BMC Psychiatry

RESEARCH Open Access

Inflammatory burden index is correlated with increased depression: a population-based study

Xiangzhi Shao[1], Zuopu Xie[2] and Lielie Zhu[1*]

Abstract

Background Depression is intricately correlated with systemic inflammatory responses. The Inflammatory Burden Index (IBI) has recently been introduced as a comprehensive metric for evaluating systemic inflammation. This study aims to explore the correlation between IBI and depression in the general population.

Methods This cross-sectional study was designed to analyze the data from National Health and Nutrition Examination Survey (NHANES) during the period from 1999 to 2018. IBI was formulated as C-reactive protein×neutrophils/lymphocytes. The correlation between the prevalence of depression and IBI was explored through multivariate logistic regression analyses, as well as subgroup, interaction, restricted cubic spline (RCS) and sensitivity analyses.

Results A total of 14,557 subjects were included in this study, of whom, 1231 (8.5%) had depression. According to multivariate logistic regression and RCS analyses, a significantly linearly positive correlation was observed between IBI and depression [odds ratio (OR) = 1.03, 95% confidence intervals (CI): 1.01, 1.05, $P = 0.007$]. Subjects in the third tertile of IBI exhibited a significantly higher prevalence of depression, with 40.0% affected, compared to those in the first tertile ($P < 0.001$). This correlation was consistently observed across all subgroups through stratified analysis (all interaction $P > 0.05$). After sensitivity analyses excluding participants with upper and lower 2.5% of IBI, the correlation between IBI and depression remained stable (OR = 1.08; 95%CI, 1.01, 1.15, $P < 0.001$).

Conclusion These findings in this study indicate a positive correlation between IBI and depression in American adults. Further large-scale prospective studies are still needed to analyze the role of IBI in depression.

Keywords Inflammatory burden index, Depression, Chronic inflammation, Depressive, C-reactive protein

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Introduction

Depression is a pervasive global phenomenon characterized by an insomnia, and diminished interest in daily activities, the onset of suicidal ideation, and a loss of enjoyment in life. This situation has adverse effects on both physical and mental health [1]. The data from the study Global Burden of Disease indicate a significant increase of 49.86% in the incidence of depression worldwide, rising from 172 million cases in 1990 to 258 million cases in 2017 [2]. Furthermore, according to the reports by the World Health Organization, depression is currently the third leading cause of global disease burden [1]. Despite advancements in antidepressant therapies, the recurrence rate of depression remains high, with nearly 80% of patients experiencing a subsequent episode [3]. Therefore, it is imperative to identify novel biomarkers for the risk of developing depression to improve intervention and prevention strategies.

Depression is pathophysiologically correlated with inflammatory processes [4–6]. Both experimental and clinical research demonstrated that immune-mediated inflammation contributes to the pathophysiology of depression. Chronic stress can initiate inflammatory responses, wherein proinflammatory cytokines, including interleukin (IL)-1, Interferon-γ, IL-6, C-reactive protein (CRP), and tumor necrosis factor-α, impacting the synthesis of critical monoamine neurotransmitters such as dopamine and serotonin (5-hydroxytryptamine). This interaction consequently influences the progression and onset of depression [7, 8]. Patients with depression often exhibit marked alterations in the peripheral or central inflammation [9, 10]. Recent studies have underscored the significance of immune and inflammatory markers derived from peripheral blood counts, including the platelet–lymphocyte ratio and neutrophil–lymphocyte ratio (NLR), which are associated with depression [11]. Nevertheless, these biomarkers relying solely on two types of immune-inflammatory cell may not comprehensively capture the complexity of inflammation, resulting in inconsistent findings [12–14]. Consequently, there is a pressing need for an easily accessible and reliable biomarker that accurately reflects systemic inflammation.

IBI is a composite index that incorporates several inflammatory markers [15], including CRP, neutrophil counts and lymphocyte counts, to provide a more comprehensive assessment on systemic inflammation and immune response. IBI is calculated as the formula: IBI = CRP* NLR. Various studies had suggested that IBI offers more precise prognostic value for disease outcomes compared to individual markers [16, 17]. To date, no studies have explored the correlation between IBI and depression. Consequently, further research is warranted to explore the significance of IBI as a novel systemic inflammatory marker in the context of depression.

Therefore, this study aims to explore the correlation between IBI and depression within a large, nationally representative cohort of American adults. The data for this analysis were sourced from NHANES 1999–2018.

Methods

Research subjects and design

NHANES, administered by National Center for Health Statistics [18], is an extensive research initiative aiming to evaluate the correlation among health promotion, disease prevention, and nutrition, which is conducted by physical examinations, taking interviews, and a range of sections that include demographic, dietary, laboratory and examination data.

This retrospective cross-sectional study was designed to analyze the data from NHANES 1999–2018. Subjects aged 18 years old or above were included ($n = 59204$). And the subjects with pregnancy ($n = 428$), missing data on Patient Health Questionnaire-9 (PHQ-9) ($n = 28013$) and IBI ($n = 16206$) were excluded by exclusion criteria. Finally, the samples in this study consisted of 14,557 subjects (as shown in Fig. 1).

Ascertainment of depression

PHQ-9 is a self-administered instrument designed for screening and assessing the depression severity. PHQ-9 yields a score ranging from 0 to 27, with each of the nine items rated on a scale of 0–3 (1 = several days; 0 = never; 3 = nearly every day; 2 = more than half the days) [19, 20]. A total score of 10 or above is considered indicative in depression [19], which is commonly utilized in epidemiological research to identify individuals with depression who has been validated through clinical evaluation [19].

Measurement of IBI

IBI was calculated for each participant by multiplying CRP by NLR, as expressed by the formula IBI = CRP×NLR [17]. Elevated IBI levels were indicative of a higher inflammatory burden. For this analysis, subjects were stratified into tertiles based on IBI, with the third tertile reflecting a high inflammatory burden and the first tertile representing a low inflammatory burden (Tertile 1: <0.19; Tertile 2: 0.19–0.67; Tertile 3: >0.67).

Covariates

The analysis incorporated a range of covariates, encompassing demographic and socioeconomic factors (such as poverty-income ratio (PIR), age, marital status, gender, education level, race, weight, height, and waist circumference), lifestyle variables (including alcohol consumption, physical activities, and smoking status), medical history (covering coronary heart disease (CHD), stroke, diabetes mellitus, cancer, and hypertension,), as well as laboratory test results [comprising urine albumin-to-creatinine ratio

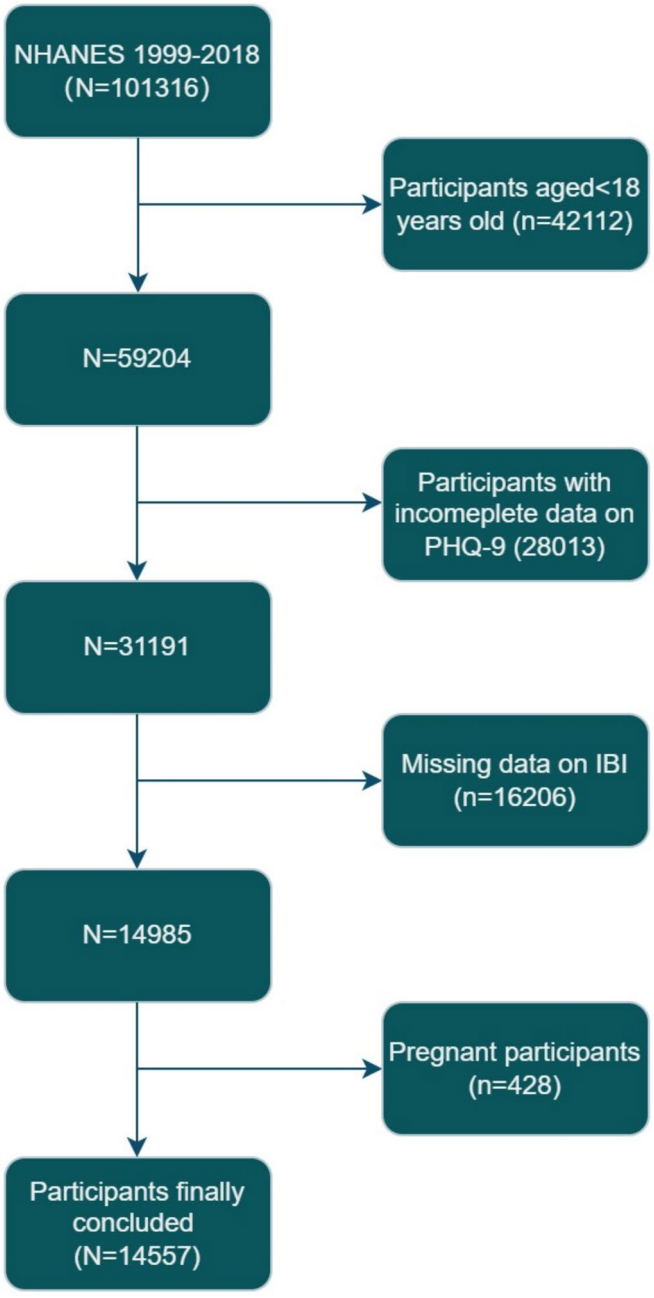

Fig. 1 Flowchart of the sample selection from the 1999–2018 NHANES

(UACR), serum triglycerides (TG), creatinine, total cholesterol, neutrophil count,

high-density lipoprotein cholesterol (HDL-C), CRP, lymphocyte count, low-density lipoprotein cholesterol (LDL-C), and glycated hemoglobin (HbA1c)]. The diagnoses of CHD, hypertension, stroke, diabetes mellitus, and cancer were determined based on self-reports provided by the participants. Estimated glomerular filtration rate (eGFR) was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [21, 22]. CKD was defined according to current clinical guidelines with a UACR exceeding 30 mg/g, an eGFR of less than 60 mL/min/1.73 m^2, or both conditions [23–26]. Further information regarding the NHANES database can be available at http://www.cdc.gov/nhanes.

Statistical analyses

Subjects in this study were classified into two distinct groups based on the PHQ-9 scores: Those without depression and those with depression [19]. Normal distribution was evaluated by determining skewness with a Kolmogorov–Smirnov test. Between-group comparisons

were conducted through Student's t-test and the Mann-Whitney U test for normally distributed and skewed continuous variables, respectively, and using the χ2 test for categorical variables. The correlation between IBI and depression was examined through multivariate logistic regression models. Variables demonstrating clinical and statistical significance in the univariate analyses ($p < 0.05$) were incorporated into the multivariate analyses. Three models were adopted in the analysis: Model 1 was unadjusted, Model 2 was adjusted for age and gender, Model 3, the final multivariable model, was further adjusted for eGFR, race, alcohol consumption, body mass index (BMI), moderate physical activities, CHD, stroke, and hyperlipidemia, diabetes mellitus, education level, PIR, marital status, HbA1c, albumin, smoking status, hypertension, and cancers. Collinearity was assessed using variance inflation factor (VIF), with all VIF values being below 5 in this study. The correlation between IBI and PHQ-9 scores were also examined through linear regression models, utilizing three analogous models as previously described. In addition, restricted cubic spline (RCS) regression was performed with 4 knots at the 5th, 35th, 65th, and 95th percentiles of IBI to assess linearity and examine the dose–response curve between IBI and depression after adjusting variables in Model 3. Using the median of IBI 0.3494 as the reference value. The impact of IBI on depression across various stratified covariates, including BMI, age, gender, educational level, and disease status (encompassing CHD, cancer, CKD, diabetes mellitus, stroke, and chronic kidney disease) was also explored through subgroup analyses. Finally, the robustness of the findings was evaluated through two sensitivity analyses. Initially, a 1:1Propensity Score Machine (PSM) with a caliper width of 0.02 was implemented with IBI (dividing the median into IBI ≤ 0.35 or IBI > 0.35) as the primary matching variable to mitigate potential confounding factors. The degree of PSM was measured with a standardized mean difference (SMD). A value < 0.1 was deemed acceptable. Finally, 2554 matched pairs were generated and used in further studies (see Supplementary Table. S1). In addition, subjects with IBI in the upper and lower 2.5% were excluded to mitigate the influence of potential outliers. Data were analyzed through Free Statistics software (Version 2.0, China) and R software (Version 4.1.1, Vienna, Austria), with statistical significance determined at a two-sided *P*-value threshold of less than 0.05.

Results

Baseline characteristics

Table 1 provides a detailed overview on the characteristics of subjects. Among the 14,557 subjects included in the analysis, 7,386 (50.7%) were males, with an average age of 48.0 ± 18.9 years old. Of the total subjects, 1,231 (8.5%) had depression. The data indicate that females constituted the majority of those with depression and those who currently or previously have smoking habits have a higher incidence of the depression (all $P < 0.001$). These individuals were more likely to live alone ($P < 0.001$) and exhibited lower levels of family PIR ($P < 0.001$) and HDL-C ($P = 0.002$). Furthermore, they tended to engage less in physical activities, with elevated measurements of BMI, HbA1c, waist circumference, NLR, CRP, TC, and IBI (all $P < 0.001$). Moreover, these individuals exhibited a higher prevalence of comorbid medical conditions, including CHD ($P = 0.028$), hypertension ($P < 0.001$), stroke ($P < 0.001$), diabetes mellitus ($P < 0.001$), and cancers ($P = 0.035$). IBI in the depression group was 1.34 ± 3.01, which was higher than 0.99 ± 2.50 observed in the non-depression group ($P < 0.001$).

Correlation between IBI and depression

In the multiple logistic regression analysis, a significantly positive correlation between IBI and depression was observed after controlling for confounding variables in Model 3 (OR = 1.03; 95%CI: 1.01, 1.05). A sensitivity analysis with adjusted models and categorizing IBI levels into tertiles indicated that subjects in Tertile 3 (with the highest IBI) exhibited a 40% increased likelihood of depression compared to those in Tertile 1 (with the lowest IBI) (OR = 1.40; 95% CI: 1.18, 1.67) (Table 2). Additionally, RCS analyses revealed a linear correlation between IBI and depression, as illustrated in Fig. 2.

The multiple linear regression analysis indicated a positive correlation between increased IBI and higher depression scores (β = 0.09; 95% CI: 0.06, 0.12; $p < 0.001$), as presented in Table 3.

Subgroup analysis

To further explore the correlation between IBI and depression across different demographic and health-related subgroups, stratified analyses were performed based on BMI, age, gender, education level, and disease status, including diabetes mellitus, CHD, CKD, cancer, and stroke. The results from the fully adjusted multivariate model revealed no significant differences in the correlation between IBI and depression across these subpopulations (all interaction $p > 0.05$) (as shown in Fig. 3).

Sensitivity analyses

The findings from the sensitivity analysis are detailed in Table 4. Following the application of PSM (OR = 1.38; 95% CI, 1.03, 1.83) or the exclusion of subjects within the upper and lower 2.5% of IBI (OR = 1.08; 95%CI, 1.01, 1.15), the correlation between IBI and depression persisted consistently.

Table 1 Characteristics of the study population based on depression

Characteristic	Total ($n=14557$)	PHQ-9 < 10 ($n=13326$)	PHQ-9 ≥ 10 ($n=1231$)	*P* value
Age	48.0 ± 18.9	48.2 ± 19.1	46.5 ± 16.3	0.059[a]
Gender, %				**< 0.001[c]**
Male	7386 (50.7)	6933 (52)	453 (36.8)	
Female	7171 (49.3)	6393 (48)	778 (63.2)	
Race, %				**< 0.001[c]**
Mexican American	2763 (19.0)	2525 (18.9)	238 (19.3)	
Other Hispanic	1240 (8.5)	1096 (8.2)	144 (11.7)	
Non-Hispanic White	7084 (48.7)	6550 (49.2)	534 (43.4)	
Non-Hispanic Black	2895 (19.9)	2624 (19.7)	271 (22)	
Other Race	575 (3.9)	531 (4.0)	44 (3.6)	
Education level, %				**< 0.001[c]**
Less than high school	3830 (28.1)	3358 (27.0)	472 (40.3)	
High school or above	9777 (71.9)	9079 (73.0)	698 (59.7)	
Marital, %				**< 0.001[c]**
Married/living with partner	8808 (62.6)	8152 (63.3)	656 (54.9)	
Separated/divorced/widowed	2666 (18.9)	2365 (18.4)	301 (25.2)	
Never married	2600 (18.5)	2362 (18.3)	238 (19.9)	
Moderate physical activity, %				**< 0.001[c]**
Yes	3931 (38.1)	3720 (39.9)	211 (21.7)	
No	6376 (61.9)	5614 (60.1)	762 (78.3)	
Alcohol status, n%				0.124[c]
Current or ever, %	9767 (71.8)	8952 (72.0)	815 (69.8)	
Never	3841 (28.2)	3489 (28.0)	352 (30.2)	
Smoking status, n%				**< 0.001[c]**
Current or ever, %	6539 (48.0)	5829 (46.8)	710 (60.7)	
Never	7077 (52.0)	6617 (53.2)	460 (39.3)	
Hypertension, %				**< 0.001[c]**
Yes	4841 (33.3)	4306 (32.4)	535 (43.6)	
No	9690 (66.7)	8997 (67.6)	693 (56.4)	
Diabetes				**< 0.001[c]**
Yes	1859 (12.8)	1616 (12.1)	243 (19.8)	
No	12,685 (87.2)	11,698 (87.9)	987 (80.2)	
Hyperlipidemia, %				**< 0.001[c]**
Yes	10,319 (70.9)	9389 (70.5)	930 (75.5)	
No	4238 (29.1)	3937 (29.5)	301 (24.5)	
CHD, %				**0.028[c]**
Yes	567 (4.2)	504 (4.1)	63 (5.4)	
No	12,999 (95.8)	11,898 (95.9)	1101 (94.6)	
Stroke				**< 0.001[c]**
Yes	508 (3.7)	427 (3.4)	81 (6.9)	
No	13,091 (96.3)	12,006 (96.6)	1085 (93.1)	
Cancer, %				**0.035[c]**
Yes	1302 (9.6)	1170 (9.4)	132 (11.3)	
No	12,302 (90.4)	11,266 (90.6)	1036 (88.7)	
Body mass index, kg/m^2	28.9 ± 6.8	28.7 ± 6.6	30.3 ± 8.0	**< 0.001[a]**
Waist circumference, cm	98.3 ± 16.2	98.0 ± 16.0	101.1 ± 18.0	**< 0.001[a]**
HbA1c, %	5.68 ± 1.03	5.66 ± 1.00	5.83 ± 1.29	**< 0.001[a]**
Albumin, g/dl	42.4 ± 3.3	42.5 ± 3.3	41.6 ± 3.4	**< 0.001[a]**
Total cholesterol, mmol/L	4.94 (4.27, 5.69)	4.94 (4.27, 5.69)	4.99 (4.27, 5.77)	0.377[b]
Triglycerides, mmol/L	1.23 (0.86, 1.79)	1.22 (0.85, 1.77)	1.33 (0.91, 1.99)	**< 0.001[b]**
HDL-cholesterol, mmol/L	1.29 (1.06, 1.58)	1.29 (1.06, 1.58)	1.27 (1.03, 1.55)	**0.002[b]**
LDL-cholesterol, mmol/L	2.87 (2.30, 3.52)	2.87 (2.30, 3.49)	2.90 (2.26, 3.52)	0.724[b]
eGFR, ml/min/1.73m^2	89.1 ± 25.0	88.8 ± 24.8	91.7 ± 26.7	**< 0.001[b]**

Table 1 (continued)

Characteristic	Total ($n=14557$)	PHQ-9 < 10 ($n=13326$)	PHQ-9 ≥ 10 ($n=1231$)	*P* value
PIR	2.54 ± 1.62	2.61 ± 1.62	1.74 ± 1.41	**< 0.001**[a]
NLR	2.16 ± 1.14	2.15 ± 1.14	2.21 ± 1.11	**< 0.001**[b]
CRP	0.41 ± 0.69	0.40 ± 0.68	0.53 ± 0.82	**< 0.001**[b]
IBI	1.02 ± 2.55	0.99 ± 2.50	1.34 ± 3.01	**< 0.001**[b]

Values are mean±SD or number (%). *P* values are for t test[a], Mann-Whitney U test[b] or $\chi 2^c$ test. $P < 0.05$ was deemed significant. TC, total cholesterol; TG, triglyceride; HDL-c, High density lipoprotein cholesterol; LDL-c, Low density lipoprotein cholesterol; PIR, poverty-income ratio; eGFR, IBI, inflammatory burden index; CHD, coronary heart disease

Table 2 Associations between IBI and depression

subgroups	Model1		Model2		Model3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
IBI	1.04 (1.02, 1.05)	< 0.001	1.04 (1.02, 1.06)	< 0.001	1.03 (1.01, 1.05)	0.007
IBI (category)						
Tertile 1	1(Ref)		1(Ref)		1(Ref)	
Tertile 2	1.18 (1.01, 1.38)	0.037	1.22 (1.04, 1.42)	0.014	1.08 (0.91, 1.29)	0.372
Tertile 3	1.77 (1.53, 2.04)	< 0.001	1.75 (1.51, 2.03)	< 0.001	1.40 (1.18, 1.67)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Model 1: None covariates were adjusted; Model 2: gender and age were adjusted; Model 3, gender, age, race, eGFR, alcohol consumption, BMI, moderate physical activities, CHD, stroke, and hyperlipidemia, diabetes mellitus, education level, PIR, marital status, HbA1c, albumin, smoking, hypertension, and cancers were adjusted

Discussion

In this population-based cross-sectional study, the correlation between IBI and depression was explored. The findings indicate a higher IBI correlated with an increased prevalence of depression in American adults, even after adjusting for potential confounding variables. This correlation persisted in various subgroup analyses. Furthermore, RCS analyses reveal a linear correlation between IBI and the prevalence of depression, underscoring the need for further fundamental and clinical research in this area.

NLR, combining both innate (neutrophils) and adaptive (lymphocytes) immune pathways, has been explored as a potential inflammation marker [27]. However, studies on the correlation between NLR and depression have yielded inconsistent results. For instance, Demircan and Demir reported elevated NLR levels in patients with depression in two relatively small Turkish cohorts [28, 29]. Similarly, Meng observed elevated NLR levels in females with depression, although this was not in males [30]. Sunbul and Ozyurt identified a positive correlation between NLR and the severity of depression [31]. In contrast, Kayhan reported no such correlation [32]. Additionally, CRP has been recognized as the most representative biomarker of systemic inflammation and has been extensively utilized in routine clinical practice [33, 34]. Elevated CRP levels have been significantly correlated with depression [35–37]. However, other studies have not corroborated these correlations [38, 39].

First, most of clinical studies were limited by the small sample size and the results were different or even opposite from each other. Second, according to the meta-analyses [13, 40], the association between NLR, PLR, or CRP and depression was significantly influenced by the design (case-control versus cross-sectional), countries, and antidepressant use of the studies. The role of NLR or CRP as an indicator for depression has not been established in the meta-analyses. Third, both CRP and NLR are nonspecific biomarkers that can be influenced by a range of factors, including infections, metabolic disorders, and lifestyle choices [35]. Consequently, the absence of a direct and consistent correlation between NLR, CRP, and depression limits their utility as identify biomarkers for depression.

In recent studies, IBI has been proposed as a measure for evaluating inflammatory status, integrating three specific inflammatory markers: neutrophils, CRP, and lymphocytes [15]. The study of Xie et al. demonstrated that IBI can be independently correlated with 0-day clinical outcomes, overall survival, 9 hospitalization costs, hospital length, and the incidence of cachexia in patients diagnosed with non-small cell lung cancer [41]. Furthermore, Xie's study established that IBI serves as an innovative inflammation-based marker for evaluating the inflammatory status across various cancers, offering significant prognostic values for predicting adverse outcomes in patients with cancers [15]. Additionally, IBI has been correlated with unfavorable prognoses in other malignancies, including advanced gastric cancer [42], hepatocellular carcinoma [43], and esophageal cancer [44]. Furthermore, Song's study identified a correlation between elevated IBI levels and adverse functional outcomes, deep vein thrombosis, and pneumonia in patients with aneurysmal subarachnoid hemorrhage [16]. Nonetheless, the correlation between IBI and depression remains unclear.

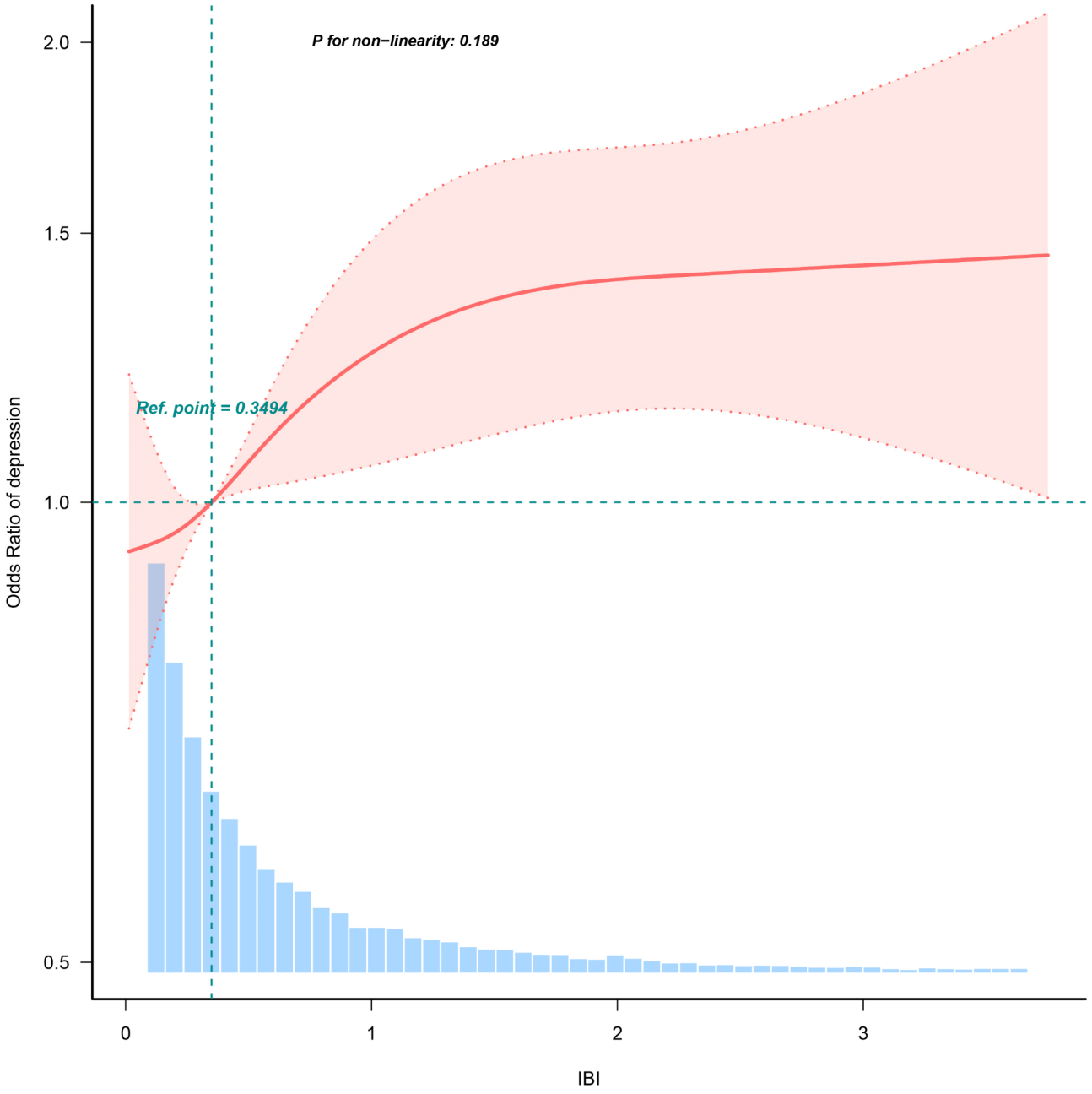

Fig. 2 Dose–response association between IBI and depression. A linear association between IBI and the prevalence of depression was found ($P < 0.05$). The solid and dashed lines indicate the predicted values and 95%CI, respectively. Adjustment factors included age, gender, eGFR, race, alcohol consumption, BMI, moderate physical activities, CHD, stroke, and hyperlipidemia, diabetes mellitus, education level, PIR, marital status, HbA1c, albumin, smoking, hypertension, and cancers

CRP is commonly used to detect inflammation in the body [35], whereas the NLR accounts for immune responses [45]. IBI can evaluate the inflammatory and immune status from a holistic perspective of a patient's health [16]. Additionally, IBI can reflect the dynamic crosstalk between inflammatory and immune responses [46]. Furthermore, IBI, including neutrophils, CRP, and lymphocytes, encompasses three distinct mechanisms implicated in the pathogenesis of depression, potentially exhibiting synergistic interactions. Therefore, in this study, a novel inflammatory index was employed to conduct a comprehensive assessment of inflammation severity. The analysis revealed that IBI is independently associated with an increased prevalence of depression.

Subsequently, the variables were adjusted for subgroup analyses to account for variations in demographic characteristics. The findings indicate that the correlation between IBI and depression remains unaffected by

Table 3 Associations between IBI and PHQ-9 score

subgroups	Model1		Model2		Model3	
	β(95%CI)	*P*-value	β(95%CI)	*P*-value	β(95%CI)	*P*-value
IBI	0.11 (0.09, 0.14)	< 0.001	0.12 (0.09, 0.14)	< 0.001	0.09 (0.06, 0.12)	< 0.001
IBI (category)						
Tertile 1	0(Ref)		0(Ref)		0(Ref)	
Tertile 2	0.18 (0.01, 0.34)	0.036	0.25 (0.09, 0.42)	0.003	0.02 (-0.16,0.19)	0.844
Tertile 3	0.86 (0.70, 1.03)	< 0.001	0.87 (0.71, 1.04)	< 0.001	0.41 (0.23, 0.60)	< 0.001
P for trend	0.43 (0.35, 0.51)	< 0.001	0.44 (0.35, 0.52)	< 0.001	0.21 (0.12, 0.30)	< 0.001

Model 1: None covariates were adjusted; Model 2: gender and age were adjusted; Model 3, gender, age, race, eGFR, alcohol consumption, BMI, moderate physical activities, CHD, stroke, and hyperlipidemia, diabetes mellitus, education level, PIR, marital status, HbA1c, albumin, smoking, hypertension, and cancers were adjusted

factors such as BMI, age, gender, educational level, and disease status. Therefore, IBI may be a more reliable indicator for identifying the prevalence of depression. However, due to the small sample size of some subgroups, the current study may still be underpowered to detect statistically significant differences. Further studies with larger samples and longer follow-ups are warranted to confirm these findings.

The exact mechanisms underlying the correlation between depression and IBI remain inadequately understood. Nonetheless, several potential pathways have been suggested. Inflammation may influence depression by altering the synthesis of key monoamine neurotransmitters, activating the hypothalamic-pituitary-adrenal (HPA) axis, and inducing oxidative stress responses, resulting in nutritional deficiencies and dysregulated glutamate functions. Furthermore, chronic stress can lead to sustained microglial activation, resulting in the production of various proinflammatory cytokines that further contribute to the progression of depression [8, 47]. Early life stress can activate the HPA axis, resulting in elevated cortisol levels, disruption of neurotransmitter equilibrium, and impaired synthesis of nerve growth factors, contributing to a reduction in hippocampal volume, correlated with the onset of depression [48, 49]. Additionally, inflammation influences the release and reuptake of glutamate by glial cells, leading to glutamate binding at extrasynaptic N-Methyl-D-Aspartate receptors, inhibiting growth factor activity and induces excitotoxicity, thereby contributing to the development of depressive disorders [50].

IBI serves as a straightforward and cost-efficient measure that reflects the equilibrium between immune and inflammatory responses. An elevated IBI is indicative of increased CRP and/or neutrophils, coupled with a decrease in lymphocyte count. Tailored interventions aimed at modulating immune-inflammatory processes may be associated with a reduction in depression symptoms. Future longitudinal studies are needed to explore the potential causal relationship between these interventions and depression symptoms.

To the best of our knowledge, the current study represents the inaugural investigation into the correlation between IBI and the prevalence of depression. Noteworthy strengths of this study include a relatively large sample size and national representativeness, derived from data sourced from the NHANES database. Furthermore, multiple analytical methods were employed in this study to explore the correlation between IBI and depression. However, despite these strengths, the study is not without its limitations. First, given that NHANES is a cross-sectional study, it is impossible to infer causality. To ascertain whether a longitudinal correlation exists between IBI and depression, further cohort studies are required. Second, the diagnosis on depression was based exclusively on PHQ-9, which is a self-reported measure and thus subject to a certain degree of subjectivity. Future research should incorporate multiple assessment scales in conjunction with clinician interviews to enhance data reliability and diagnostic accuracy. Third, the data were derived from a single blood test. Implementing serial tests could yield more comprehensive insights, given the short lifespan of blood cells. Prospective studies are essential to validate these findings. Furthermore, randomized controlled trials should explore the efficacy of inflammation-targeted interventions for IBI in modulating depression.

Conclusion

The findings in this study indicate a significant positive linear correlation between IBI and depression. Future studies should aim to elucidate the mechanisms underlying this correlation to assess the potential of therapeutically targeting IBI for the treatment or prevention of depression.

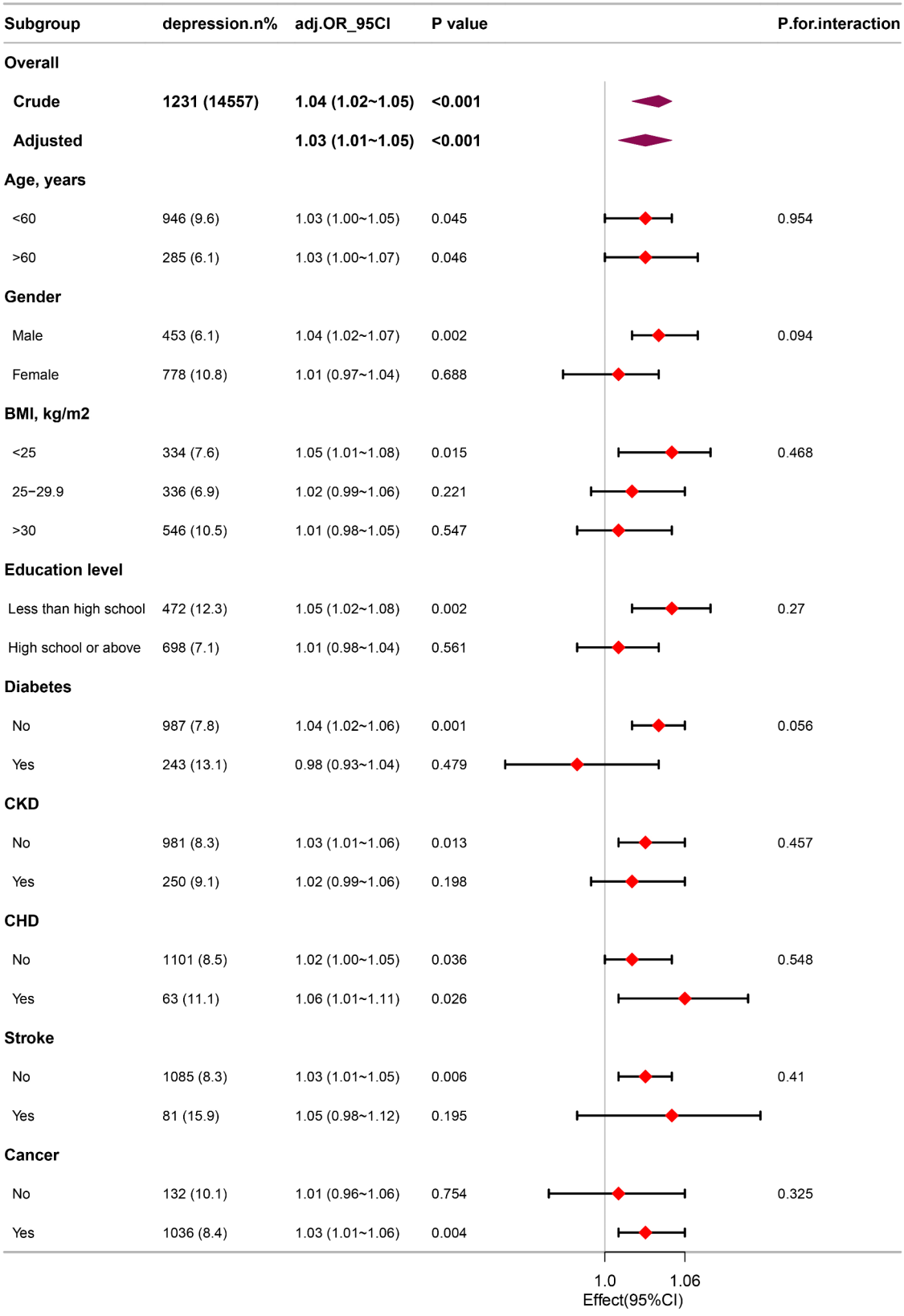

Fig. 3 Association between IBI and the prevalence of depression in various subgroups. No significant interaction effects were found between IBI and subgroup variables in predicting depression

Table 4 Sensitivity analyses

	Adjusted OR (95CI%)	*P*
Propensity Score Machine		
IBI		
IBI ≤ 0.35	1(Ref)	
IBI > 0.35	1.38 (1.03 ~ 1.83)	0.030
Excluding participants with upper and lower 2.5% of the IBI		
IBI (continuous)	1.08 (1.01, 1.15)	< 0.001
IBI		
Tertile 1	1(Ref)	
Tertile 2	1.10 (0.92 ~ 1.32)	0.279
Tertile 3	1.41 (1.18 ~ 1.69)	< 0.001

Gender, age, race, eGFR, alcohol consumption, BMI, moderate physical activities, CHD, stroke, and hyperlipidemia, diabetes mellitus, education level, PIR, marital status, HbA1c, albumin, smoking, hypertension, and cancers were adjusted

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06730-6.

Supplementary Material 1

Acknowledgements
We would like to thank the NHANES database for providing the data source for this study.

Author contributions
LLZ designed the study; ZPX collected biochemical data; XZS drafted the manuscript. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
The datasets generated and analysis during the current study are available in the NHANES, www.cdc.gov/nchs/NHANEs/.

Declarations

Ethics approval and consent to participate
The National Center for Health Statistics Ethics Review Board has approved the implementation of NHANES, and every participant signed informed consent. This study also was approved by the Ethics Committee of the Wenzhou TCM Hospital of Zhejiang Chinese Medical University (No. LCKY2024-06, date: Jan 2024).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Received: 27 November 2024 / Accepted: 17 March 2025
Published online: 31 March 2025

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