.1186/s13098-018-0376-8
23. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab*. 2010;95(7):3347–3351. doi:10.1210/jc.2010-0288
24. Er LK, Wu S, Chou HH, et al. Triglyceride glucose-body mass index is a simple and clinically useful surrogate marker for insulin resistance in nondiabetic individuals. *PLoS One*. 2016;11(3):e0149731. doi:10.1371/journal.pone.0149731
25. Wang G, Zhu Z, Wang Y, et al. The association between METS-IR, an indirect index for insulin resistance, and lung cancer risk. *Eur J Public Health*. 2024;34(4):800–805. doi:10.1093/eurpub/ckad234
26. Baneu P, Văcărescu C, Drăgan SR, et al. The triglyceride/HDL ratio as a surrogate biomarker for insulin resistance. *Biomedicines*. 2024;12(7):1493. doi:10.3390/biomedicines12071493
27. Qin Y, Qiao Y, Yan G, Wang D, Tang C. Relationship between indices of insulin resistance and incident type 2 diabetes mellitus in Chinese adults. *Endocrine*. 2024;85(3):1228–1237. doi:10.1007/s12020-024-03830-3
28. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45(8):742–747. doi:10.1001/archpsyc.1988.01800320058007
29. Liu L, Xu M, Marshall IJ, Wolfe CD, Wang Y, O'Connell MD. Prevalence and natural history of depression after stroke: a systematic review and meta-analysis of observational studies. *PLoS Med*. 2023;20(3):e1004200. doi:10.1371/journal.pmed.1004200
30. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. *Int J Stroke*. 2022;17(1):18–29. doi:10.1177/17474930211065917
31. Lépine JP, Briley M. The increasing burden of depression. *Neuropsychiatr Dis Treat*. 2011;7(Suppl 1):3–7. doi:10.2147/NDT.S19617

32. Cai W, Mueller C, Li YJ, Shen WD, Stewart R. Post stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis. *Ageing Res Rev*. 2019;50:102–109. doi:10.1016/j.arr.2019.01.013
33. Deng XL, Liu Z, Wang C, Li Y, Cai Z. Insulin resistance in ischemic stroke. *Metab Brain Dis*. 2017;32(5):1323–1334. doi:10.1007/s11011-017-0050-0
34. Deng QW, Li S, Wang H, et al. The short-term prognostic value of the triglyceride-to-high-density lipoprotein cholesterol ratio in acute ischemic stroke. *Aging Dis*. 2018;9(3):498–506. doi:10.14336/AD.2017.0629
35. Miao M, Bi Y, Hao L, et al. Triglyceride-glucose index and short-term functional outcome and in-hospital mortality in patients with ischemic stroke. *Nutr, Metab Cardiovasc Dis*. 2023;33(2):399–407. doi:10.1016/j.numecd.2022.11.004
36. Yu XR, Du JL, Jiang M, et al. Correlation of TyG-BMI and TyG-WC with severity and short-term outcome in new-onset acute ischemic stroke. *Front Endocrinol (Lausanne)*. 2024;15:1327903. doi:10.3389/fendo.2024.1327903
37. Huo RR, Liao Q, Zhai L, You XM, Zuo YL. Interacting and joint effects of triglyceride-glucose index (TyG) and body mass index on stroke risk and the mediating role of TyG in middle-aged and older Chinese adults: a nationwide prospective cohort study. *Cardiovasc Diabetol*. 2024;23(1):30. doi:10.1186/s12933-024-02122-4
38. Zhou Y, Pan Y, Yan H, et al. Triglyceride glucose index and prognosis of patients with ischemic stroke. *Front Neurol*. 2020;11:456. doi:10.3389/fneur.2020.00456
39. Behnoush AH, Mousavi A, Ghondaghsaz E, Shojaei S, Cannavo A, Khalaji A. The importance of assessing the triglyceride-glucose index (TyG) in patients with depression: a systematic review. *Neurosci Biobehav Rev*. 2024;159:105582. doi:10.1016/j.neubiorev.2024.105582
40. Ren J, Lv C, Wang J. Association between triglyceride-glucose index and depression in patients with type 2 diabetes: a cross-sectional study from NHANES. *Medicine (Baltimore)*. 2024;103(32):e39258. doi:10.1097/MD.0000000000039258
41. Guo YX, Wang AQ, Gao X, et al. Obesity is positively associated with depression in older adults: role of systemic inflammation. *Biomed Environ Sci*. 2023;36(6):481–489. doi:10.3967/bes2023.059
42. Shao Y, Hu H, Li Q, Cao C, Liu D, Han Y. Link between triglyceride-glucose-body mass index and future stroke risk in middle-aged and elderly Chinese: a nationwide prospective cohort study. *Cardiovasc Diabetol*. 2024;23(1):81. doi:10.1186/s12933-024-02165-7
43. Liu X, Li J, He D, Zhang D, Liu X. Association between different triglyceride glucose index-related indicators and depression in premenopausal and postmenopausal women: NHANES, 2013-2016. *J Affect Disord*. 2024;360:297–304. doi:10.1016/j.jad.2024.05.084
44. Shen H, Tu X, Luan X, Zeng Y, He J, Tang W. Serum lipid profiles and post-stroke depression in acute ischemic stroke patients. *Neuropsychiatr Dis Treat*. 2019;15:1573–1583. doi:10.2147/NDT.S204791
45. Cai X, Hu J, Zhu Q, et al. Relationship of the metabolic score for insulin resistance and the risk of stroke in patients with hypertension: a cohort study. *Front Endocrinol (Lausanne)*. 2022;13:1049211. doi:10.3389/fendo.2022.1049211
46. 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;355:355–362. doi:10.1016/j.jad.2024.03.129
47. Uruska A, Zozulinska-Ziolkiewicz D, Niedzwiecki P, Pietrzak M, Wierusz-Wysocka B. TG/HDL-C ratio and visceral adiposity index may be useful in assessment of insulin resistance in adults with type 1 diabetes in clinical practice. *J Clin Lipidol*. 2018;12(3):734–740. doi:10.1016/j.jacl.2018.01.005
48. Deng QW, Wang H, Sun CZ, et al. Triglyceride to high-density lipoprotein cholesterol ratio predicts worse outcomes after acute ischaemic stroke. *Eur J Neurol*. 2017;24(2):283–291. doi:10.1111/ene.13198
49. Cheng Y, Zhu H, Chen J, et al. Serum TG/HDL-C level at the acute phase of ischemic stroke is associated with post-stroke cognitive impairment. *Neurol Sci*. 2022;43(10):5977–5984. doi:10.1007/s10072-022-06267-6
50. Khalfan AF, Campisi SC, Lo RF, McCrindle BW, Korczak DJ. The association between adolescent depression and dyslipidemia. *J Affect Disord*. 2023;338:239–245. doi:10.1016/j.jad.2023.06.017
51. Pomytkin I, Costa-Nunes JP, Kasatkin V, et al. Insulin receptor in the brain: mechanisms of activation and the role in the CNS pathology and treatment. *CNS Neurosci Ther*. 2018;24(9):763–774. doi:10.1111/cns.12866
52. Belfiore A, Malaguarnera R, Vella V, et al. Insulin receptor isoforms in physiology and disease: an updated view. *Endocr Rev*. 2017;38(5):379–431. doi:10.1210/er.2017-00073
53. Marks JL, Porte D Jr, Stahl WL, Baskin DG. Localization of insulin receptor mRNA in rat brain by in situ hybridization. *Endocrinology*. 1990;127(6):3234–3236. doi:10.1210/endo-127-6-3234
54. Kleinridders A, Pothos EN. Impact of brain insulin signaling on dopamine function, food intake, reward, and emotional behavior. *Curr Nutr Rep*. 2019;8(2):83–91. doi:10.1007/s13668-019-0276-z
55. Singh MK, Leslie SM, Packer MM, et al. Brain and behavioral correlates of insulin resistance in youth with depression and obesity. *Horm Behav*. 2019;108:73–83. doi:10.1016/j.yhbeh.2018.03.009
56. Biessels GJ, Reagan LP. Hippocampal insulin resistance and cognitive dysfunction. *Nat Rev Neurosci*. 2015;16(11):660–671. doi:10.1038/nrn4019
57. Park HS, Park SS, Kim CJ, Shin MS, Kim TW. Exercise alleviates cognitive functions by enhancing hippocampal insulin signaling and neuroplasticity in high-fat diet-induced obesity. *Nutrients*. 2019;11(7):1603. doi:10.3390/nu11071603
58. Maynard KR, Hobbs JW, Rajpurohit SK, Martinowich K. Electroconvulsive seizures influence dendritic spine morphology and BDNF expression in a neuroendocrine model of depression. *Brain Stimul*. 2018;11(4):856–859. doi:10.1016/j.brs.2018.04.003
59. Zheng Y, Yu X, Wei L, et al. LT-102, an AMPA receptor potentiator, alleviates depression-like behavior and synaptic plasticity impairments in prefrontal cortex induced by sleep deprivation. *J Affect Disord*. 2024;367:18–30. doi:10.1016/j.jad.2024.08.176
60. Aleksandrova LR, Wang YT, Phillips AG. Evaluation of the Wistar-Kyoto rat model of depression and the role of synaptic plasticity in depression and antidepressant response. *Neurosci Biobehav Rev*. 2019;105:1–23. doi:10.1016/j.neubiorev.2019.07.007
61. Casaril AM, Dantzer R, Bas-Orth C. Neuronal mitochondrial dysfunction and bioenergetic failure in inflammation-associated depression. *Front Neurosci*. 2021;15:725547. doi:10.3389/fnins.2021.725547