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Trends in Immunotherapy

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Systemic Immune-Inflammation Index and Depressive Symptoms in US Adults: Implications for Immunomodulatory Interventions—A Cross-Sectional Study from NHANES 2005–2020

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Received: 3 December 2025; **Revised:** 13 January 2026; **Accepted:** 27 January 2026; **Published:** 10 March 2026

Abstract: Inflammatory responses play a crucial role in the pathogenesis of depression. The Systemic Immune Inflammatory Index (SII) is a novel composite inflammatory marker that integrates the counts of neutrophils, lymphocytes, and platelets. However, the relationship between it and depressive symptoms is still not very clear at present. This exploratory study conducted in this article aims to investigate the relationship between SII and other immune inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and depressive symptoms. This can provide some epidemiological evidence for intervening in mental health through immune regulation. Data from the National Health and Nutrition Examination Survey (NHANES) 2005–2020, which included 32,683 adults 18 years of age and older, were used in this exploratory cross-sectional analysis. Because this study generated hypotheses, subgroup and sensitivity analyses were carried out, restricted cubic spline (RCS) analysis was utilized to investigate dose-response relationships, and weighted multivariable logistic regression was utilized to evaluate association strength. The highest quartile of SII was significantly associated with elevated depression risk (odds ratio (OR) = 1.23, 95% confidence interval (CI): 1.05–1.44, p for trend = 0.008), with a J-shaped dose-response relationship. The association was stronger among participants with diabetes (OR = 1.56, p for interaction = 0.038). NLR showed a borderline association, while PLR and MLR demonstrated no significant associations. SII was independently and positively associated with depressive symptoms and may serve as a potential biomarker for depression risk stratification, with implications for developing immunomodulatory intervention strategies.

Keywords: Systemic Immune-Inflammation Index; Depressive Symptoms; NHANES; Inflammation; Dose-Response Relationship

1. Introduction

One of the most difficult public health problems in the world today is depression. With an estimated 280 million people affected in 2019, epidemiological analyses show that the prevalence of depression is still rising globally, and the percentage increase in disability-adjusted life years is greater than that of the majority of other diseases [1]. Adult depression prevalence in the US is concerning; it reached 13.1% between 2021 and 2023, indicating clear trends in both age and income inequality [2]. These figures reflect high socioeconomic costs. About one-third of patients have insufficient responses to conventional antidepressant therapies, despite the widespread use of selective serotonin reuptake inhibitors and other antidepressants [3]. The pathophysiology underlying the development of depression cannot be sufficiently explained by the monoamine hypothesis, which

has prompted research into alternative pathogenic mechanisms.

Research on depression has shown a great deal of interest in inflammatory processes. People with depression have been found to have significantly higher peripheral blood concentrations of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Numerous populations and research designs have confirmed this mild persistent inflammation [4,5]. Several pathways are involved in the ways that inflammatory processes impact mood: cytokines cross the blood-brain barrier and activate microglia, disrupt tryptophan metabolism by increasing diversion to the kynurenine pathway (which reduces serotonin synthesis), and concurrently inhibit hippocampal neurogenesis and neuroplasticity [6,7]. There is a historical precedent with inflammation relating to depression and the corresponding inflammatory marker, C-reactive protein (CRP). Mild inflammation, with CRP levels ranging from 3 mg/L to 10 mg/L, is present in 25% of depressed individuals [8]. Yet, CRP is only one specific marker and cannot represent the entire immune-inflammatory process.

Systemic immune-inflammatory index (SII) provides an innovative way of approaching this problem. SII was first introduced by Hu et al. [9] to describe the prognosis of hepatocellular carcinoma and is defined as the product of platelet and neutrophil count divided by lymphocyte count. SII is a marker of immune and inflammatory regulation based on the data of platelets (anuclear cell fragments from megakaryocytes) and neutrophils and lymphocytes (leucocytes). Compared to individual inflammatory markers: neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR), SII serves better to describe cancer, cardiovascular, and other disorders [10]. This comprehensive inflammatory profile has also shown promise in psychiatric conditions, with clinical evidence demonstrating elevated SII levels in patients with major depression [11] and moderate to severe depressive disorders [12]. SII and depression associations have been studied in large-scale NHANES-based studies. Li et al. [13] analyzed NHANES data from 2005–2018 and described an association between systemic inflammatory biomarkers and risk of depression, while Zheng et al. [14] presented an association between depression and immune-inflammation-based prognostic indicators. There is, however, a disparity in the methodologies, population subsets, and focus of those studies, which overlooks the more comprehensive analyses of inflammatory indices and the potential of immunomodulatory interventions.

Multiple gaps in previous studies remain unexplored. Most studies have focused on specific, targeted clinical populations (e.g., post-stroke or hemodialysis patients), and have examined little in the way of generalizability to the general population. Most studies have examined SII alone and have neglected to make direct comparisons with other inflammation markers (NLR, PLR, and MLR) in predicting the risk of depression. The effects of diabetes mellitus and other metabolic disorders as potential effect modifiers have been unexplored. This study aims to address these gaps utilizing the NHANES 2005–2020 dataset with the following aims: (1) to evaluate the association of SII with the risk of depressive symptoms, (2) to evaluate SII in comparison to NLR, PLR, and MLR, (3) to assess the existence of dose-response relationships, and (4) to determine potential effect modifiers by conducting specified subgroup analyses.

2. Materials and Methods

2.1. Data Source

Data were obtained from the NHANES survey from the National Center for Health Statistics in the Centers for Disease Control and Prevention (CDC). This study uses a unique and complicated multi-stage, stratified, and probability sampling design to assess the health and nutrition status of the civilian population of the United States, not living in institutionalized facilities. The study has household interviews and physical exams in mobile examination centers. NHANES publishes its data every two years. In order to have enough data for the subgroup analyses, the current analysis used data from eight (8) cycles spanning from 2005–2006 to 2019–2020.

2.2. Study Population

Study participants were chosen systematically and included all people aged ≥18 years. These included people who were excluded due to a lack of data for the Patient Health Questionnaire-9 (PHQ-9), absence of complete blood count data required for the calculation of immune-inflammatory markers, and absence of data for pertinent covariates. Participants who reported a history of chronic infection, malignancy, or autoimmune disorders, or who have taken immunosuppressive drugs were excluded. Participants were also excluded if they had a current infection and

their white blood count was above normal. The flowchart in the results section shows the final analytical sample and the exclusion numbers at each step of the selection process.

The criteria for inclusion were as follows: (1) participants were aged 18 years and older and took part in the NHANES 2005–2020 cycles, (2) participants had to have complete PHQ-9 depression screening data, (3) participants had to have complete data for the blood count variables needed to compute the immune-inflammatory markers (i.e., blood count variables: platelet, neutrophil, lymphocyte, and monocyte counts), and (4) participants had to have complete covariate data for multivariable adjustments regarding demographics, socioeconomic factors, lifestyle, and health.

2.3. Exposure Variables

The exposure variables were SII and three other commonly used immune-inflammatory ratio markers. The formula for calculating SII is:

$$SII = \frac{P \times N}{L} \tag{1}$$

where P represents platelet count ($\times 10^9$/L), N represents neutrophil count ($\times 10^9$/L), and L represents lymphocyte count ($\times 10^9$/L). This index incorporates data from platelets, neutrophils, and lymphocytes and captures both the degree of inflammatory activation and the status of immune regulation. NLR, PLR, and MLR were computed as the respective ratios of each blood cell type to the relevant denominator. Whole blood samples were collected at the NHANES mobile examination sites and cell counts were performed using a Beckman Coulter automated blood analyzer. For each immune-inflammatory marker, data were divided into quartiles for the total study population, and continuous variables were assessed for a dose response.

2.4. Outcome Variable (PHQ-9)

Symptoms of depression were assessed using the PHQ-9. The PHQ-9 is a validated self-report measure based on the DSM-IV criteria. The PHQ-9 is a 9-item measure scored on a 0–3 point scale. Respondents indicate how often they experienced each of the symptoms in the last 2 weeks. Total scores range from 0 to 27. The measure has been shown to have an 88% sensitivity and specificity at the cut-off score of 10 for the diagnosis of major depression [15]. The measure also has good cross-group invariance across sex, race, and education in the United States, justifying comparisons across these groups [16]. PHQ-9 scores of 10 or more were used as the indicator of the presence of depression. Additionally, scores of 5, 10, 15, and 20 were used to indicate the presence of mild, moderate, moderately severe, and severe depression, respectively.

2.5. Covariates

The selection of covariates was based not only on an extensive literature review but also on four constituent domains entailing, demographics, socioeconomics, lifestyle, and health. Age was factored both as a continuous and a categorical variable of three ranges (18–39, 40–59, and ≥60 years) for stratified analysis. The World Health Organization (WHO) classifies body mass index (BMI) into three categories: normal weight people with a BMI less than 25 kg/m^2, overweight individuals with a BMI between 25–29.9 kg/m^2, and obese individuals with a BMI equal to or greater than 30 kg/m^2. The smoking variable was stratified into three categories: never, former, and current smokers, while, for the alcohol variable, the three categories were never, moderate, and heavy drinkers, based on the accounting of the last 12 months. The Global Physical Activity Questionnaire classifies the activity variable into insufficient (less than 150 min of exercise/week) and sufficient (at least 150 min of exercise/week) physical activity. A history of chronic disease included physician-diagnosed cases of hypertension, diabetes, cardiovascular disease (CVD), and chronic kidney disease (CKD), and the respective laboratory and examination findings.

2.6. Statistical Analysis

A full case analysis strategy was adopted, and cases were omitted that lacked necessary variable data, analyzing under the assumption of random missing data, and with the consideration that the percentage of missing data was low (<15%). Statistical modeling was done considering the intricacies of the NHANES study. All analyses included the sample weight, strata, and primary sampling unit variables to ensure the estimates and standard errors

were robust and nationally representative. Weights were recalibrated and harmonized according to the NHANES guidelines for analysis of multiple survey cycles.

Continuous variables were evaluated using means ± standard errors, and medians (interquartile ranges) and analyzed groups with weighted *t*-tests or analysis of variance. Categorical variables were assessed with frequencies (weighted percentages) and analyzed using weighted chi-square tests. Standardized mean differences (SMD) assessed the magnitude of difference for the metrics of the two groups, and |SMD| > 0.1 was considered a substantial discrepancy.

Weighted multiple logistic regressions were used to analyze the relationship between immune-inflammatory markers and depression in three different models. Model 1 controlled for age and sex. Model 2 also controlled for race/ethnicity, education, poverty-income ratio (PIR), and marital status. Model 3 controlled for all the variables in the previous models and also included BMI, smoking, alcohol consumption, physical inactivity, and the presence of chronic diseases. Results were given as odds ratios (ORs) and 95% confidence intervals (CIs). To assess multicollinearity, the variance inflation factors (VIFs) were calculated and analyzed.

Using knots at the 5th, 35th, 65th, and 95th percentiles, the regression analysis of the Immune-Inflammatory markers and Depressive Symptoms was used. RCS estimated the Odds Ratio (OR) at the specified knotted percentiles with the median serving as the reference. To explore the different age, sex, and BMI categories, as well as smoking and chronic disease status, the data were subdivided, and the interactions using these variables were assessed with multiple regression models using interaction terms. Sensitivity analysis encompassed the exclusion of the participants on antidepressant medications, different PHQ-9 threshold adjustments, and the analysis of immune-inflammatory markers in logarithmic (log) form.

All the statistical analyses were carried out using R software version 4.3.0, where the survey package was used for analyses involving complex survey samples. A two-tailed *p*-value of less than 0.05 was considered statistically significant. In comparison to the other individual ratio indices, SII was noted to have higher discrimination ability. As such SII was noted to have higher discrimination ability, NLR, PLR, and MLR were considered as secondary exposures. Given that the analyses were exploratory in nature, *p*-values were not adjusted, and results should be interpreted with caution.

3. Results

3.1. Participant Selection and Baseline Characteristics

The original sample had 80,312 individuals from NHANES 2005–2020. After systematic screening, 28,476 individuals were aged under 18 years, 753 were pregnant, and 2400 had missing age information, leaving 48,683 adults for further screening. Subsequently, 4,892 individuals without PHQ-9 depression data, and 3,856 individuals without complete blood count data for SII calculations, were removed. In order to reduce confounding, 1,876 adults were removed for having a cancer history, 892 adults for having an autoimmune history, and 356 adults for having white blood cell abnormalities due to infection or a hematologic disorder. 4,128 adults were removed for missing complete data on covariates. This left a final analytic sample of 32,683 adults (**Figure 1**).

Using PHQ-9 scores of 10 or more as an indicator of depressive symptomatology, 2,874 respondents qualified, resulting in a weighted prevalence of 8.79%. There were significant differences in baseline characteristics between groups (**Table 1**). The depression group was younger (43.8 vs. 47.6 years), had a larger female cohort (63.1% vs. 50.8%), lower educational levels, and was more impoverished (25.3% vs. 12.1% below the poverty line). The depression group had more current smokers (35.2% vs. 20.7%), and reported more insufficient physical activity (57.8% vs. 44.1%), diabetes (17.2% vs. 10.8%), and CVD (13.1% vs. 6.4%). SMD values for all variables are shown in **Figure 2**.

3.2. Distribution Characteristics of Immune-Inflammatory Markers

Table 2 shows how the four immune-inflammatory biomarkers were distributed in the depression and non-depression cohorts. For the depression group, the median SII value was 521.7 (interquartile range [IQR]: 391.4–702.8) and for the non-depression group it was 486.3 (IQR: 364.5–651.2) with a statistically significant difference ($p < 0.001$, SMD = 0.16). In the quartile distribution analysis, the depression group had a higher prevalence for the top quartile at 29.8% versus 24.9% in the non-depression group, and for the bottom quartile, it was 21.3% in the

depression group and 25.1% in the non-depression group, showing a shift to the right.

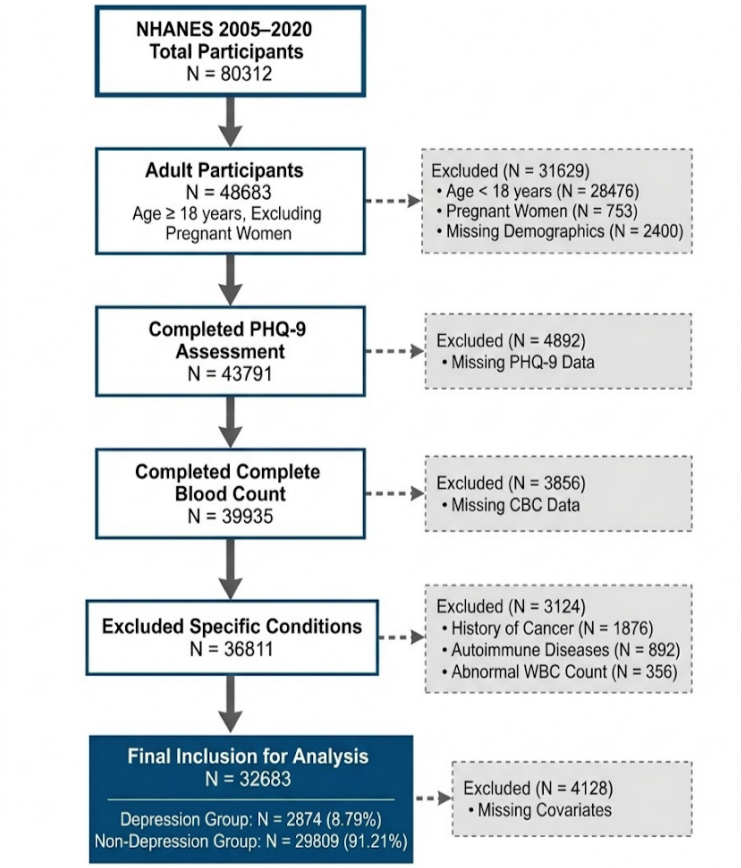

Figure 1. Participant Selection Flowchart.

Table 1. Baseline Characteristics of Study Participants.

Variable	Non-Depression Group (n = 29,809)	Depression Group (n = 2,874)	*p*-Value
Age (years)	47.6 ± 18.3	43.8 ± 18.9	<0.001
Female, %	50.8	63.1	<0.001
	Race/Ethnicity, %		**<0.001**
Non-Hispanic White	44.0	38.5	
Non-Hispanic Black	20.8	23.3	
Mexican American	17.0	17.0	
Other	18.2	21.2	
	Education Level, %		**<0.001**
Less than high school	21.9	33.4	
High school graduate	23.8	24.6	
College or above	54.3	42.0	
Below poverty line, %	12.1	25.3	<0.001
	Smoking Status, %		**<0.001**
Never smoker	57.1	44.7	
Former smoker	22.2	20.1	
Current smoker	20.7	35.2	
Heavy drinking, %	13.6	18.2	<0.001
Insufficient physical activity, %	44.1	57.8	<0.001
BMI (kg/m^2)	28.9 ± 6.7	30.2 ± 7.4	<0.001
Hypertension, %	37.3	45.1	<0.001
Diabetes, %	10.8	17.2	<0.001
CVD, %	6.4	13.1	<0.001
CKD, %	16.6	21.1	<0.001

Note: Data are presented as mean ± SE for continuous variables and percentages for categorical variables. *p*-values were calculated using weighted *t*-tests or chi-square tests.

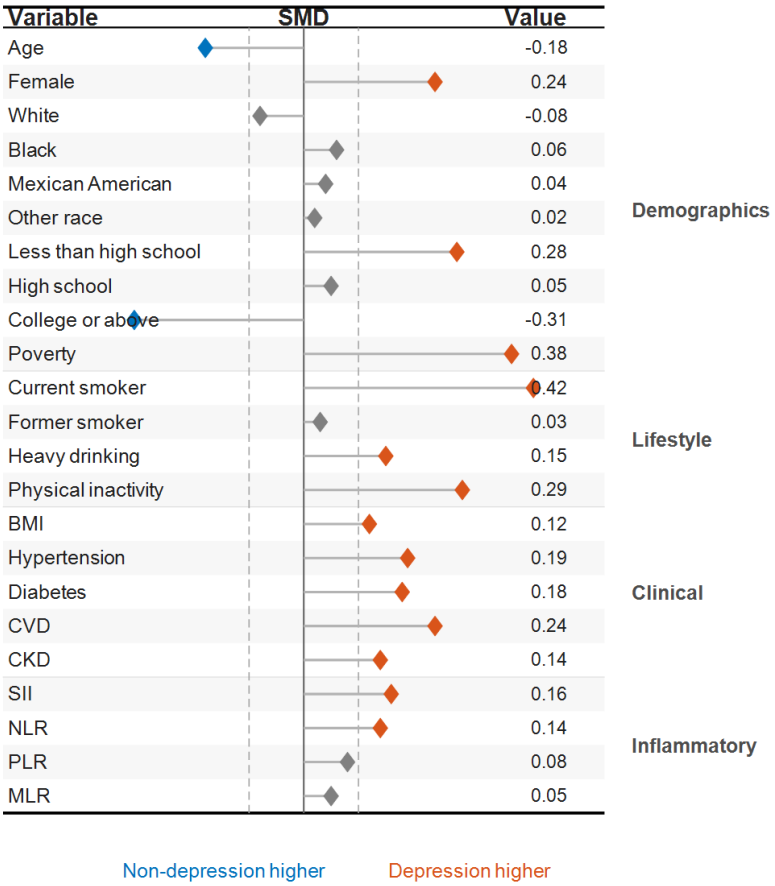

Figure 2. Standardized Mean Difference Plot.

Table 2. Distribution of Immune-Inflammatory Markers in Depression and Non-Depression Groups.

Marker	Non-Depression Group (n = 29,809)	Depression Group (n = 2,874)	*p*-Value
	SII (×10^9/L)		**<0.001**
Median (*IQR*)	486.3 (364.5–651.2)	521.7 (391.4–702.8)	
Q1, %	25.1	21.3	
Q2, %	25.0	23.9	
Q3, %	25.0	25.0	
Q4, %	24.9	29.8	
	NLR		**<0.001**
Median (*IQR*)	1.85 (1.37–2.52)	2.01 (1.48–2.78)	
Q1, %	25.2	21.9	
Q2, %	25.1	24.1	
Q3, %	24.9	25.6	
Q4, %	24.8	28.4	
	PLR		**0.024**
Median (*IQR*)	111.6 (87.1–142.8)	115.3 (89.8–149.2)	
Q1, %	25.2	23.4	
Q2, %	25.0	24.7	
Q3, %	25.0	25.4	
Q4, %	24.8	26.5	
	MLR		**0.103**
Median (*IQR*)	0.25 (0.19–0.33)	0.26 (0.20–0.34)	
Q1, %	25.2	24.3	
Q2, %	25.1	24.8	
Q3, %	25.0	25.3	
Q4, %	24.7	25.6	

Note: *p*-values derived from weighted Chi-square tests for quartile comparisons and weighted Mann-Whitney U tests for median comparisons, accounting for NHANES complex survey design using the survey package in R software. Quartile cutoff points for SII: Q1 < 364.5, Q2: 364.5–486.3, Q3: 486.3–651.2, Q4 > 651.2 (×10^9/L). IQR = interquartile range.

NLR indicated statistical differences between cohorts, with medians of 2.01 for the depression group vs. 1.85 for the non-depression group ($p < 0.001$, SMD = 0.14). Of the depression group, 28.4% were in the highest NLR quartile compared to 24.8% of the non-depression group. There were moderate statistical differences noted for PLR ($p = 0.024$, SMD = 0.08), and for MLR these differences were statistically non-significant ($p = 0.103$, SMD = 0.05). These distributions show that SII and NLR had stronger relations to depressive symptoms when compared to PLR and MLR.

3.3. Association Analysis between Immune-Inflammatory Markers and Depressive Symptoms

Three modifiable lifestyle factors, with differential associations, were tested with immune-inflammation markers and depression symptoms (**Table 3**). In comparison to the lowest SII quartile, the depression risk was significantly high in the highest quartile in Model 1 (age and sex adjusted) with an OR = 1.46 (95% CI: 1.26–1.69). In Model 2, after adjusting for race/ethnicity, education, family income, and marital status, the association was somewhat attenuated but was still significant (OR = 1.32, 95% CI: 1.13–1.54). The association was again attenuated in the fully adjusted Model 3 (which included lifestyle factors and chronic conditions) but remained significant (OR = 1.23, 95% CI: 1.05–1.44, *p* for trend = 0.008).

Table 3. Multivariable Logistic Regression Analysis of Associations between Immune-Inflammatory Markers and Depressive Symptoms.

Marker	Model 1	Model 2	Model 3
		SII	
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.12 (1.00–1.26)	1.08 (0.96–1.22)	1.04 (0.89–1.22)
Q3	1.21 (1.08–1.36)	1.16 (1.02–1.31)	1.11 (0.94–1.31)
Q4	1.46 (1.26–1.69)	1.32 (1.13–1.54)	1.23 (1.05–1.44)
p for trend	<0.001	<0.001	0.008
Per *SD* increase	1.12 (1.07–1.18)	1.09 (1.04–1.15)	1.07 (1.01–1.14)
		NLR	
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.09 (0.97–1.23)	1.05 (0.93–1.19)	1.02 (0.87–1.20)
Q3	1.16 (1.03–1.30)	1.10 (0.97–1.25)	1.06 (0.90–1.25)
Q4	1.34 (1.16–1.55)	1.24 (1.06–1.45)	1.17 (0.99–1.38)
p for trend	<0.001	0.006	0.072
Per *SD* increase	1.10 (1.05–1.16)	1.07 (1.02–1.13)	1.05 (0.99–1.12)
		PLR	
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.06 (0.94–1.19)	1.04 (0.92–1.17)	1.02 (0.87–1.20)
Q3	1.10 (0.98–1.24)	1.06 (0.94–1.20)	1.04 (0.88–1.22)
Q4	1.18 (1.02–1.36)	1.12 (0.96–1.30)	1.08 (0.91–1.28)
p for trend	0.018	0.112	0.356
Per *SD* increase	1.05 (1.00–1.11)	1.03 (0.98–1.09)	1.02 (0.95–1.09)
		MLR	
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.02 (0.91–1.15)	1.00 (0.89–1.13)	0.98 (0.84–1.15)
Q3	1.04 (0.92–1.17)	1.01 (0.89–1.14)	0.98 (0.83–1.15)
Q4	1.07 (0.93–1.23)	1.02 (0.88–1.18)	0.97 (0.82–1.15)
p for trend	0.326	0.724	0.864
Per *SD* increase	1.02 (0.97–1.08)	1.01 (0.95–1.07)	1.01 (0.94–1.09)

Note: Model 1 adjusted for age and sex. Model 2 additionally adjusted for race/ethnicity, education, PIR, and marital status. Model 3 further adjusted for BMI, smoking, alcohol, physical activity, and chronic diseases.

The diagnostics confirmed a lack of multicollinearity (all VIF values < 2.5). It is also important to note that in the full model, the second and third quartiles had non-significant results (OR = 1.04, 95% CI: 0.89–1.22 and OR = 1.11, 95% CI: 0.94–1.31), which may suggest a possible threshold for which depression risk could be observable. In the case of the SII being a continuous variable, each one standard deviation increase produced an OR of 1.07 (95% CI: 1.01–1.14), which was statistically significant.

NLR had a positive correlation compared to SII, but had a slightly smaller effect size. In Model 1, the highest quartile OR was 1.34 (95% CI: 1.16–1.55), and after full adjustment, it decreased to 1.17 (95% CI: 0.99–1.38) and was at borderline statistical significance (*p* for trend = 0.072). PLR had an OR of 1.18 (95% CI: 1.02–1.36) for the

highest quartile in Model 1, which decreased to 1.08 (95% CI: 0.91–1.28) in the fully adjusted model and was not significant (p for trend = 0.356). MLR showed no association in all models, and the highest quartile OR was 0.97 (95% CI: 0.82–1.15) after full adjustment (p for trend = 0.864).

3.4. Dose-Response Relationships

In RCS models, immune-inflammatory factors and depression were evaluated for dose-response associations (**Figure 3**). Beyond 460 × 10^9/L, SII and depression risk were significantly heightened (p overall = 0.009, p non-linearity = 0.064). The non-linear association did not achieve statistical significance (p = 0.064), but there was an overall association, and the J-shaped curve provides evidence for threshold effects as opposed to a linear association. There may be biological thresholds, J-shaped patterns with increased non-linearity and curve association. This is where inflammation is stressful, but not crossed SII > 460 × 10^9/L, which is associated with pathological threshold and depression risk.

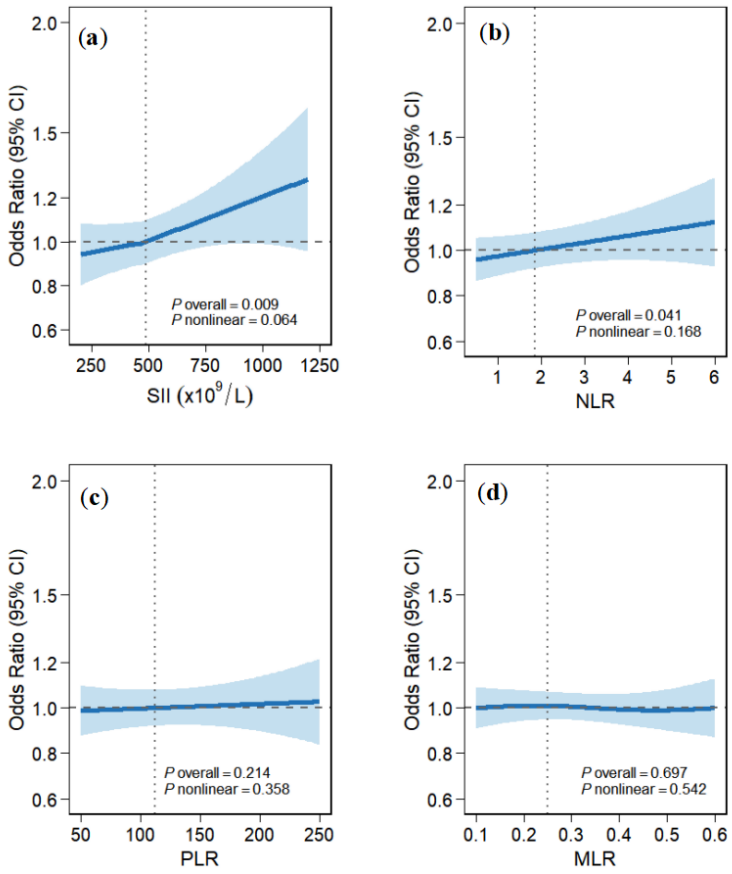

Figure 3. Dose-Response Relationship Curves between Immune-Inflammatory Markers and Depression Risk. (**a**) SII; (**b**) NLR; (**c**) PLR; (**d**) MLR.

Note: Restricted cubic spline analysis of dose-response relationships. Solid lines represent OR estimates; shaded areas, 95% CIs. The horizontal dashed line indicates OR = 1. Models were fully adjusted (Model 3).

NLR exhibited a linear dose-response relationship (p overall = 0.041, p nonlinearity = 0.168), with a meaningful overall association and no statistically significant non-linear trend. PLR and MLR showed non-significant relationships for dose-response (p overall = 0.214 and 0.697, respectively).

3.5. Subgroup Analyses

The pre-defined subgroup analyses examined the differences in the SII-depression relationship across the various groups in the population (**Figure 4**). With the exception of some heterogeneity, the positive relationship between SII and depression held across the majority of the subgroups.

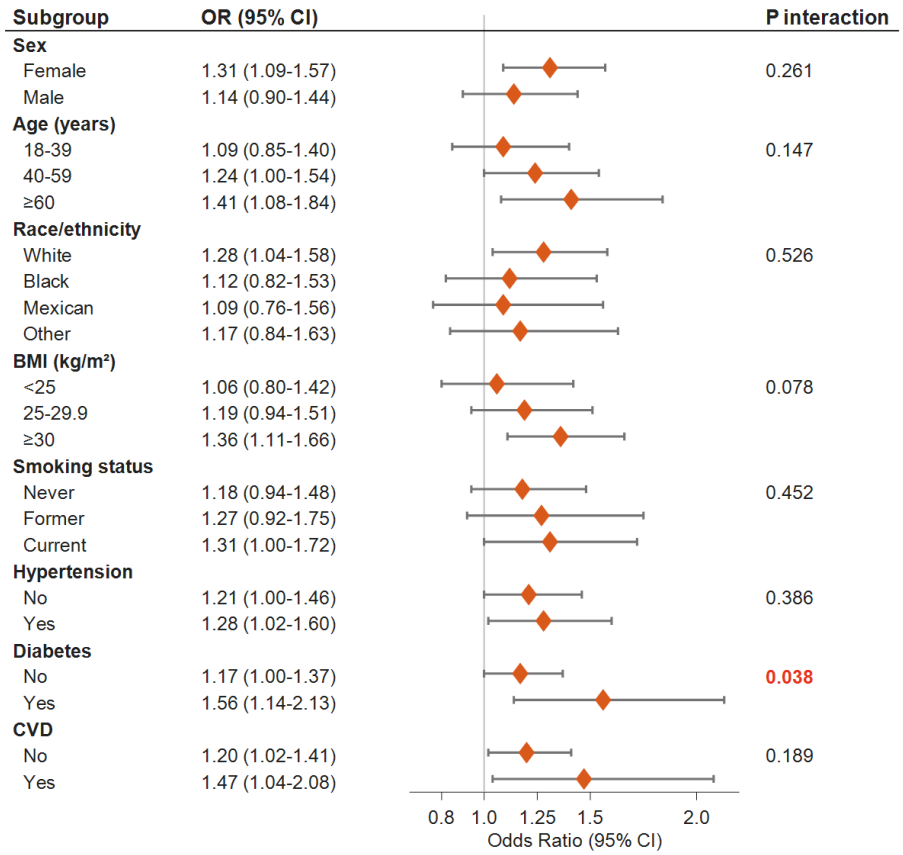

Figure 4. Forest Plot of Subgroup Analyses for the Association between SII and Depressive Symptoms.
Note: ORs compare the highest versus the lowest SII quartile with 95% confidence intervals. Models were fully adjusted (Model 3). *p*-values for interaction: Sex p = 0.261, Age p = 0.147, Race/Ethnicity p = 0.526, BMI p = 0.078, Smoking p = 0.452, Hypertension p = 0.386, Diabetes p = 0.038, CVD p = 0.189.

The female association noted was more pronounced for females: (OR = 1.31, 95% CI: 1.09–1.57), contrary to the association for males (OR = 1.14, 95% CI: 0.90–1.44; p interaction = 0.261). There was an age gradient, with even more pronounced associations for older adults (≥60 years: OR = 1.41; 40–59 years: OR = 1.24; 18–39 years: OR = 1.09). Although the interaction was not significant (p = 0.147), there was an absence of significant interactions for race/ethnicity (p = 0.526) or BMI (p = 0.078).

The most notable finding involved the analyses done per diabetes status. The association between SII and depression was further strengthened among participants with diabetes (OR = 1.56, 95% CI: 1.14–2.13), while the association was weaker among participants without diabetes (OR = 1.17, 95% CI: 1.00–1.37, marginally significant). The p for interaction for diabetes status was 0.038, and this was the only statistically significant effect modifier, which shows that the presence of diabetes strengthened the SII-depression association. CVD stratification indicated a similar, though less pronounced, trend (OR = 1.47, 95% CI: 1.04–2.08 among those with CVD and OR = 1.20, 95% CI: 1.02–1.41 among those without), but with P for interaction equal to 0.189, which may be a result of the smaller sample size of the CVD subgroup.

3.6. Sensitivity Analyses

Multiple sensitivity analyses examined the robustness of primary findings (**Table 4**). After 1842 subjects on antidepressant medication were removed, the new OR for the highest SII quartile changed from 1.23 to 1.29 (95% CI: 1.09–1.52). This minor improvement could indicate that depressed individuals with PHQ-9 scores <10, who were classified as non-depressed in the primary analysis, may have been included.

There were expected gradients regarding the variations with the PHQ-9 cutoffs. When the cutoffs were relaxed to 5 (any depressive symptoms), the sample depression prevalence increased to 23.4%, but the OR decreased to 1.12 (95% CI: 1.01–1.24), and it was still statistically significant. With a stricter cutoff at 15 (moderately severe depression), the prevalence decreased to 3.2% but the OR increased to 1.42 (95% CI: 1.10–1.83). The SII \\“extreme

values\\" are not a problem when the SII is log-transformed (OR = 1.24, 95% CI: 1.07–1.44), and it also holds when \\"extreme values\\" of the SII are not calculated (OR = 1.21, 95% CI: 1.03–1.42).

Table 4. Sensitivity Analysis Results.

Analysis	n	OR (95% CI)	*p*-Value
Main analysis	32,683	1.23 (1.05–1.44)	0.011
Excluding antidepressant users	30,841	1.29 (1.09–1.52)	0.003
PHQ-9 ≥ 5 defining depressive symptoms	32,683	1.12 (1.01–1.24)	0.032
PHQ-9 ≥ 15 defining moderate-severe depression	32,683	1.42 (1.10–1.83)	0.007
Log-transformed SII	32,683	1.24 (1.07–1.44)	0.004
Excluding extreme SII values	32,028	1.21 (1.03–1.42)	0.019
Participants without chronic diseases only	14,876	1.12 (0.92–1.36)	0.241
Additionally adjusted for CRP	28,462	1.16 (0.98–1.37)	0.089
Participants with any chronic disease only	18,807	1.31 (1.08–1.58)	0.006
Participants with diabetes only	3716	1.56 (1.14–2.13)	0.005

Of the 28,462 participants, in the case of one with CRP values, the CRP adjustment resulted in a positive SII association shift (OR from 1.23 to 1.16, 95% CI: 0.98–1.37, $p = 0.089$), which became non-significant. This finding suggests that the SII and CRP measures have some features in common, which partially define them in terms of the overlap of SII and CRP pertaining to inflammation related to depression. Since the SII captures data from several types of blood cells and CRP is an acute phase protein, the SII could be providing additional details not completely represented by a CRP related to dysfunction of the immune system.

The most important of these overlapping inflammatory pathways becomes apparent with the adjustment of CRP level whereby SII-depression associations are diminished. Given that the SII association was not completely removed, it suggests that the sub-acute inflammatory response was less informative than the chronic dys-immune cellular response. SII, in a clinical setting, could detect depression-related immune dysregulation in patients with CRP levels within the normal range, thus increasing the patient population amenable to such immune-based interventions.

4. Discussion

4.1. Summary of Main Findings

This study, using NHANES data from 2005–2020, examined the relationship between SII and other immune-inflammatory indices with depressive symptoms in 32,683 adults in the United States. Depression risk increased by 23% for the highest quartile SII when compared to the lowest quartile. The dose-response relationship showed a J-shaped confounder-adjusted pattern. The association was modified by the presence of diabetes (OR = 1.56; p for interaction = 0.038). Of the four inflammatory indices (SII, NLR, PLR, MLR), only SII retained statistical significance in the fully adjusted model. Sensitivity analyses showed that the association was stronger in those with more severe depression. In those with no chronic diseases, the association was not significant, indicating that chronic disease burden is likely important.

4.2. Comparison with Previous Studies

The present findings support and build upon recent NHANES-based studies [13,14]. This study's unique contributions are: (1) thorough comparison and statistical superiority testing for each of the four inflammatory indices (SII, NLR, PLR, MLR); (2) the most engagement on immunomodulatory interventions with thorough mechanisms and clinical implications; (3) diabetes, for the first time, as an effect modifier (p for interaction = 0.038); (4) the first use of restricted cubic splines for the systematic evaluation of the dose-response; and (5) an extensive analysis of chronic disease stratification which seems to suggest various patterns by disease subgroups.

The lack of subpar performance of SII compared to individual inflammatory component ratios (NLR, PLR, MLR) is perhaps SII being able to capture more thoroughly the immune deregulation phenomena. SII combines three different cellular elements: neutrophils (which reflect acute inflammatory activation), lymphocytes (which reflect adaptive immune response), and platelets (which reflect thromboinflammatory). Perhaps this three-dimensional cellular combination captures more thoroughly the perspective of the immune dysregulation phenomena in de-

pression, of which the dual phenomena are the activation of inflammatory innates and the suppression of adaptive immunity. In single ratios like NLR, which capture only the neutrophil-lymphocyte ratios, the perspective is, at best, incomplete, and is more likely to exclude the thromboinflammatory dimension, which is largely regarded as the contribution of platelets in the pathophysiology of depression via regulation of serotonin and inflammatory microvasculature.

The link between SII and depression severity has been documented in clinical settings, where SII among hospitalized depression cases has been found to be associated with 25.3% elevated severe depression risk per standard deviation increase in SII [11]. In high SII groups, large sample studies have noticed a 3.6-fold increase in the risk of moderate to severe depression compared to low SII groups [12]. The fairly smaller effect size in the current general population study is justified since clinical populations usually show more elevated levels of inflammation. In certain clinical populations, such as post-stroke patients [17,18] and patients with end-stage renal disease on hemodialysis [19], stronger associations have been noted, which is in line with the chronic disease effect modification noted in the current study.

In terms of other inflammatory biomarkers, meta-analyses show increased NLR in cases of depression, with effect sizes in the range of 0.33, and a more variable signal in the case of PLR and a very variable signal in the case of MLR [20,21]. Analyses based on NHANES showed depression correlated non-linearly with NLR, PLR, and MLR [22]. The current findings mostly concur with previous findings, with the exception of PLR, which became non-significant after full adjustment, which may reflect differences in the selection of covariates.

4.3. Biological Mechanisms

The relationship between inflammation and depression is complex and bidirectional at the same time. Systemic inflammation can reach the central nervous system (CNS) through several routes, including crossing the blood-brain barrier (BBB), vagus nerve activation, microglia activation, and disruption of tryptophan metabolism, which decreases serotonin levels [23]. IL-6 is a key player, and levels of this cytokine correlate with symptom severity [24]. Longitudinal studies show that inflammation can precede the onset of depression [25,26]. Around 25% of patients with depression show signs of low-grade inflammation (CRP > 3 mg/L) [8]. Increased levels of CRP have been associated with depression severity and worse treatment response [27].

In this case, adjusting SII and CRP showed a lesser association, but literature indicates that dysregulation of the immune system in depression is CRP independent, given that immune-related gene expression is upregulated in individuals with low CRP < 1 mg/L [28]. SII is made up of neutrophils, lymphocytes, and platelets. The diabetes-related effect modification could be explained as hyperglycemic states promote inflammation and this may increase the effect of elevated SII on the neural system.

4.4. Implications for Immunomodulatory Interventions

The inflammation hypothesis opens a novel approach to the treatment of depression. Meta-analyses document the effectiveness in treating depressive episodes of anti-inflammatory medications, non-steroidal anti-inflammatory drugs, and cytokine inhibitors [29]. Anti-inflammatory medications show particular promise in personalized treatment approaches. Also, in the spirit of precision medicine, strategies focused on the anti-inflammatory approach have relied on patient stratification based on anti-inflammatory levels to guide treatment for those who may benefit most [30]. Individual inflammatory indices may represent different aspects of immune dysregulation. Across different studies, NLR appears to be more accurately predictive of depression and suicide, and PLR more accurately of treatment response [31]. The prospects of immunotherapy for depression are promising, although most available data are from patients suffering from inflammatory diseases, and the primary depression studies have yielded inconsistent results [32].

Since SII originates from standard complete blood counts, it is easily available to clinicians. It may indicate an increased need for depression screening among patients with diabetes, obesity, and cardiovascular disease when SII is markedly elevated. It is also important to note that SII could be an independent predictor of mortality even among individuals suffering from depression. In this instance, with every 100-unit increase in SII, the risk of all-cause mortality increases by roughly 5% [33].

4.5. Study Limitations and Future Directions

There are several important limitations of this research that need to be addressed first. Given that this study employed a cross-sectional design, there is no way to determine causal relationships. In this study, the relationship between depression and inflammation is complicated by the fact that depression and inflammation are bidirectionally related. Given the cross-sectional study design, this study is unable to disentangle the complexity of the various relationships. Chronic inflammation can genetically and biologically predispose a person to depression through the neural pathways which are associated with inflammation, and are involved in the regulation of neurotransmitters and the structure and connectivity of the neural pathways. On the other hand, depression can lead to inflammation through behavioral pathways (poor sleep, physical inactivity, unhealthy diet) and biological mechanisms (HPA axis dysregulation, autonomic nervous system dysfunction). Longitudinal studies that measure the same variables several times during the study period in the future are necessary to determine the rate and presence of changes in the study variables, as well as to determine the validity of the Social Inflammation Index as a predictive rather than an associative biomarker.

In relation to generalizability of depression severity assessment, current findings have shown general consistent gradient relationships for varying PHQ-9 thresholds with effect sizes strengthening with increase in severity, thus: OR = 1.12 (95% CI: 1.01–1.24) for mild (PHQ-9 ≥ 5), OR = 1.23 (95% CI: 1.05–1.44) for moderate (PHQ-9 ≥ 10), and OR = 1.42 (95% CI: 1.10–1.83) for moderately severe (PHQ-9 ≥ 15) symptoms. The SII depression association gradient supports its generalizability and suggests that SII's immune-inflammatory dysregulation is more severe at higher depression symptoms. Self-reported PHQ-9 has no direct measurement of inflammation, such as cytokines, and blood cell counts were only assessed at single time points.

While a number of various confounding variables were controlled, residual confounding is still a possibility. There were several statistical tests applied without a formal adjustment for multiple comparisons, especially in the subgroup analyses for the eight demographic and clinical strata. Given that the secondary analyses were still exploratory and the balance, or more so the need, between Type I and Type II error, this was a reasonable choice. The confidence in the robustness of the primary findings is bolstered by the pre-specified nature of the analyses which were subgroups based on identified effect modifiers (age, sex, diabetes) and the overall consistency of the findings with the sensitivity analyses. Nonetheless, the results of the subgroup analyses need to be considered with the possibility of reporting a high number of false positives, and subsequent studies to confirm these findings should apply a multiple comparisons adjustment of a statistical nature.

A number of possible confounding factors were either not accessible or not included, such as: (1) the use of anti-inflammatory medications (NSAIDs, statins, corticosteroids) which may affect both the SII and the risk of depression; (2) sleep and its quantity and quality which may be related to depression and its inflammatory correlates; (3) psychosocial support and feelings of loneliness which are recognized as psychosocial risk factors for depression; (4) prior episodes of depression which may affect current levels of inflammation; (5) and the dietary inflammation score. Participants with subclinical immunodeficiencies—individuals with immune dysfunction who lack discernible clinical symptoms—might have evaded the exclusion criteria. The broad sample size (n = 32,683) and population-based approach will probably have some effect, and the uniformity of the results across different sensitivity analyses suggests that subclinical immunodeficiency is unlikely to have skewed the main results. Research taking more sophisticated immune system evaluations will be able to answer the questions raised by the aforementioned potential confounding factors.

The results are applicable to the US population, while applying the results to other countries should be approached with caution. There are differences in the rates of global depression by country or region [34,35]. There is an important need to replicate the current study in other countries/regions. There are potential gaps in the current study that future studies should address. Cohort studies are needed to establish causation. More research should focus on the youth population, considering one-fifth of the global youth population are experiencing depressive symptoms, and the prevalence is increasing [36]. There are a limited number of studies examining the relationship between suicidality and self-injury (SII) and depression in this population [37]. Further research in the field of multi-omics and the mechanisms of SII in the treatment of depression may be useful.

5. Conclusion

The current study focuses on verifying an independent and positive association of SII with depression among 32,683 US adults using NHANES 2005–2020 data. A J-shaped dose-response for the association was observed, which was stronger for diabetes and older age. Unlike NLR, PLR, and MLR, which were none/less significant with depression, SII seems to be a more promising indicator for depression than other systemic inflammatory markers. From sensitivity analyses, the role of chronic diseases on the SII-depression association was elucidated, along with the validity of a direct relationship between the severity of depression and the strength of the association. Findings corroborate the inflammation-depression hypothesis and indicate SII, along with diabetes, older age, and chronic disease, to be potential targets/health markers for depression patients who may benefit from immunomodulatory treatment.

Funding

This work received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting this study are publicly available from the National Health and Nutrition Examination Survey (NHANES) database at https://www.cdc.gov/nchs/nhanes/index.htm. The datasets analyzed include NHANES cycles 2005–2020.

Conflicts of Interest

The author declares no conflict of interest.

AI Use Statement

The author used Claude (Anthropic) solely for grammar checking, sentence structure refinement, and improving the readability of the English text in this manuscript. The author takes full responsibility for all academic content, including all ideas, data, analyses, and conclusions presented herein. The use of AI was thoroughly reviewed and supervised by the author.

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