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The Relationship between the ZJU Index and Depression among American Adults: Insights from NHANES 2005–2018

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Zhejiang University index (ZJU index) is an innovative composite metabolic marker combining triglycerides, fasting plasma glucose, body mass index, and transaminases. Existing literature demonstrates a clear association between metabolic state and depressed conditions. However, research exploring the relationship between overall metabolic condition and depression remain limited. This paper investigates the association between susceptibility to depressive symptoms and the ZJU index. Baseline data and laboratory values were collected from a cohort of 6244 individuals to calculate the ZJU index. Following a summary of the participants' baseline characteristics, adjustments for covariables were performed. Piecewise logistic regression analysis was employed to assess the association between the ZJU index and depression. Nonlinear relationships were analyzed using restricted cubic spline regression, while the receiver operating characteristic curve and area under the curve were employed to evaluate the ZJU index's advantage over single lipid metabolism indicators and a single metabolic index. Subgroup analyses were conducted based on demographics information, lifestyle factors, and chronic diseases. The piecewise logistic regression analysis revealed that individuals in the highest quartile (Q4) of the ZJU index had a significantly higher likelihood of depression compared to those in the lowest quartile (Q1) (OR = 1.4495, CI: 1.01–2.06, P = 0.046). A U-shaped nonlinear link between the ZJU index and depression (P-nonlinear = 0.03, inflection point = 35.47) was identified through restricted cubic spline analysis. Subgroup analysis revealed that the association between the ZJU index and depression was more pronounced in smokers and individuals with cardiovascular diseases. The area under the curve showed that in depression prediction, the ZJU index outperformed individual metabolic index. The ZJU index is strongly linked to a heightened chance of depression in American adults. Therefore, monitoring high ZJU index levels may contribute to the effective prevention of depression.

Keywords: *ZJU index, depression, metabolism, metabolic status, cross-sectional study, NHANES*

1. Introduction

As a mental health disorder, Depression is marked by continuous low moods, diminished interest in activities, and potentially suicidal ideation [1]. Statistics indicate a 49.86% increase in global depression cases from 1990 to 2017 [2]. Approximately 350 million people worldwide are affected by depression, with its prevalence rising as a result of rapid economic growth and population expansion. As a complex mental illness, the etiology of depression extends beyond traditional psychological factors to include significant socioeconomic influences. Depression prevalence is inversely linked with low income, unemployment, poor education levels, and lack of social support [3]. Additionally, decreased physical activity, poor sleep quality, and unhealthy dietary habits contribute to the onset of depression [4,5]. Numerous metabolic disorders exhibit a significant association with depression. Obesity, in particular, not only contributes to negative body image perceptions but is also intricately connected to the pathophysiological mechanisms underlying depression. Empirical studies indicate that individuals with obesity experience higher rates of depression compared to those with normal weight [6]. Dyslipidemia is similarly associated with depression, as diabetes patients, due to long-term hyperglycemia-induced neuropathy and endocrine dysregulation, are more susceptible to depressive symptoms [7]. Therefore, a comprehensive consideration of multiple indicators and factors is crucial for management and in-depth

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exploration of depression.

The Zhejiang University index (ZJU index) is an innovative metabolic marker combining aspartate aminotransferase (AST), alanine aminotransferase (ALT), fasting plasma glucose (FPG), body mass index (BMI) and triglycerides (TG) [8]. Compared to individual biochemical markers, the ZJU index provides a more holistic evaluation of both normal and pathological metabolic conditions in the human body, exhibiting robust potential for assessing disease risk and predicting prognosis. Originally devised to forecast non-alcoholic fatty liver disease, the ZJU index has shown significant predictive efficacy and is associated with insulin resistance, lipid metabolism, and obesity [8–10]. Studies have also shown associations between the ZJU index and conditions such as obstructive sleep apnea[11] and diabetes [12].

Depression has been established to have a significant association with metabolic status [13–15]. At the mechanistic level, abnormalities in lipid metabolism and liver function may disrupt metabolic homeostasis and the immune system, thereby increasing the risk of mood disorders such as depression [16,17] Furthermore, there exists a shared genetic pathway between glucose metabolism abnormalities and depression [18]. While numerous studies have explored the connections between specific metabolic abnormalities and depression, there is a paucity of research addressing the relationship between overall metabolic status and the incidence of depression. Consequently, the potential linkage between the ZJU index and depression, as well as its predictive utility, necessitates further exploration. Such investigation is essential for the early identification of depression, timely intervention, and the prevention of severe complications.

2. Methods

2.1 Study population and Design

Data from the National Health and Nutrition Examination Survey (NHANES) was used the nationwide cross-sectional study. NHANES employs a sophisticated, stratified, multistage random sampling method to ensure national representativeness and evaluates the health and nutritional status of U.S. citizens through a variety of data collection techniques, including laboratory tests, physical examinations, and interviews [19]. Participants in NHANES encompass a diverse range of ages, sexes, races, and socioeconomic backgrounds. Following ethical approval, informed consent was obtained from each participant in the NHANES study [20]. The National Center for Health Statistics provides detailed information regarding ethical approval procedures and informed consent policies. Additionally, the datasets are supplemented by extensive protocols and documentation, which are available to the public on the NHANES website.

The study examined NHANES data from 2005 to 2018. From the initial cohort of 70,190 participants, individuals were excluded according to specific criteria: (1) minors (aged < 18, n = 28,047), (2) participants with incomplete ZJU index data (n = 24,345), (3) participants who refused or lacked PHQ-9 questionnaire scores (n = 1,479), (4) participants with missing covariables data (n = 9620) and (5) participants with missing weight coefficients (n = 443). Ultimately, 6244 people in all satisfied the inclusion requirements and were thus included into the study (Figure 1).

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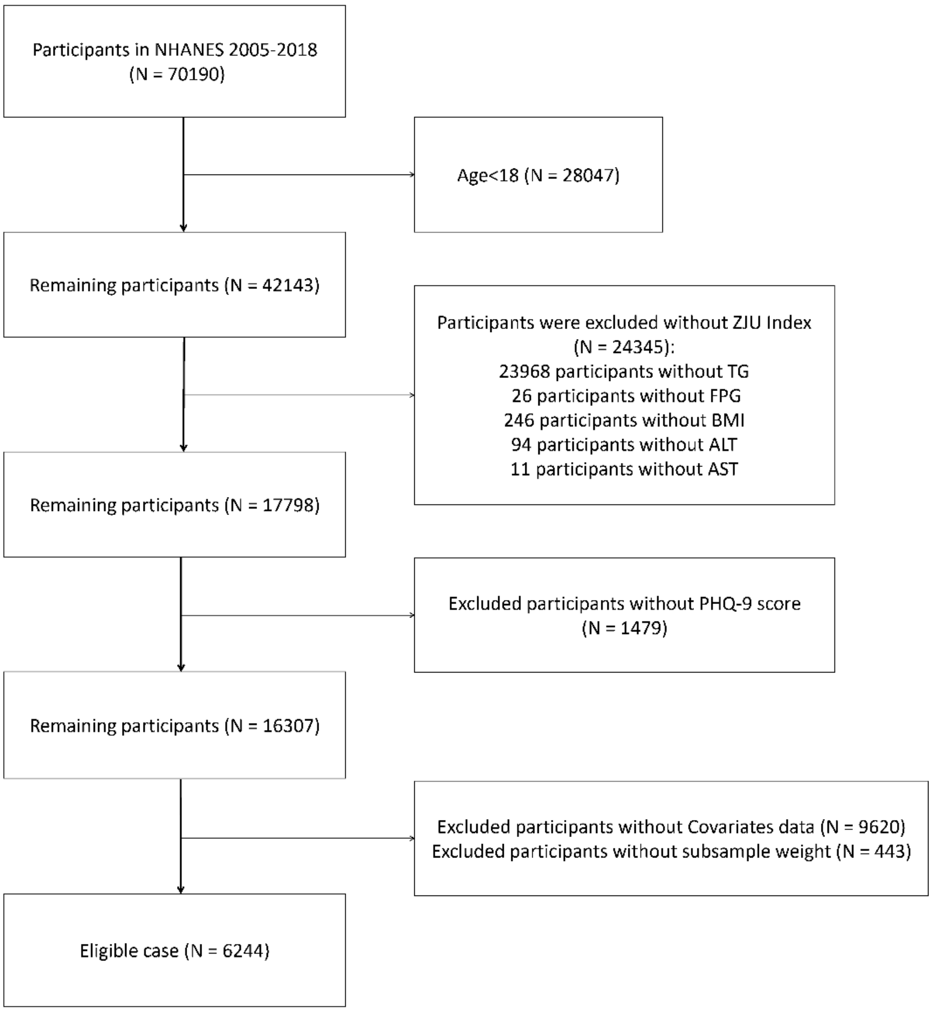

Fig 1. Flowchart of the sample selection from NHANES 2005–2018.

Note: NHANES: National Health and Nutrition Examination Survey; TG, triglycerides; FPG, fasting plasma glucose; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PHQ, patient health questionnaire.

2.2 Assessment of the ZJU Index

The calculation integrates gender and multiple metabolic parameters, including AST, ALT, TG, BMI and FPG. This comprehensive approach reflects the metabolic status of individuals and indicates the risk for various diseases, such as obesity, insulin resistance, and liver disease [21]. The ZJU index is determined by the equation: ZJU index = 3 × AST/ALT + BMI + FPG + 2 (for women) + TG, where AST and ALT are measured in U/L, BMI in kg/m², and FPG and TG in mmol/L. In this study, AST, ALT, TG, BMI, and FPG were derived from laboratory and physical measurement data, with the ZJU index treated as a continuous variable.

2.3 Assessment of Depression Symptoms

Patient Health Questionnaire-9 (PHQ-9) data from the NHANES 2005-2018 were used to analyze depression symptoms and their severity [22]. The PHQ-9 includes nine items, each representing a core symptom of depression. Participants assess how often each symptom occurred in the last two weeks, and the overall score is the sum of the individual item scores. An item offers response options scored from 3 to 0, ranging from frequent occurrence to none. The PHQ-9 score spans from 0, indicating no symptoms, to 27, representing severe symptoms. Individuals scoring 10 or above are considered to have depressive

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symptoms, while those scoring below 10 are regarded as not having depressive symptoms. Depression scores are classified as: severe (≥15), moderate (10-14), mild (5-9), and none (0-4).

2.4 Evaluation of Covariables

The covariables considered in the study include widely recognized factors associated with depression, as well as variables commonly used in numerous studies. Demographic variables encompass age, race, marital status and educational attainment. Additionally, factors obtained from the questionnaire include smoking status, alcohol consumption and the presence of cardiovascular disease (CVD). Laboratory tests included glycosylated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein (HDL), and C-reactive protein (CRP). Individuals were classified as having cardiovascular disease if they had been diagnosed with coronary heart disease, myocardial infarction, heart failure, or stroke. Both questionnaire responses and laboratory data were employed to evaluate the presence of hypertension and hyperlipidemia.

2.5 Statistical Analysis

To achieve nationally representative estimates, all analyses were conducted using NHANES fasting subsample weights between 2005 and 2018. Considering the stratification and clustering effects arising from the complex sample design, the weight adjustment was performed by multiplying the survey weights from 2005-2018 by 1/7. Categorical variables are presented with counts and their corresponding weighted proportions (%), and associations were evaluated using the χ^2 test; continuous data were compared using t-tests. Continuous variables that do not follow a normal distribution are presented using the median and interquartile range (IQR). Continuous variables across multiple groups are analyzed using one-way analysis of variance.

Logistic regression models were used to examine the relationship between a 10-point increment in the ZJU index and the occurrence of depression. In the preliminary multiple logistic regression models, the ZJU index was treated as a continuous variable. Nonetheless, the appropriateness of utilizing the ZJU index as a continuous variable requires validation through restricted cubic spline (RCS) analysis. In the subsequent， to assess the differential impact of these ZJU index classifications on depression likelihood, the ZJU index was stratified into four categories: Q1 (22.7–35.8), Q2 (35.8–39.3), Q3 (39.3–43.4), and Q4 (43.4–140.1) and logistic regression model was developed. Age, race, education, marital status, smoking, alcohol use, hypertension, hyperlipidemia, HbA1c, TC, HDL, CVD and CRP were among the factors used to adjust both regression models. Model 1 did not account for any covariables. Model 2 included demographic parameters, smoking and drinking, while Model 3 incorporated modifications across all variables.

Soothing curve fitting approach were utilized to investigate the nonlinear association between depression and the ZJU index among U.S. adults. The nonlinear relationship was defined using RCS regression analysis. The Akaike Information Criterion was employed within the RCS model to determine the optimal number and placement of knots, thereby ensuring an ideal fit and preventing overfitting. Five nodes exhibiting significant differences were chosen for the synthesis of the RCS curve. The fitted models produced adjusted odds ratios. The inflection point's location, along with the trend changes before and after it, were determined through threshold effect analysis.

Subgroup analyses were performed to investigate variations in the impact of the ZJU index on the development of depression across diverse populations. The final analytical sample was stratified according to the previously mentioned covariables.

Predictors were identified using both univariate and multifactorial regression analyses, leading to the development of an initial prediction model applicable to the entire population for assessing the predictive capability of the ZJU index in relation to depression. Receiver operating characteristic curve (ROC) and area under the curve (AUC) were used to assess whether the inclusion of the ZJU index provides additional advantages to the simple prediction model. Given that the ZJU index includes TG, ROC and AUC were used to evaluate the ZJU index's advantage over single lipid metabolism indicators, such as HDL, TG and TC. Furthermore, comparisons were made between the ZJU index and its constituent components, including FPG, BMI, AST, and ALT. Statistical significance was determined by a two-tailed test for p-values less than 0.05 and data analysis was performed using R software version 4.4.1.

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3. Results

3.1 Participants Baseline Characteristics

The study encompassed 6244 participants, representing approximately 8.3 million non-institutionalized U.S. inhabitants, with a mean age of 46 years. Of these participants, 3199 were female and 3045 were male. Among the 6244 participants, 8.2% identified as Mexican American, 11% as non-Hispanic Black, 4.4% as other Hispanic, 71% as non-Hispanic White, and 7.0% as other races. Table 1 presents participant characteristics based on depression levels. Significant group differences were found in the ZJU index, age, gender, race, smoke, drink, marital, education, ALT, AST, TG, FPG, BMI, HbA1c, TC, HDL, CRP, and the prevalence of hypertension, hyperlipidemia, and CVD ($P < 0.05$). The median and IQR of the ZJU index are was 38.69 (34.26, 44.24) overall, with 38.34 (34.14, 43.58) for non-depressed participants and 40.48 (34.99, 46.70), 39.18 (33.93, 46.63) and 41.43 (38.01, 48.50) for those with Mild, Moderate and Severe (Table 1).

Table 1. Weighted baseline characteristics of participants.

Characteristic	Overall N = 6244	No N =4184	Mild N =889	Moderate N = 337	Severe N = 182	*P*-Value
ZJU index, median (IQR)	38.69 (34.26, 44.24)	38.34 (34.14, 43.58)	40.48 (34.99, 46.70)	39.18 (33.93, 46.63)	41.43 (38.01, 48.50)	<0.001
Gender, N (%)						<0.001
Male	3045 (49%)	2519 (52%)	352 (39%)	121 (38%)	53 (32%)	
Female	3199 (51%)	2287 (48%)	567 (61%)	216 (62%)	129 (68%)	
Age, median (IQR)	46.00 (33.00, 59.00)	46.00 (33.00, 59.00)	43.00 (31.00, 56.00)	47.00 (33.00, 58.00)	46.00 (37.00, 56.00)	0.008
TC, median (IQR)	193.00 (167.00, 222.00)	193.00 (168.00, 222.00)	194.00 (166.00, 222.00)	191.00 (160.00, 218.00)	192.00 (165.00, 219.00)	0.846
HbA1c, median (IQR)	5.40 (5.10, 5.70)	5.40 (5.10, 5.70)	5.40 (5.10, 5.70)	5.50 (5.20, 5.80)	5.50 (5.30, 5.90)	0.002
CRP, median (IQR)	0.18 (0.07, 0.43)	0.17 (0.07, 0.39)	0.23 (0.09, 0.57)	0.27 (0.10, 0.64)	0.32 (0.11, 0.77)	<0.001
HDL, median (IQR)	52.00 (43.00, 63.00)	52.00 (43.00, 64.00)	52.00 (42.00, 63.00)	53.00 (43.00, 62.00)	50.00 (40.00, 59.00)	0.025
TG, median (IQR)	109.00 (77.00, 158.00)	107.00 (76.00, 154.00)	114.00 (81.00, 168.00)	116.00 (84.00, 170.00)	119.00 (82.00, 193.00)	<0.001
BMI, median (IQR)	27.54 (24.03, 32.04)	27.32 (23.98, 31.46)	28.85 (24.33, 33.94)	27.69 (23.48, 34.70)	30.28 (25.57, 33.95)	<0.001
FPG, median (IQR)	99.00 (92.00, 107.00)	99.00 (92.00, 107.00)	98.00 (91.00, 107.00)	100.00 (92.00, 113.00)	101.00 (95.00, 109.00)	0.05
AST, median (IQR)	23.00 (20.00, 28.00)	23.00 (20.00, 28.00)	22.00 (19.00, 27.00)	22.00 (19.00, 27.00)	22.00 (18.00, 27.00)	<0.001
ALT, median (IQR)	21.00 (17.00, 29.00)	22.00 (17.00, 29.00)	21.00 (16.00, 29.00)	20.00 (16.00, 28.00)	21.00 (16.00, 28.00)	0.004
Education, N (%)						<0.001
<High school	730 (5.9%)	518 (5.4%)	116 (6.4%)	60 (11%)	36 (12%)	

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Completed high school	984 (12%)	691 (10%)	178 (16%)	82 (21%)	33 (16%)	
>High school	4530 (82%)	3597 (84%)	625 (77%)	195 (68%)	113 (72%)	
Marital, N (%)						<0.001
Never married	968 (17%)	708 (16%)	171 (20%)	55 (16%)	34 (15%)	
Married/Living with partner	3909 (66%)	3126 (68%)	529 (60%)	173 (55%)	81 (49%)	
Widowed/Divorced/Separated	1367 (18%)	972 (16%)	219 (20%)	109 (30%)	67 (36%)	
Smoke, N (%)						<0.001
Never	3318 (53%)	2634 (55%)	477 (50%)	134 (34%)	73 (40%)	
Former	1630 (26%)	1303 (26%)	219 (24%)	75 (22%)	33 (17%)	
Now	1296 (22%)	869 (19%)	223 (26%)	128 (44%)	76 (43%)	
Race, N (%)						0.003
Mexican American	1176 (8.2%)	899 (8.1%)	181 (8.5%)	62 (8.5%)	34 (7.9%)	
Other Hispanic	569 (4.4%)	415 (4.1%)	85 (4.9%)	43 (7.2%)	26 (7.3%)	
Non-Hispanic White	3099 (71%)	2423 (72%)	447 (69%)	152 (64%)	77 (64%)	
Non-Hispanic Black	1148 (11%)	874 (10%)	164 (11%)	69 (16%)	41 (18%)	
Other Race	252 (5.5%)	195 (5.5%)	42 (6.0%)	11 (4.3%)	4 (2.7%)	
Drink, N (%)						<0.001
Never	835 (11%)	635 (11%)	117 (11%)	51 (14%)	32 (15%)	
Former	1242 (16%)	923 (16%)	208 (18%)	74 (18%)	37 (17%)	
Mild	1989 (36%)	1635 (38%)	238 (29%)	77 (24%)	39 (26%)	
Moderate	888 (16%)	668 (16%)	146 (18%)	43 (15%)	31 (20%)	
Heavy	1290 (21%)	945 (21%)	210 (23%)	92 (29%)	43 (23%)	
Hyperlipidemia, N (%)						0.64
No	1573 (27%)	1224 (28%)	230 (26%)	84 (28%)	35 (22%)	
Yes	4671 (73%)	3582 (72%)	689 (74%)	253 (72%)	147 (78%)	
Hypertension, N (%)						<0.001
No	3699 (64%)	2919 (66%)	520 (62%)	180 (55%)	80 (48%)	
Yes	2545 (36%)	1887 (34%)	399 (38%)	157 (45%)	102 (52%)	
CVD						<0.001
No	5554 (91%)	4341 (92%)	799 (89%)	277 (85%)	137 (81%)	
Yes	690 (8.6%)	465 (7.5%)	120 (11%)	60 (15%)	45 (19%)	

ZJU: Zhejiang University index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CVD, Cardiovascular disease; BMI: body mass index; CRP: C-reactive protein; FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin; HDL: high-density lipoprotein; TC: total cholesterol; TG: triglycerides; IQR: interquartile range.

The continuous variables were shown as median and IQR. The categorical variables were shown as weighted number with weighted proportion. All estimates were weighted to be nationally representative

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3.2 Association between ZJU Index and Depression

The logistic regression analysis revealed that the ZJU index consistently correlated with depression across both unadjusted (Model 1) and adjusted models (Model 2 and Model 3). In Model 1, which did not adjust for covariates, individuals in the Q4 of the ZJU index exhibited a significantly higher likelihood of experiencing depression compared to those in the Q1 (Odds Ratio [OR]: 1.72; 95% CI: 1.33–2.33, P < 0.001). In Model 2, after controlling for demographic variables and smoking, the OR increased to 1.79 (95% CI: 1.36–2.35, P < 0.001). In Model 3, after controlling for all included confounding variables, the OR was 1.44 (95% CI: 1.01–2.06, P = 0.046). When considering the ZJU index as a continuous variable, each 10-point increment was associated with depression across Models 1–3. Nonetheless, RCS analysis suggested that ZJU index should not be treated as a continuous variable for exploring this association. (Table 2)

Table2. Association of the ZJU index with depression.

	Characteristic (Per 10 points increase)	Model 1 (OR ,95% CI)	P-value	Model 2 (OR ,95% CI)	P-value	Model 3 (OR ,95% CI)	P-value
	ZJU (categorical)						
	Q1	Reference		Reference		Reference	
	Q2	1.06(0.73, 1.55)	0.8	1.14(0.76, 1.71)	>0.5	1.09(0.7, 1.69)	0.7
Depress	Q3	0.91(0.62, 1.36)	0.7	0.98(0.63, 1.52)	>0.9	0.91(0.56, 1.49)	0.7
	Q4	1.72(1.33, 2.33)	<0.001	1.79(1.36, 2.35)	<0.001	1.44(1.01, 2.06)	0.046
	ZJU (continuity)	1.30 (1.16,1.46)	<0.001	1.31 (1.17, 1.47)	<0.001	1.16 (1.01, 1.33)	0.033
				U-shape P-Nonlinear < 0.05			

CI, Confidence interval; OR, Odds ratio; ZJU, ZJU index; Q, Quartiles.
Model 1: No covariables adjusted;
Model 2: Adjusted for Age, Race, Education, Marital status, Smoke, Alcohol;
Model 3: Adjusted for Age, Race, Education, Marital status, Smoke, Alcohol, Hyperlipidemia, Hypertension, CVD, TC, HDL, HbA1c, CRP

3.3 Nonlinear link Between ZJU Index and Depression

A U-shaped nonlinear association was detected between the ZJU index and depression (P-nonlinear = 0.03), with an inflection point at 35.47 (Figure 2). This threshold effect indicates a negative association before the inflection point and a positive association thereafter.

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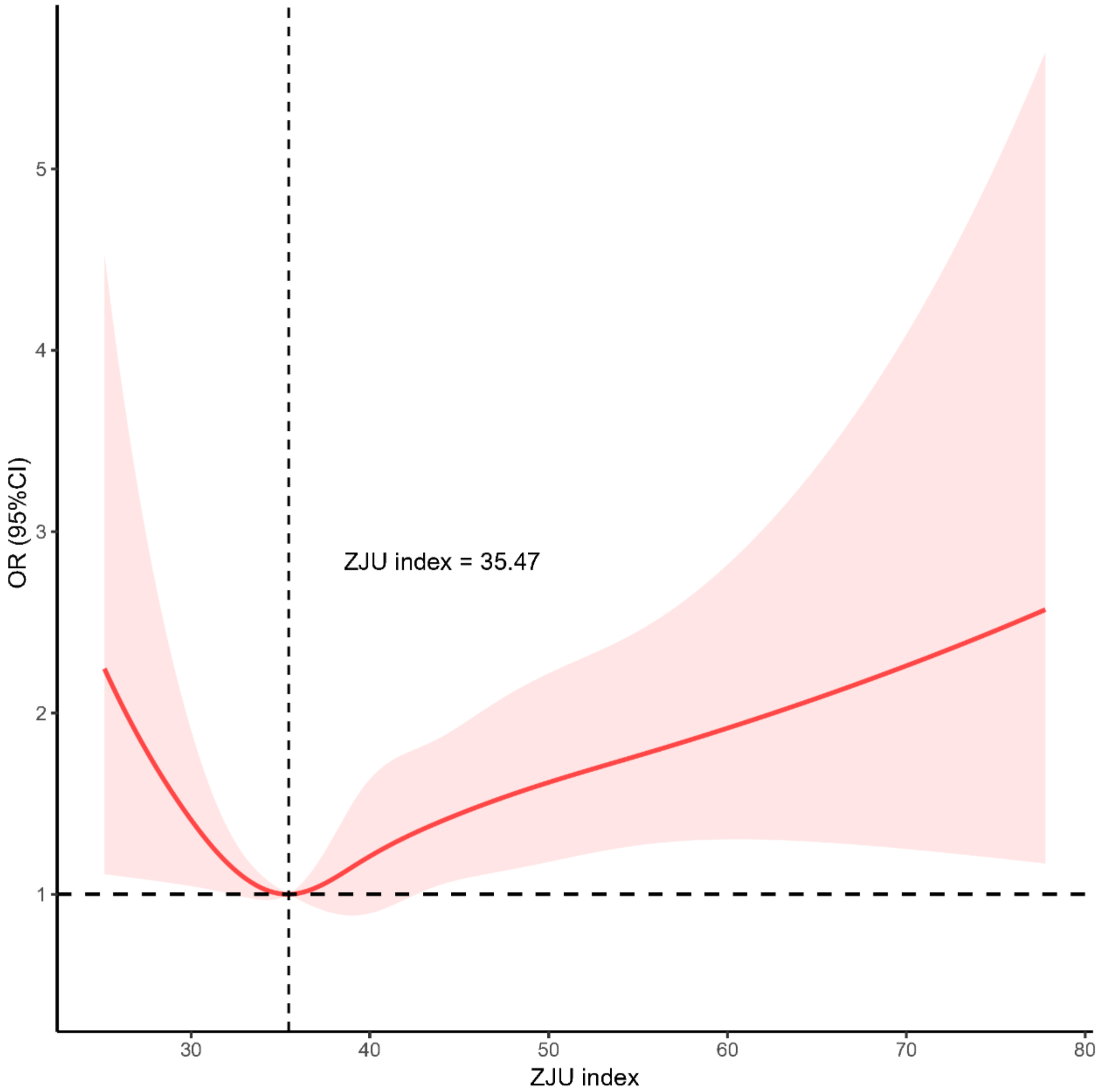

Fig 2. RCS curve fits the Association of ZJU index with depression.

Note: Adjusted for age, race, education, marital status, smoking, alcohol use, hypertension, hyperlipidemia, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, cardiovascular disease and C-reactive protein. ZJU index, Zhejiang University index; OR, odds ratio; CI, confidence interval.

3.4 Subgroup Analysis

The relationship strength between the ZJU score and depression was evaluated using stratified weighted multivariable analysis. Analyses were stratified by age, race, sex, education, smoking, alcohol use, marital status, hyperlipidemia, CVD and hypertension. A significant difference in the ZJU index was observed between the smoking and CVD groups (P for interaction < 0.05), indicating that smokers exhibit heightened sensitivity to the effects of the ZJU index, while CVD patients are more susceptible to the effects of the ZJU index (Figure 3).

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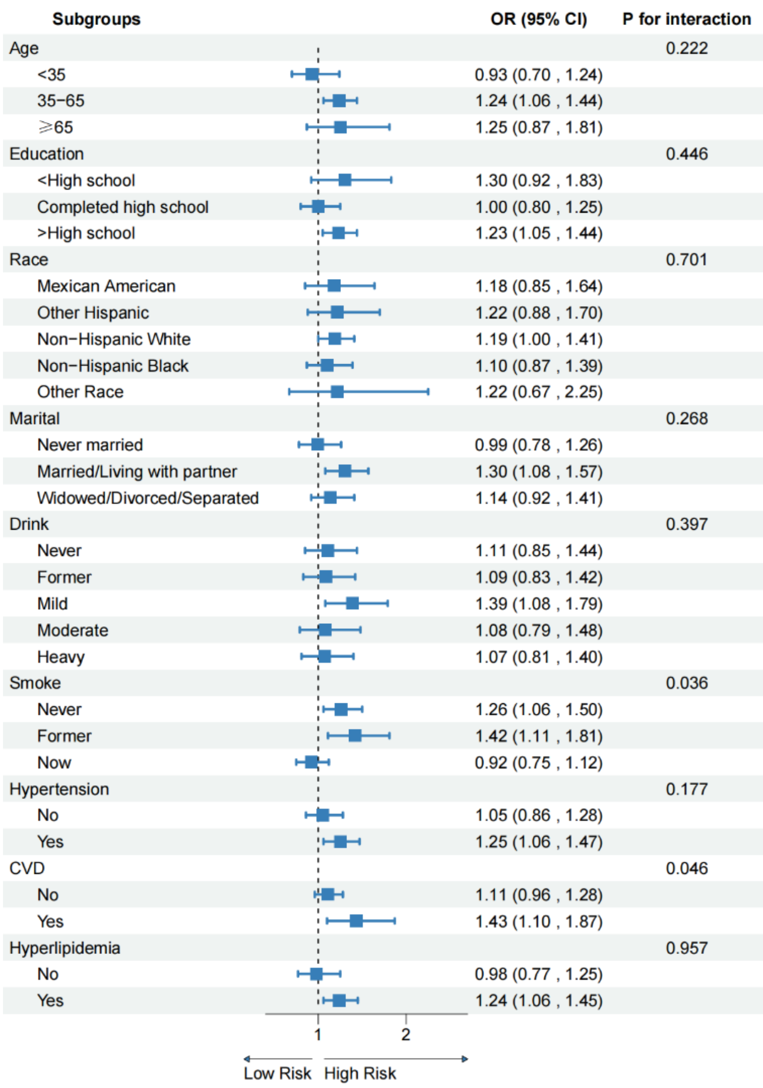

Fig 3. Subgroup analysis of the association of the ZJU index and depression.

Note: ORs were calculated as each 10 points increase in ZJU index. Each stratification was adjusted for age, race, education, marital status, smoking, alcohol use, hypertension, hyperlipidemia, glycosylated hemoglobin, total cholesterol, high-density lipoprotein, cardiovascular disease and C-reactive protein. OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease.

3.5 Predictive Value of ZJU Index for Depression

Multivariable regression models are frequently employed to develop conventional predictive models, incorporating predictors including age, race, education level, marital status, smoking, alcohol consumption, serum CRP levels, and the presence of CVD. The ZJU index and other related metabolic indicators were incorporated into the conventional predictive models. Our findings indicate that the inclusion of the ZJU index significantly enhanced the model's performance. Specifically, the AUC of the original conventional model was 0.706, while the AUC of the model with the inclusion of the ZJU index increased to 0.714. Through the DeLong test, the conventional model with the ZJU index significantly outperforms the original conventional model without the ZJU index in terms of discrimination ($P < 0.05$). In comparison, the AUC values of models including other metabolic indicators were as follows: TG (AUC = 0.708), TC (AUC = 0.706), HDL (AUC = 0.706), BMI (AUC = 0.710), FPG (AUC = 0.707), AST (AUC = 0.705), and ALT (AUC = 0.706). These results suggest that the inclusion of the ZJU index more effectively augments the predictive capability of the model compared to other metabolic indicators (Figure 4).

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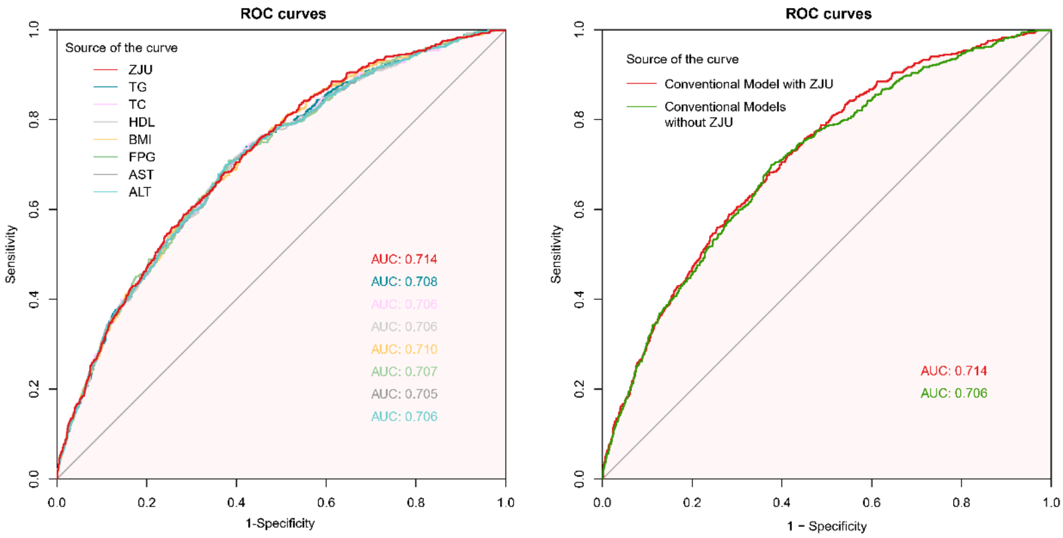

Fig 4. Evaluation of the Predictive Value of ZJU Index Using ROC Curves and AUC.

Note: Fig4A, ROC Curve Comparison of ZJU Index and Other Metabolic Indicators in Conventional Predictive Models. Fig4B, ROC Curves of Predictive Model with and without ZJU Index. ROC, receiver operating characteristic; ZJU, Zhejiang University index; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein; BMI, body mass index; FPG, fasting plasma glucose; AST, aspartate transaminase; ALT, alanine transaminase; AUC, area under the curve.

4. Discussion

This study found a significant association between the ZJU index and depression, with a non-linear relationship identified through RCS. Piecewise logistic regression revealed that individuals in the Q4 group of the ZJU index had a significantly higher likelihood of experiencing depression compared to those in the Q1 group. This demonstrates that the ZJU index was significantly associated with an increased likelihood of depression, and this relationship remained robust even after adjusting for multiple confounding factors. When the ZJU index is below 35.47, the likelihood of depression gradually decreases with an increase in the ZJU index. However, when the ZJU index exceeds 35.47, its increase elevates the probability of depression. The ROC curve analysis revealed that the ZJU index outperformed traditional metabolic indicator in predicting depression. The ZJU index offers a more comprehensive assessment of the collective metabolic factors influencing depression compared to other metabolic indices.

Several studies have shown that changes in lipids and glucose levels within the ZJU index influence the occurrence of depression through their effects on the pathophysiological mechanisms of obesity and diabetes. The reciprocal link between depression and obesity is largely influenced by changes in homeostatic regulatory systems, such as the immune-inflammatory system, neuroendocrine regulators, and the hypothalamic-pituitary-adrenal axis. Additionally, this association involves the role of brain functional regions in integrating homeostatic and emotional regulatory responses [16]. Transcriptomic data reveal that genes linked to obesity are prominently expressed in brain regions like the hippocampus and limbic system [23]. The investigators employed Mendelian randomization to establish a positive causal relationship between TG levels and, to a lesser extent, alterations in cholesterol levels with five depression phenotypes [24]. Obese patients often influence their gut microbiota through dietary changes, thereby improving metabolic indicators and alleviating depressive symptoms. Studies have found that dietary restrictions and low-energy diets implemented in obese youth resulted in a reduction of some depressive symptoms [25]. In terms of diabetes, although the mechanisms by which type 1 diabetes exacerbates depression remain unclear, type 2 diabetes shares common mechanisms with depression related to genetic and biochemical metabolic pathways [18]. Previous studies have explained the association of metabolic factors with depression through single indicators. The impact of liver function changes on depression, as reflected by alterations in ALT and AST within the ZJU index, should not be overlooked. Kim et al. [17] examined the link between metabolic dysfunction-related fatty liver and depression, revealing an association with significant liver fibrosis using regression models. In 2023, He et al [26] identified a causal link between elevated BMI and depression through a Mendelian randomization study. In the same year, Kwon et al [27] utilized the National Health Insurance Service-National Sample Cohort database and identified an association between FPG levels and depression. In 2024, Chourpiliadis et al [28], by analyzing participants from the Apolipoprotein-Related Mortality Risk cohort, concluded that elevated levels of glucose and triglycerides are associated with future risk of depression, anxiety, and stress-related disorders. Furthermore, sex is a significant factor that cannot be overlooked. A meta-analysis revealed that the prevalence of major depression is higher in females across all populations, underscoring the importance of gender as a factor influencing depression [29]. The components of the ZJU index suggest that changes in the index may lead to various metabolic alterations, including those related to liver function, thus increasing probability of depression. Compared to single indicators, the ZJU index integrates multiple metabolic factors, such as FPG, BMI, TG, AST, ALT, to provide a more comprehensive reflection of metabolic status. Furthermore, the ZJU index accounts for gender differences, effectively considering the metabolic variations between males and females, and provides a thorough assessment of the association between various metabolic diseases and depression from the perspective of metabolic factors.

The ZJU index serves as a crucial clinical marker for forecasting liver fibrosis and non-alcoholic cirrhosis, with liver damage significantly influencing depression onset [17,30]. Research has elucidated the critical role of the gut-microbiome-brain axis in the pathogenesis of depression, highlighting the vagus nerve as a key mediator of communication between gut microbiota and the brain [31,32]. Systemic inflammation triggered by metabolic dysregulation may also contribute to the onset of depression [33]. Evidence from animal studies suggests that dietary supplementation can enhance metabolic regulation and mitigate depression-like behaviors caused by liver ischemia/reperfusion injury, mediated through the gut-liver-brain axis [34,35]. The ZJU index indicates alterations in liver function and systemic metabolism, highlighting shifts in metabolic factors that impact the brain and contribute to depression.

In the selection process of study participants, it was found that lifestyle and chronic disease factors significantly influence depression. This suggests that lifestyle habits and chronic diseases are important determinants of depressive symptoms [36]. When faced with major or chronic illnesses, individuals may experience heightened psychological stress and negative emotions, making them more susceptible to depression. Lifestyle and disease factors like smoking [37], alcohol consumption [38], hypertension [39], and diabetes [40], can impact metabolic levels. These factors may lead to liver damage or increased body fat, thereby affecting the ZJU index and potentially elevating probability of depression onset. Several studies have demonstrated a correlation between depression and the human immune response [41,42]. CRP, as an inflammatory marker, is strongly associated with major depressive disorder. This association is a key reason for its inclusion in this predictive model. Moreover, this form of depression, often referred to as "inflammatory depressive disorder," is characterized by its immunological diagnosis and may respond favorably to treatment with anti-inflammatory medications [42].

The ZJU index possesses clinical significance and plays a crucial role in monitoring the mental state of patients with chronic diseases. By integrating multiple metabolic indicators, the ZJU index facilitates the clinical screening for early depression in patients with specific chronic conditions, particularly those with hyperlipidemia, diabetes mellitus, and liver diseases. The progression of chronic diseases can be tracked using laboratory blood tests, biochemical markers, and body mass index (BMI). Concurrently, the early assessment of patients' mental and neurological states through the ZJU index can contribute to reducing depression rates in this patient population.

5. Advantages and limitations

This study possesses several notable strengths. Firstly, the NHANES database utilizes a multi-stage sampling methodology, which ensures that the weighted data accurately represent the entire U.S. population. Secondly, the study encompasses a substantial sample size of 12,637 participants spanning from 2005 to 2018, thereby providing both an extensive temporal scope and a large cohort. Lastly, the study integrates multiple covariables and employs multivariable analyses, enabling a comprehensive evaluation of the research question. Nevertheless, this study is subject to certain limitations. The reliance on a singular set of depression scoring criteria may compromise the accuracy of depression diagnoses, and the absence of specific subtyping restricts a more nuanced clinical analysis of the relationship between depression and other variables. Consequently, future research should incorporate more comprehensive evaluation metrics and employ more sophisticated subtyping methodologies to improve the accuracy and clinical relevance of the findings.

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6. Conclusion

Elevated ZJU index were positively associated with depression. Based on the study's findings, it is recommended that clinicians consider utilizing the ZJU index as a preliminary screening tool for identifying potential depression in patients.

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