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U-Shaped Associations Between Metabolic Indices and Depression in Middle-aged and Older Adults: A Data-Driven Cross-Sectional Study from CHARLS

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Abstract

Objective: While the relationship between metabolic dysregulation and depression is well-established, its specific nature in the elderly remains obscure, partially due to the limitations of traditional metrics like BMI in distinguishing visceral fat. This study aimed to systematically investigate the associations between novel composite metabolic indices and depressive symptoms in community-dwelling Chinese middle-aged and older adults, with a particular focus on non-linear threshold effects. Methods: This cross-sectional analysis utilized nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS), comprising 10,195 participants aged ≥45 years. Depressive symptoms were assessed using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10). Four novel indices were calculated: China Visceral Adiposity Index (CVAI), Lipid Accumulation Product (LAP), Metabolic Score for Insulin Resistance (METS-IR), and Metabolic Score for Visceral Fat (METS-VF). Besides conventional statistics, we employed multivariable logistic regression to decode the independent associations, with a particular focus on identifying non-linear threshold effects. Results: After adjusting for sociodemographic, lifestyle, and clinical confounders, CVAI, LAP, METS-IR, and METS-VF allexhibited significant U-shaped nonlinear associations with depressive symptoms. Contrary to linear expectations, moderate levels of these indices (typically corresponding to the third quartile) were associated with the lowest risk of depression, conferring a protective effect that diminished or disappeared at extremely high or low levels. Conclusion: In Chinese community-dwelling middle-aged and older adults, moderate visceral adiposity or insulin resistance may be associated with a reduced risk of depression, demonstrating a U-shaped threshold effect. These findings underscore the value of utilizing composite metabolic indices as computational biomarkers for precise mental health screening in aging populations.

Keywords

database-derived analysis, Computational Metabolic Biomarkers, depression, U-shaped association, data-driven phenotyping

1. Introduction

Depression, characterized by significant and persistent low mood, has emerged as one of the leading causes of disability worldwide, posing a substantial challenge to public health systems [1]. This burden is particularly acute in China, where an accelerating aging population faces physiological decline, multi-morbidity, and social marginalization [2-5]. While these psychosocial stressors are critical, <growing evidence from psychosomatic medicine suggests> that the onset of depression is not merely psychological but inextricably linked to systemic metabolic homeostasis.

Central to this physiological dysregulation is Insulin Resistance (IR), a core pathology of metabolic syndrome often implicated in depression's pathophysiology. Mechanisms linking IR to depressive symptoms include chronic low-grade inflammation, oxidative stress, and hypothalamic-pituitary-adrenal (HPA) axis dysfunction, all of which impair neuroplasticity and cerebral energy metabolism [6-11].However, capturing such metabolic subtleties in large-scale geriatric epidemiology remains technically challenging. The widely used Body Mass Index (BMI), for instance, fails to distinguish between subcutaneous fat, visceral fat, and muscle mass. This lack of specificity is especially problematic for the Chinese elderly, who frequently exhibit "Metabolically Obese Normal Weight" or "Sarcopenic Obesity"—phenotypes where metabolic dysregulation co-occurs with a normal BMI [12]. Reliance on BMI alone, therefore, risks obscuring the true association between metabolic abnormalities and depressive symptoms

To overcome these methodological limitations, researchers have developed computational biomarkers that integrate anthropometric and biochemical parameters, offering accessible alternatives to the invasive "gold-standard" clamp technique. Foremost among indices targeting visceral adiposity are the China Visceral Adiposity Index (CVAI) and the Lipid Accumulation Product (LAP). The former (CVAI) has demonstrated superior sensitivity in capturing visceral fat heterogeneity and cardiovascular risk in Chinese populations [12-15] , while the latter (LAP) specifically reflects excessive lipid accumulation associated with obstructive sleep apnea and fatty liver disease[16, 17]. Complementing these adiposity markers are indicators of insulin sensitivity, including the Triglyceride-Glucose Index (TyG), the Metabolic Score for Insulin Resistance (METS-IR), and its derivative, the Metabolic Score for Visceral Fat (METS-VF). These surrogate markers have shown excellent efficacy in predicting type 2 diabetes and cardiovascular events[18-25] .

While these metrics have established predictive value in metabolic diseases in the fields of Bioinformatics and Intelligent Computing[26, 27],their specific epidemiological relationship with geriatric depression—particularly among community-dwelling Chinese adults—remains inadequately investigated. To elucidate this relationship, leveraging large-scale cohort data to mine novel biomarkers and construct interpretable, discriminative computational models has emerged as a pivotal approach in computational biology for enabling early disease warning and advancing precision health management. Previous literature has largely been confined to single-indicator analyses, often neglecting potential non-linear dose-response patterns (e.g., U-shaped or J-shaped associations) that may define the "metabolic-depression" interface. Addressing this gap, the current study leverages nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS) to: (1) systematically compare the associations of five novel indices (CVAI, LAP, METS-IR, METS-VF, and TyG) with depressive symptoms; and (2) elucidate potential non-linear threshold effects. Such insights aim to validate metabolic health as computational biomarkers, providing empirical evidence for early screening and precise intervention in geriatric mental health.

2. Materials and Methods

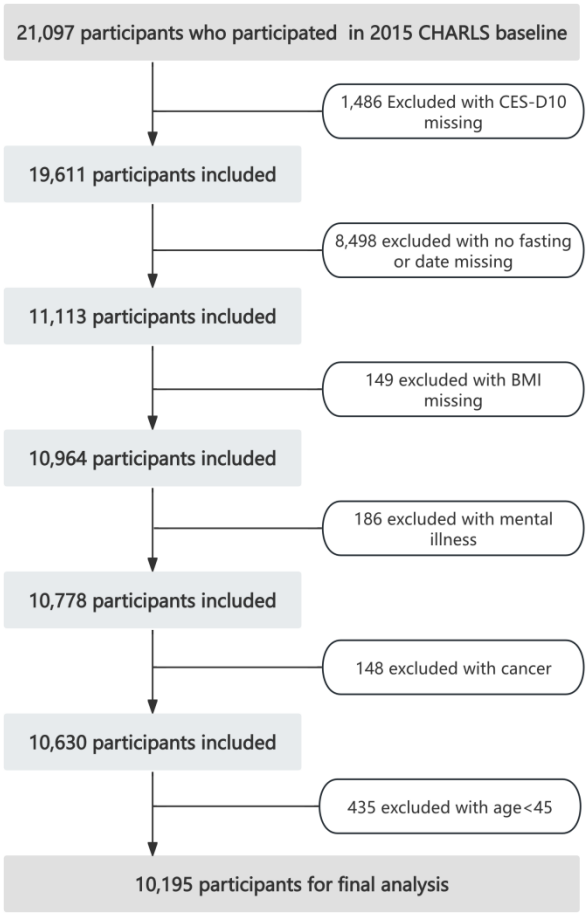
2.1 Data Source and Study Design

This study employed a cross-sectional design using data from the CHARLS database for empirical analysis. CHARLS is a nationally representative longitudinal social survey project designed to comprehensively assess the socioeconomic status and health conditions of the Chinese population aged 45 and above. Its sample covers 150 county-level units and 450 communities/villages across 28 provinces (autonomous regions/municipalities). Although CHARLS includes multiple waves of follow-up data from 2011 to 2020, considering the completeness of core variables and research timeliness, this study primarily utilized data from the 2015 survey for analysis. The project's ethical review was approved by the Biomedical Ethics Committee of Peking University (Approval No.: IRB00001052-11015), and all participants provided written informed consent before enrollment.

2.2 Study Participants

The participant selection process is detailed in Figure 1. Based on the CHARLS 2015 dataset, 21,097 respondents were initially included. To ensure analytical rigor, stringent exclusion criteria were applied to remove ineligible samples: (1) those with missing data for the key variable (CES-D-10 score); (2) those lacking basic parameters required for calculating IR-related indicators (e.g., unclear fasting status, missing BMI data); (3) individuals with a prior diagnosis of severe psychiatric disorders or malignancies and other comorbidities that might interfere with depression risk assessment; and (4) individuals aged <45 years (non-target population). After this strict screening, a total of 10,195 respondents were included in the final analytical cohort for this study.

Figure1: Data Curation and Analytical Cohort Selection Pipeline



2.3 Variable Definitions and Measurements

2.3.1 Assessment of Depressive Symptoms.

Depressive status was assessed using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10). This scale has demonstrated good reliability and validity and effectively discriminates between normal mood and clinical depressive states in the Chinese elderly community population[28-30] . The scale comprises 10 items, requiring respondents to report the frequency of specific emotions or behaviors during the past week. Responses are scored on a 4-point scale ranging from 0 (rarely or none of the time, <1 day) to 3 (most or all of the time, 5–7 days), yielding a total score between 0 and 30 [31]. Based on established cut-off values from prior research, a CES-D-10 total score of ≥10 was defined as the presence of depressive symptoms (coded as 1), while a score <10 was defined as the absence of depressive symptoms (coded as 0).

2.3.2 Insulin Resistance Related computational biomarkers

The integration of multiple readily available clinical variables(height, weight, waist circumference (WC), body mass index (BMI), and waist-to-height ratio (WHtR)) and biochemical markers (fasting plasma glucose (FPG), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C))through specific algorithms enables the construction of composite computational models built upon routinely available clinical metrics. This data-driven approach aims to derive more effective predictive or diagnostic tools than any single parameter alone.

Five computational biomarkers were selected to multidimensionally assess insulin resistance and visceral adiposity: CVAI, LAP, METS-IR, METS-VF, and TyG. The specific formulas for each index are as follows (Note: Units for FPG, TG, and HDL-C are mmol/L):

(1) China Visceral Adiposity Index (CVAI) [15]

male:$CVAI=-267.93+0.68\times age+0.03\times BMI+4.00\times WC+22.00\times \log_{10} TG-16.32\times HDL\_C$;

female:$CVAI=-187.32+1.71\times age+4.23\times BMI+1.12\times WC+39.76\times \log_{10} TG-11.66\times HDL\_C$.

(2) Lipid Accumulation Product (LAP)[32]

male: $LAP=(WC-65)\times TG$;

female: $LAP=(WC-58)\times TG$.

(3) Metabolic Score for Insulin Resistance (METS-IR)[20]_$IR=\ln(2\times FPG+TG)\times BMI/\ln(HDL_C)$

(4) Metabolic Score for Visceral Fat (METS-VF)[22]:

male: $METS\_VF=4.466+0.011*[\ln(METS\_IR)]^3+3.239*[\ln(WHtR)]^3+0.319+0.504*[\ln(age)]$;

female: $METS\_VF=4.466+0.011*[\ln(METS\_IR)]^3+3.239*[\ln(WHtR)]^3+0.594*[\ln(age)]$

(5) Triglyceride-Glucose Index (TyG)[33]:$\ln(TG\times FPG/2)$

2.3.3 Covariates.

To control for potential confounding factors, three categories of covariates were included: sociodemographic characteristics, lifestyle factors, and clinical health status. Sociodemographic variables included age, sex, educational attainment (categorized as below primary school, primary/junior high school, and high school or above), residence (urban/rural), annual household income, and per capita consumption expenditure. Health behavior and clinical characteristics included current smoking status, current alcohol consumption status (both as binary variables: yes/no), as well as BMI and biochemical markers (TG, FPG, HDL-C) obtained through standardized physical examinations.

2.4 Data Analysis Pipeline

All data preprocessing, including cleaning, variable calculation, and management, was conducted using a computational pipeline implemented in R (version 4.3.1). The analysis comprised two main steps: (1) Conventional statistical analysis including descriptive statistics and chi-square tests performed in SPSS 26.0; and (2) Core association analysis utilizing multivariable logistic regression models in R to elucidate the independent associations, with a specialized focus on non-linear pattern discovery by treating metabolic indices as categorical variables (quartiles). Data visualization, including the patient selection flowchart (Figure 1) and comparative box plots (Figure 2), was generated to enhance the interpretability of the complex dataset."

For descriptive statistics, the normality of continuous variables was assessed first. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median (interquartile range, IQR). Categorical variables are presented as frequency (percentage). For group difference analysis, Chi-square tests were used for categorical variables. To determine the independent association between each IR-related index and depressive symptoms, multivariable logistic regression models were constructed, with results expressed as odds ratios (OR) and their 95% confidence intervals (95% CI). To rigorously control for confounding bias, a stepwise adjustment strategy was employed for the models:
Model 1: The basic adjustment model, including only sex, age, educational level, and BMI.

Model 2: Based on Model 1, further adjusted for household income, per capita consumption, smoking, and alcohol consumption status to account for the influence of socioeconomic status and lifestyle factors.
All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

A total of 10,195 participants were included in this study, with a mean age of 60.5 ± 9.5 years, of whom 53.0% (n=5,407) were women. Based on the CES-D-10 criteria, the overall sample was divided into a depressive symptoms group (n=3,359, 32.95%) and a non-depressive symptoms group (n=6,836, 67.05%). The comparative results of baseline characteristics between the two groups are detailed in Table 1.

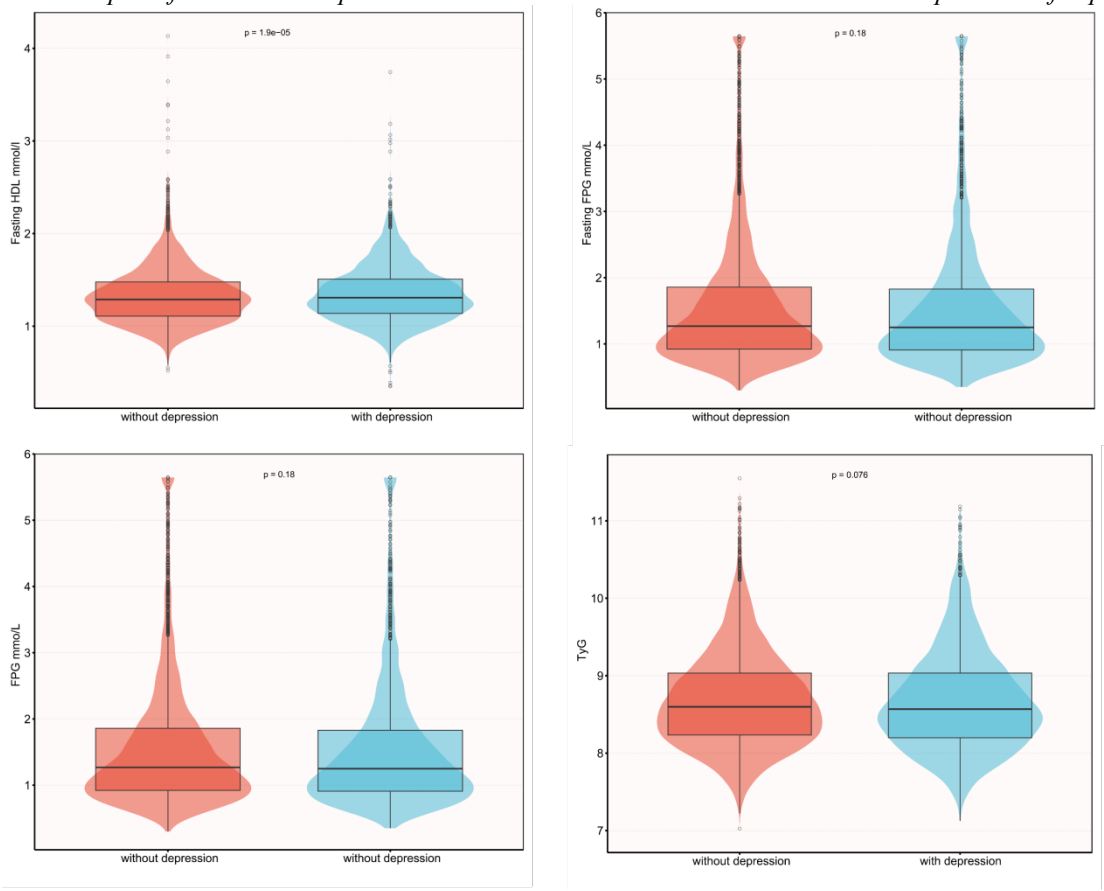
Table1: Baseline characteristics of participants.

Variables	Total (n = 10195)	0 (n = 6836)	1 (n = 3359)	p
WHtR(Mean ± SD)	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.598
BMI (Mean ± SD)	24.5 ± 13.4	24.5 ± 12.3	24.5 ± 15.4	0.765
FPG (Mean ± SD)	5.6 ± 1.7	5.6 ± 1.6	5.6 ± 1.8	0.883
Fasting TG (Mean ± SD)	1.6 ± 1.0	1.6 ± 1.0	1.6 ± 1.0	0.58
Fasting HDL (Mean ± SD)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	< 0.001
CVAI., Median (IQR)	101.9 (73.5, 129.9)	103.4 (74.5, 131.3)	99.5 (71.0, 127.4)	< 0.001
LAP., Median (IQR)	31.0 (16.7, 55.2)	31.4 (17.1, 55.2)	30.3 (16.0, 55.0)	0.035
METS-IR.(Mean ± SD)	36.5 ± 19.3	36.6 ± 17.5	36.3 ± 22.6	0.493
METS-VF., Median (IQR)	6.6 (6.2, 7.0)	6.6 (6.2, 6.9)	6.6 (6.2, 7.0)	0.743
TyG, Mean ± SD	8.7 ± 0.6	8.7 ± 0.6	8.7 ± 0.6	0.237
Age, Mean ± SD	60.5 ± 9.5	60.3 ± 9.6	60.9 ± 9.2	0.006
Edu, n (%)				< 0.001
High school or above	1011 (9.9)	837 (12.2)	174 (5.2)	
Elementary school	2859 (28.1)	1994 (29.2)	865 (25.8)	
below Elementary school	4312 (42.3)	2508 (36.7)	1804 (53.8)	
Middle school	2007 (19.7)	1494 (21.9)	513 (15.3)	
Gender, n (%)				< 0.001
male	4788 (47.0)	3550 (51.9)	1238 (36.9)	
female	5407 (53.0)	3286 (48.1)	2121 (63.1)	
Habitation, n (%)				< 0.001
Town	3807 (37.3)	2818 (41.2)	989 (29.4)	
Rural	6388 (62.7)	4018 (58.8)	2370 (70.6)	
Total household income, Median (IQR)	4065.0 (1020.0, 27075.0)	5400.0 (1200.0, 32390.0)	2942.5 (885.0, 13975.0)	< 0.001
Per capita household consumption, Median (IQR)	8791.0 (4920.0, 15382.7)	9092.0 (5175.0, 15876.2)	8340.0 (4569.3, 14281.0)	< 0.001
currently drink, n (%)				< 0.001
no	6536 (64.1)	4168 (61)	2368 (70.5)	
yes	3655 (35.9)	2665 (39)	990 (29.5)	
currently smoke, n (%)				< 0.001
no	7362 (72.2)	4819 (70.5)	2543 (75.7)	
yes	2828 (27.8)	2013 (29.5)	815 (24.3)	

Note: WHtR denotes waist-to-height ratio, BMI denotes body mass index, FPG denotes fasting plasma glucose, CVAI de notes China Visceral Adiposity Index, LAP denotes Lipid Accumulation Product, METS-IR denotes Metabolic Score for Insulin Resistance, METS-VF denotes Metabolic Score for Visceral Fat, and TyG denotes Triglyceride-Glucose Index.

Significant differences were observed in sociodemographic and behavioral characteristics between the two groups. The depressive symptoms group had a significantly higher proportion of women, individuals with lower educational attainment, rural residents, and those with lower household income ($P < 0.001$). Notably, smoking and alcohol consumption were more prevalent in the non-depressive symptoms group ($P < 0.001$). In the comparison of metabolic and insulin resistance (IR)-related indices, the depressive symptoms group exhibited a relatively more favorable metabolic profile. Specifically, the CVAI level in this group [99.5 (71.0, 127.4)] was significantly lower than that in the non-depressive group [103.4 (74.5, 131.3), $P < 0.001$]. A similar trend was observed for METS-IR levels [34.5 (29.9, 39.9) vs. 35.4 (30.6, 40.4), $P < 0.001$]. Regarding routine biochemical indicators, fasting plasma glucose (FPG) levels were significantly higher in the non-depressive group ($P = 0.0068$). Although triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and the TyG index did not show statistically significant differences between the groups, data distributions indicated a tendency for the non-depressive group to have higher TG and TyG levels.

Figure2: Box plot of the relationship between conventional biochemical indicators and the presence of depression.



3.2 Univariate Analysis

Table 2 presents the results of the univariate logistic regression analysis examining the impact of each variable on the risk of depressive symptoms. Sociodemographic and lifestyle factors demonstrated significant predictive value. Higher levels of education and household income were associated with a lower risk of depression. The risk of developing depression was 85% higher in women compared to men (OR = 1.85). Interestingly, smoking and alcohol consumption showed a statistically significant protective effect against depressive symptoms in the univariate analysis.

For the IR-related indices (CVAI, LAP, METS-IR, METS-VF), which exhibited a skewed distribution, analysis was performed after grouping the data into quartiles (Q1-Q4).

CVAI: Showed a significant negative trend. As CVAI levels increased, the risk of depression progressively decreased. Compared to the lowest quartile (Q1), individuals in the highest quartile (Q4) had a 20% lower risk of depression.

METS-IR: Similarly demonstrated a protective effect, with the Q4 group showing a 20% reduced risk compared to the Q1 group.

Other Indices: LAP and METS-VF did not show a significant linear trend in the univariate analysis. However, METS-VF indicated a potential nonlinear U-shaped association.

Table 2: Results of Univariate Analysis.

Variable	OR_95CI	P_value
WHtR	0.89 (0.59~1.36)	0.598
BMI	1 (1~1)	0.766
FPG	1 (0.97~1.02)	0.882
Fasting TG	0.99 (0.95~1.03)	0.58
Fasting HDL	1.26 (1.11~1.44)	<0.001
CVAI.	1 (1~1)	0.016
LAP.	1 (1~1)	0.366
METS. IR.	1 (1~1)	0.497
METS. VF.	1 (0.99~1.01)	0.754
TyG	0.96 (0.9~1.03)	0.237
Age	1.01 (1~1.01)	0.006
High school or above	1(Ref)	
below Elementary school	3.46 (2.91~4.12)	<0.001
Elementary school	2.09 (1.74~2.5)	<0.001
Middle school	1.65 (1.36~2)	<0.001
Female	1.85 (1.7~2.01)	<0.001
Rural	1.68 (1.54~1.84)	<0.001
Total household income	1 (1~1)	<0.001
Per capita household consumption	1 (1~1)	0.001
currently drink	0.65 (0.6~0.71)	<0.001
currently smoke	0.77 (0.7~0.84)	<0.001
CVAI		
Q1	1(Ref)	
Q2	0.95 (0.84~1.06)	0.36
Q3	0.86 (0.76~0.96)	0.009
Q4	0.8 (0.71~0.9)	<0.001
LAP		
Q1	1(Ref)	
Q2	0.91 (0.81~1.02)	0.095
Q3	0.85 (0.76~0.96)	0.007
Q4	0.91 (0.81~1.02)	0.101
METS-IR		
Q1		
Q2	0.93 (0.83~1.04)	0.195
Q3	0.79 (0.7~0.89)	<0.001
Q4	0.8 (0.71~0.9)	<0.001
METS-VF		

Q1	1(Ref)	
Q2	0.89 (0.79~1)	0.042
Q3	0.87 (0.77~0.97)	0.017
Q4	1 (0.89~1.13)	0.961

Note: CVAI, LAP, METS-IR, and METS-VF were converted into quartiles for analysis (first quartile [Q1]: lowest 25%; fourth quartile [Q4]: highest 25%).

3.3 Multivariable Logistic Regression Analysis

To control for confounding factors and elucidate the independent effects of each IR-related index, two adjusted models were constructed: Model 1 adjusted for age, sex, education, and BMI; Model 2 further adjusted for income, consumption, smoking, and alcohol consumption.

3.3.1 CVAI and Depressive Symptoms.

As shown in Table 3, in Model 1, CVAI maintained a significant linear protective effect, with the Q4 group showing a 25% reduced risk (P < 0.001). However, in the fully adjusted Model 2, the relationship between CVAI and depression risk transformed into a nonlinear U-shaped curve. The protective effect peaked at the third quartile (Q3) (OR = 0.68, P < 0.001), while this protective effect attenuated in the Q4 group (OR approached 1, though it remained significant with P = 0.039).

Table 3: Results of Multivariable Analysis for CVAI.

CVAI Model 1						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M1. OR (95%CI)	adj. P value
Q1	2534	895 (35.3)	1(Ref)		1(Ref)	
Q2	2534	864 (34.1)	0.95 (0.84~1.06)	0.36	0.85 (0.76~0.96)	0.009
Q3	2534	807 (31.8)	0.86 (0.76~0.96)	0.009	0.76 (0.67~0.86)	<0.001
Q4	2535	768 (30.3)	0.8 (0.71~0.9)	<0.001	0.75 (0.66~0.85)	<0.001
Trend.test	10137	3334 (32.9)	0.92 (0.89~0.96)	<0.001	0.91 (0.87~0.94)	<0.001
CVAI Model 2						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M2. OR (95%CI)	adj. P value
Q1	2534	895 (35.3)	1(Ref)		1(Ref)	
Q2	2534	864 (34.1)	0.95 (0.84~1.06)	0.36	0.77 (0.62~0.95)	0.013
Q3	2534	807 (31.8)	0.86 (0.76~0.96)	0.009	0.68 (0.55~0.84)	<0.001
Q4	2535	768 (30.3)	0.8 (0.71~0.9)	<0.001	0.8 (0.64~0.99)	0.039
Trend.test	10137	3334 (32.9)	0.92 (0.89~0.96)	<0.001	0.92 (0.86~0.99)	0.025

Note: CVAI was converted into quartiles for analysis (first quartile [Q1]: lowest 25%; fourth quartile [Q4]: highest 25%). Model 1 adjusted for age, sex, education, and BMI. Model 2 further adjusted for income, consumption, smoking, and alcohol consumption on the basis of Model 1.

3.3.2 METS-IR and Depressive Symptoms.

As shown in Table 4, METS-IR exhibited a typical U-shaped protective relationship in both models. As the index increased, the depression risk initially decreased and then subsequently increased. In Model 2, the Q3 group demonstrated the strongest protective effect (OR = 0.76, P = 0.012), whereas the associations for the Q2 and Q4 groups did not reach statistical significance. This suggests that a moderate level of METS-IR may be associated with the lowest risk of depression.

Table 4: Results of Multivariable Analysis for METS-IR.

METS-IR Model 1						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M1. OR (95%CI)	adj. P value
Q1	2537	910 (35.9)	1(Ref)		1(Ref)	
Q2	2537	866 (34.1)	0.93 (0.83~1.04)	0.195	0.89 (0.79~1)	0.056
Q3	2537	776 (30.6)	0.79 (0.7~0.89)	<0.001	0.78 (0.69~0.88)	<0.001
Q4	2538	787 (31)	0.8 (0.71~0.9)	<0.001	0.8 (0.7~0.9)	<0.001
Trend.test	10149	3339 (32.9)	0.92 (0.89~0.96)	<0.001	0.92 (0.88~0.96)	<0.001
METS-IR Model 2						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M2. OR (95%CI)	adj. P value
Q1	2537	910 (35.9)	1(Ref)		1(Ref)	

Q2	2537	866 (34.1)	0.93 (0.83~1.04)	0.195	0.91 (0.74~1.11)	0.352
Q3	2537	776 (30.6)	0.79 (0.7~0.89)	<0.001	0.76 (0.62~0.94)	0.012
Q4	2538	787 (31)	0.8 (0.71~0.9)	<0.001	0.99 (0.8~1.23)	0.933
Trend.test	10149	3339 (32.9)	0.92 (0.89~0.96)	<0.001	0.98 (0.91~1.05)	0.555

Note: METS-IR was converted into quartiles for analysis (first quartile [Q1]: lowest 25%; fourth quartile [Q4]: highest 25%). Model 1 adjusted for age, sex, education, and BMI. Model 2 further adjusted for income, consumption, smoking, and alcohol consumption on the basis of Model 1.

3.3.3 LAP and Depressive Symptoms.

As shown in Table 5, although no significance was observed in the univariate analysis, LAP demonstrated a robust U-shaped protective effect after adjusting for covariates. In both Model 1 and Model 2, the Q3 group exhibited the lowest risk of depression (Model 2: OR = 0.72, P = 0.003), suggesting that a moderate level of lipid accumulation may be associated with lower depressive symptoms.

Table 5: Results of Multivariable Analysis for LAP.

LAP Model 1						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M1. OR (95%CI)	adj. P value
Q1	2545	889 (34.9)	1(Ref)		1(Ref)	
Q2	2546	833 (32.7)	0.91 (0.81~1.02)	0.095	0.82 (0.73~0.93)	0.002
Q3	2546	798 (31.3)	0.85 (0.76~0.96)	0.007	0.75 (0.66~0.84)	<0.001
Q4	2546	834 (32.8)	0.91 (0.81~1.02)	0.101	0.78 (0.69~0.89)	<0.001
Trend.test	10183	3354 (32.9)	0.96 (0.93~1)	0.058	0.92 (0.89~0.96)	<0.001
LAP Model 2						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M2. OR (95%CI)	adj. P value
Q1	2545	889 (34.9)	1(Ref)		1(Ref)	
Q2	2546	833 (32.7)	0.91 (0.81~1.02)	0.095	0.79 (0.65~0.97)	0.027
Q3	2546	798 (31.3)	0.85 (0.76~0.96)	0.007	0.72 (0.58~0.89)	0.003
Q4	2546	834 (32.8)	0.91 (0.81~1.02)	0.101	0.78 (0.63~0.97)	0.024
Trend.test	10183	3354 (32.9)	0.96 (0.93~1)	0.058	0.92 (0.86~0.99)	0.021

Note: LAP was converted into quartiles for analysis (first quartile [Q1]: lowest 25%; fourth quartile [Q4]: highest 25%). Model 1 adjusted for age, sex, education, and BMI. Model 2 further adjusted for income, consumption, smoking, and al cohol consumption on the basis of Model 1.

3.3.4 METS-VF and Depressive Symptoms.

As shown in Table 6, the pattern observed for METS-VF was similar to that of CVAI. Model 1 indicated a linear protective association (with a 24% risk reduction in Q4). Model 2, however, revealed a transition to a U-shaped relationship, where the protective effect was most pronounced in the Q3 group (OR = 0.76, P = 0.011). Notably, a very high level (Q4) of METS-VF did not confer additional benefit in terms of risk reduction.

Table 6: Results of Multivariable Analysis for METS-VF.

METS-VF Model 1						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M1. OR (95%CI)	adj. P value
Q1	2534	870 (34.3)	1(Ref)		1(Ref)	
Q2	2534	802 (31.6)	0.89 (0.79~1)	0.042	0.84 (0.74~0.95)	0.005
Q3	2534	790 (31.2)	0.87 (0.77~0.97)	0.017	0.78 (0.69~0.88)	<0.001
Q4	2535	872 (34.4)	1 (0.89~1.13)	0.961	0.76 (0.67~0.87)	<0.001
Trend.test	10137	3334 (32.9)	1 (0.96~1.04)	0.947	0.91 (0.88~0.95)	<0.001
METS-VF Model 2						
Variable	n.total	n.event_%	crude. OR (95%CI)	crude. P value	M2. OR (95%CI)	adj. P value
Q1	2534	870 (34.3)	1(Ref)		1(Ref)	
Q2	2534	802 (31.6)	0.89 (0.79~1)	0.042	0.77 (0.62~0.94)	0.013
Q3	2534	790 (31.2)	0.87 (0.77~0.97)	0.017	0.76 (0.61~0.94)	0.011
Q4	2535	872 (34.4)	1 (0.89~1.13)	0.961	0.83 (0.67~1.04)	0.102
Trend.test	10137	3334 (32.9)	1 (0.96~1.04)	0.947	0.94 (0.88~1.01)	0.108

Note: METS-VF was converted into quartiles for analysis (first quartile [Q1]: lowest 25%; fourth quartile [Q4]: highes t 25%). Model 1 adjusted for age, sex, education, and BMI. Model 2 further adjusted for income, consumption, smoking, and alcohol consumption on the basis of Model 1.

4. Discussion

Utilizing nationally representative data from CHARLS 2015, this study is the first to systematically evaluate the associations between four novel Computational Metabolic Biomarkers (CVAI, LAP, METS-IR, METS-VF) and depressive symptoms among middle-aged and older adults. The core findings diverge significantly from conventional perspectives that view metabolic dysregulation solely as a pathogenic risk. Instead of a linear positive correlation, our multivariable-adjusted analysis revealed that these metabolic indices conferred significant protective effects. Specifically, a distinct U-shaped nonlinear association emerged, wherein moderate levels of CVAI, METS-IR, LAP, and METS-VF (typically the Q3 range) corresponded to the lowest incidence of depression.

This observed "protective threshold" aligns with recent findings by Miyuan Wang et al. [34] and lends empirical support to the "Jolly Fat" hypothesis [35]. Underpinning this hypothesis is the premise that moderate fat reserves may optimize mood regulation through distinct neurobiological pathways. Behaviorally, <dietary intake activates> the brain's reward system, promoting dopamine release to produce anxiolytic and antidepressant effects. Endocrinologically, <adipose tissue functions as an active organ> capable of converting androstenedione into estrone. Elevated estrogen levels, in turn, exert confirmed neuroprotective effects conducive to mood stability [36]. Moreover, from a physiological standpoint, <moderate nutritional reserves> act as a metabolic buffer against chronic wasting diseases in the elderly, thereby mitigating the psychological distress triggered by physical frailty.

Despite these plausible mechanisms, our results stand in contrast to prior literature—particularly studies on LAP [37]and METS-IR[38] often report linear positive correlations with depression. Such discrepancies likely stem from three methodological dimensions. The first is population heterogeneity: <previous research predominantly relied> on Western databases (e.g., NHANES) or younger cohorts (20 years), whereas CHARLS focuses exclusively on Chinese adults aged ≥45. Given that metabolic flexibility and psychological resilience vary significantly across the lifespan, moderate adiposity in the elderly may reflect robust nutritional status rather than pathological burden—a phenomenon known as the "obesity paradox." Second, variation in assessment tools plays a role, as distinct scales (e.g., PHQ-9 vs. CES-D-10) capture different symptom dimensions. Finally, statistical modeling approaches differ; <prior studies on indices like METS-VF> often assumed linearity [39], potentially overlooking the non-linear U-shaped threshold effect characteristic of this specific demographic.

The U-shaped trajectory revealed herein carries substantial public health implications. It suggests that for middle-aged and older adults, <overly stringent weight control or minimal body fat> may not represent the optimal state for mental health. Conversely, maintaining moderate nutritional intake and adiposity

(corresponding to the Q3 level) may confer a protective benefit against depression. These findings do not advocate for pathological obesity, but rather <challenge the "thinner is always better" misconception> in clinical guidance, promoting instead a balanced energy metabolic state.

The strengths of this investigation lie in its large-scale, nationally representative sampling and the innovative comparative analysis of multiple novel IR indices. Future research could leverage more advanced machine learning techniques, such as explainable AI (e.g., SHAP analysis), to automate the detection of non-linear thresholds and improve the predictive power of these indices. Furthermore, integrating our findings with multi-omics data could pave the way for developing more sophisticated computational models for geriatric depression[27]. Interpretations, however, must be tempered by several limitations. First, <the cross-sectional design precludes causal inference>, leaving open the possibility of reverse causation (e.g., depression-induced weight loss). Second, <reliance on self-reported scales> reflects symptom severity rather than a clinical diagnosis. Third, <residual confounding may persist> despite rigorous adjustment for socioeconomic and lifestyle covariates.

5. Conclusions

This study reveals U-shaped associations between novel metabolic indices (CVAI, LAP, METS-IR, METS-VF) and depressive symptoms among Chinese middle-aged and older adults, indicating that moderate metabolic levels may confer mental health benefits. These findings challenge the conventional linear risk perspective and highlight the potential of computational biomarkers for precise depression screening in aging populations. However, the cross-sectional design limits causal inference, and self-reported measures may introduce bias. Future longitudinal studies and advanced modeling approaches are warranted to validate these non-linear patterns and inform targeted interventions for geriatric mental health

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Conflicts of Interest
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