Article

Tong Wei[1,*]
Maihemutijiang Muzhapa[1]
Aliqing Abudusalamu[1]

Specific Associations of Varicose Vein Severity, Systemic Inflammatory Burden, and Somatic Depressive Phenotypes: A Cross-Sectional Study

[1]Department of Vascular Intervention, Fifth Affiliated Hospital of Xinjiang Medical University, 830000 Urumqi, Xinjiang Uygur Autonomous Region, China

Abstract

Background: Accumulating evidence indicates an association between vascular disorders and depressive symptoms, however, the relationship between varicose veins and specific dimensions of depressive symptoms, particularly somatic symptoms, remains insufficiently characterized at the population level.

Methods: Data were extracted from the National Health and Nutrition Examination Survey (NHANES) 2005–2018, encompassing 35,646 adults aged ≥20 years. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9), with the somatic subscale employed to quantify the burden of somatic depressive symptoms. Systemic inflammation was evaluated using the Systemic Immune-Inflammation Index (SII) and related biomarkers, including C-reactive protein (CRP). Survey-weighted regression analyses were conducted to examine associations between varicose veins, inflammatory markers, and depressive symptoms. A nomogram based on multivariable logistic regression was developed to estimate the probability of elevated somatic depressive symptoms, and model performance was evaluated using discrimination, calibration, and decision curve analysis. Sensitivity analyses were performed to assess robustness.

Results: Among the study population, 1584 participants (4.0%) reported a diagnosis of varicose veins. Compared with individuals without varicose veins, those affected exhibited higher levels of systemic inflammatory markers as well as significantly higher PHQ-9 somatic and total scores. After multivariable adjustment, varicose veins were consistently associated with an increased likelihood of elevated somatic depressive symptoms, and these findings remained robust across sensitivity analyses. The nomogram incorporating varicose vein status, inflammatory indicators, and demographic factors demonstrated moderate discrimination (area under the curve = 0.645) and good calibration.

Conclusions: Varicose veins are independently associated with a higher burden of somatic depressive symptoms in U.S. adults, concurrent with elevated systemic inflammatory markers. These findings highlight the importance of considering specific of depressive symptoms in individuals with chronic venous disease and support the adoption of integrated approaches to vascular and mental health assessment.

Keywords

varicose veins; depression; somatic symptoms; inflammation; risk assessment

Introduction

Depression is one of the most prevalent mental disorders globally and a major contributor to global disability and morbidity [1,2]. Mounting evidence suggests that depression extends beyond a purely psychological condition, representing a systemic disorder involving complex interactions among the immune, vascular, and neuroendocrine systems [3–5]. Chronic low-grade inflammation has been identified as a key biological pathway underlying depressive symptoms, particularly somatic dimensions such as fatigue, sleep disturbance, and psychomotor slow-

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*Corresponding author details: Tong Wei, Department of Vascular Intervention, Fifth Affiliated Hospital of Xinjiang Medical University, 830000 Urumqi, Xinjiang Uygur Autonomous Region, China. Email: 13579839231@163.com

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ing, which frequently manifest in individuals with chronic medical conditions [6–8].

At the same time, varicose veins, a common manifestation of chronic venous disease (CVD), are particularly prevalent among women and older adults. In Western adult populations, the prevalence may be as high as approximately one-third. The reported prevalence rates vary among studies, ranging from 2% to 56% for men and 1% to 60% for women, with the differences mainly attributed to the study populations and diagnostic criteria. A review by Wasan on chronic venous insufficiency also indicates that varicose veins are one of the most common manifestations in the CVD/chronic venous insufficiency spectrum. The estimated prevalence of varicose veins in the general adult population is approximately 5% to 30%, indicating that this disease is highly prevalent in the general population and closely associated with age [9,10]. Traditionally regarded as a benign peripheral vascular condition, varicose veins are now recognized as a chronic inflammatory–vascular disorder, characterized by endothelial dysfunction, leukocyte activation, oxidative stress, and sustained cytokine release [11,12]. These inflammatory responses parallel those observed in depression, suggesting that both disorders may share overlapping biological mechanisms involving immune activation and microvascular dysregulation.

Despite this biological plausibility, the mental health burden associated with varicose veins has received limited attention. Most studies to date have focused primarily on the physical consequences of venous disease—such as leg pain, swelling, and impaired mobility—whereas the psychological sequelae, especially depression, have been largely overlooked. Existing clinical evidence is fragmented, often derived from small-scale or single-centre studies, and rarely incorporates mechanistic insights. Moreover, it remains unclear whether varicose veins are specifically linked to somatic depressive symptoms, which may better reflect the biological interplay between vascular inflammation and mood disturbance.

Mounting evidence indicates that systemic inflammation may serve as a key bridge between vascular dysfunction and depression [4,13]. Circulating inflammatory biomarkers—such as C-reactive protein (CRP), Systemic Immune-Inflammation Index (SII), and platelet-to-lymphocyte ratio (PLR)—have been widely associated with the severity and prognosis of cardiovascular and cerebrovascular diseases. SII and neutrophil-to-lymphocyte ratio (NLR) have been reported as predictors of stroke severity in patients with large-artery atherosclerosis [14,15]. However, few population-based studies have examined whether these inflammatory pathways mediate the relationship between varicose veins and depression, or whether inflammation-related indices can improve the prediction of depression risk among individuals with venous disease.

Against this background, the present study utilized data from the National Health and Nutrition Examination Survey (NHANES, 2005–2018) a nationally representative U.S. cohort, to investigate the relationship between varicose veins and depressive symptoms. Specifically, we aimed to examine whether varicose veins are independently associated with depressive symptoms—particularly somatic manifestations—and to evaluate the role of systemic inflammatory burden in this association.

We hypothesized that individuals with varicose veins would exhibit higher levels of systemic inflammation and greater severity of somatic depressive symptoms. Furthermore, we sought to explore whether inflammatory markers contribute to the observed relationship between varicose veins and depressive symptoms after adjusting for demographic and clinical covariates.

Methods

Study Population

This cross-sectional study utilized data from the NHANES, encompassing survey cycles from 2005 to 2018. NHANES is a nationally representative program conducted by the U.S. Centers for Disease Control and Prevention (CDC) to assess the health and nutritional status of the civilian, non-institutionalized U.S. population through a multistage, stratified, and probability sampling design.

Eligibility criteria included adults aged 20 years and older with complete data on varicose vein status, depressive symptoms (Patient Health Questionnaire-9 (PHQ-9)), and inflammatory biomarkers. Individuals with missing data for any of these key variables were excluded from the analysis.

A total of 70,190 adults aged ≥20 years were initially identified from the NHANES 2005–2018 cycles. Participants were sequentially excluded if they had missing information on lower extremity varicose vein diagnosis (n = 30,522). Among the remaining participants, those lacking data on inflammatory biomarker (including components required to calculate the systemic immune–inflammation index and C-reactive protein) or PHQ-9 data were further excluded (n = 3547). An additional 475 participants were excluded due to missing covariate information. The fi-

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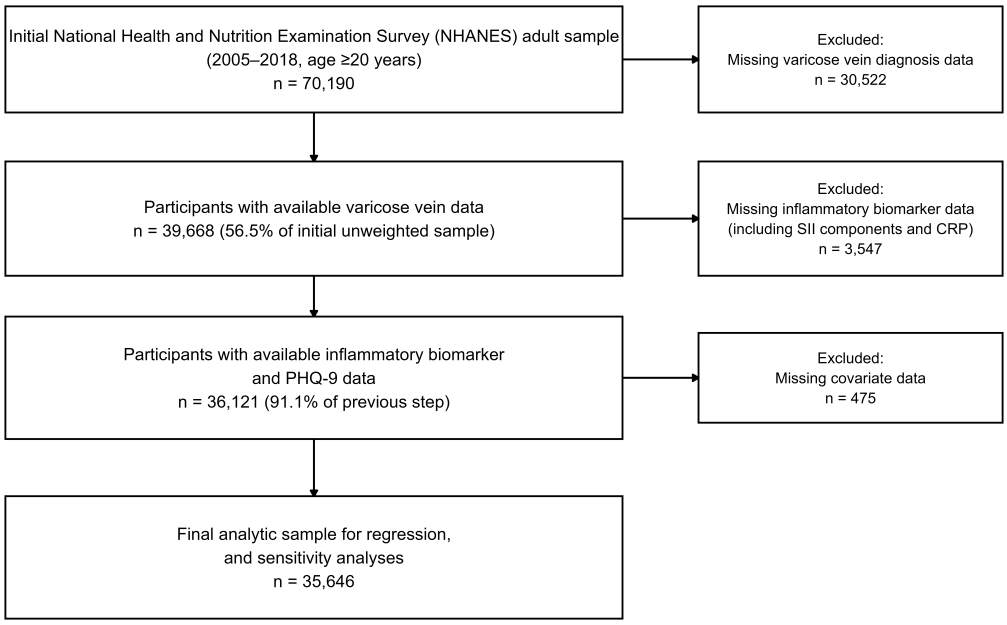

Fig. 1. Flowchart of Participant Selection from NHANES 2005–2018. The figure illustrates the stepwise selection of adults aged ≥20 years from the NHANES 2005–2018 cycles. Numbers shown represent unweighted participant counts at each selection stage. The final analytic sample (n = 35,646) was used consistently for all regression, predictive modeling, and sensitivity analyses. NHANES sampling weights were applied in subsequent analyses to obtain nationally representative estimates. NHANES, National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9.

nal analytic sample comprised of 35,646 participants (unweighted sample size), which was used consistently for all regression, mediation, predictive modeling, and sensitivity analyses. All sample sizes reported in Fig. 1 represent unweighted participant counts, whereas NHANES sampling weights were applied in subsequent analyses to obtain nationally representative estimates. The stepwise participant selection process is illustrated in Fig. 1.

All NHANES data are publicly accessible via the NCHS website, and the survey protocols were approved by the NCHS Institutional Review Board. Written informed consent was obtained from all participants prior to data collection.

Assessment of Varicose Veins

Varicose vein status was determined based on the self-reported medical condition questionnaire, where participants were asked whether a healthcare provider had ever diagnosed them with "varicose veins in the legs". Participants responding "yes" were classified as having varicose veins.

Although self-reported data may be subject to misclassification, NHANES validation studies have demonstrated good reliability for physician-diagnosed chronic conditions.

Assessment of Depressive Symptoms

Depressive symptoms were assessed using the PHQ-9, a validated instrument widely used for population-based screening and severity assessment of depression [16]. Each item is rated on a 4-point Likert scale ranging from 0 ("not at all") to 3 ("nearly every day"), yielding a total score from 0 to 27, with higher scores indicating greater overall severity of depressive symptom. Consistent with established conventions, PHQ-9 total scores were further categorized to describe depression severity as follows: 0–4 (none or minimal); 5–9 (mild); 10–14 (moderate); 15–19 (moderately severe); and 20–27 (severe depressive symptoms). These categories were used for descriptive purposes rather than clinical diagnosis.

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Consistent with prior validation studies, a total score of ≥10 on the PHQ-9 was additionally used to indicate clinically significant depressive symptoms, as this threshold has been shown to provide an optimal balance between sensitivity and specificity for identifying major depressive disorder in both clinical and population-based settings [16]. In the present study, this cutoff was applied for descriptive and comparative purposes rather than for clinical diagnosis.

To further characterise symptom dimensions, the PHQ-9 was partitioned into two subscales based on established factor-analytic and symptom-domain frameworks. The Somatic Depression Factor comprised four items assessing sleep disturbance, fatigue, appetite or weight change, and psychomotor retardation, with a possible score range of 0–12 [17,18]. The Cognitive Depression Factor consisted of five items reflecting depressed mood, anhedonia, feelings of worthlessness or guilt, concentration difficulties, and suicidal ideation, with a score range of 0–15 [19,20]. For both subscales, higher scores indicate a greater burden of symptoms within the corresponding dimension.

The two-factor structure of the PHQ-9 has been supported by previous psychometric studies, demonstrating good internal consistency and construct validity across diverse populations, including community-based samples. In the present study, subscale scores were used to characterise dimensional patterns of depressive symptoms rather than to establish clinical diagnoses. Although the primary analytical focus was placed on the Somatic Depression Factor, the Cognitive Depression Factor was analysed in parallel as a comparative symptom dimension, allowing assessment of whether the observed associations were specific to somatic depressive symptoms rather than reflecting a genera increase in overall depressive symptomatology.

The PHQ-9 somatic subscore was analyzed primarily as a continuous variable. In the study population, the somatic score demonstrated a right-skewed distribution with low median values (median = 0 in participants without varicose veins and median = 1 in those with varicose veins). As no universally accepted clinical cutoff has been established specifically for the PHQ-9 somatic subscale, a somatic subscore ≥3 was additionally defined as an operational, data-informed threshold indicating relatively elevated somatic symptom burden. This threshold approximately corresponded to the upper distribution of somatic scores within the study sample and reflects at least mild symptoms across multiple somatic items or moderate severity in a single item. Sensitivity analyses using an alternative threshold (≥4) yielded consistent findings [16]. The robustness of this definition was further evaluated through prespecified sensitivity analyses using alternative thresholds and model specifications (see **Supplementary Fig. 1**). Total PHQ-9 scores were additionally analysed as continuous variables in order to capture overall depressive symptom severity.

Measurement of Inflammatory Markers

Systemic inflammation was evaluated using both composite indices and individual biomarkers. The SII was calculated according to the formula originally proposed by Hu *et al*. [21]:

("SII = (Platelet count × Neutrophil count) / Lymphocyte count")

with all components derived from absolute blood cell counts rather than percentages, as routinely reported in the NHANES laboratory dataset. This calculation approach has been widely adopted in both clinical and population-based studies as it reflects the balance between innate immune activation and adaptive immune regulation [22–24].

Additional inflammatory indices included the NLR and the platelet-to-lymphocyte ratio (PLR), both calculated using absolute cell counts. CRP levels concentrations were measured using a high-sensitivity latex-enhanced nephelometric assay, following standardised NHANES laboratory protocols.

Given the right-skewed distribution of inflammatory indices in the general population, all inflammatory markers (including SII, NLR, PLR, and CRP) were natural log–transformed prior to analysis in order to reduce the influence of extreme values and improve model stability.

Covariates

Potential confounding variables were selected a priori based on previous literature linking sociodemographic, lifestyle, and health-related factors with both venous disease and depression. Covariates included age (continuous and categorized as <60 or ≥60 years), sex (male/female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), education level (less than high school, high school, college or above), poverty income ratio (PIR) as an indicator of socioeconomic status, additional covariates included body mass index (BMI; continuous and categorized as <25, 25–30, or ≥30 kg/m^2), smoking status, alcohol use, and comorbid chronic conditions including hypertension, diabetes, and cardiovascular disease. Participants with missing covariate data were excluded, and all analyses were conducted using complete-case data. All

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covariates were simultaneously included in fully adjusted multivariable models across all analyses in order to minimise residual confounding.

Statistical Analysis

All statistical analyses were conducted using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 17.0 (StataCorp LLC, College Station, TX, USA), incorporating NHANES survey weights to account for the complex sampling design and to obtain population-representative estimates. Analyses were performed in a stepwise manner according to analytical purpose. Descriptive and distributional analyses were conducted among participants with available data for the variables of interest, whereas all primary regression, predictive modelling, and sensitivity analyses were restricted to the final analytic sample with complete exposure, outcome, and covariate data.

Continuous variables were summarized as weighted means (standard errors) or medians (interquartile ranges), and categorical variables as weighted percentages. Prior to between-group comparisons, the distributional characteristics of continuous variables were assessed using tests for normality (e.g., the Shapiro–Wilk test) and homogeneity of variances (e.g., Levene's test). Between-group comparisons were subsequently performed using the *t*-test for approximately normally distributed variables with homogeneous variances, the Wilcoxon rank-sum test for variables violating normality assumptions, or the Rao–Scott χ^2 test for categorical variables, as appropriate.

Weighted multivariable linear and logistic regression models were applied to estimate associations between varicose veins and depressive symptoms (including both total PHQ-9 score and somatic subscore), with sequential adjustment for sociodemographic and clinical covariates. For regression analyses, inflammatory markers exhibiting right-skewed distributions were natural log–transformed to improve normality and reduce the influence of extreme values. All regression-based analyses were conducted in the final analytic sample.

A nomogram-based predictive model was constructed using multivariable logistic regression, incorporating predictors that were statistically significant ($p < 0.05$) in the fully adjusted model. Model performance was evaluated in terms of discrimination (area under the ROC curve), calibration (calibration slope and Hosmer–Lemeshow test), and clinical utility (decision curve analysis).

Sensitivity analyses were conducted within the final analytic sample to assess robustness, including: (1) exclusion of extreme BMI values (<18.5 or >40 kg/m^2); (2) Application of a stricter PHQ-9 somatic symptom threshold (≥4); (3) Additional adjustment for education level. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

Results

Characteristics of the Study Population and Core Variable Distribution

A total of 39,668 NHANES participants from the 2005–2018 cycles with available information on lower extremity varicose vein status were included in the descriptive baseline analysis, among whom 1584 (weighted prevalence: 4.0%) were diagnosed with lower extremity varicose veins. Baseline characteristics stratified by varicose vein status for this descriptive sample are presented in Table 1, **Supplementary Tables 1–3**, and **Supplementary Fig. 2**.

Compared with participants without varicose veins, those with varicose veins were significantly older (mean age: 57 vs. 49 years, $p < 0.001$) and included a higher proportion of men (53.2% vs. 48.2%, $p < 0.001$). Significant differences were also observed across several sociodemographic characteristics, including race/ethnicity, educational attainment, and the poverty income ratio (all $p < 0.001$).

Regarding health-related indicators, individuals with varicose veins had a higher mean BMI (29 vs. 28 kg/m^2, $p < 0.001$) and a greater prevalence of obesity (43.3% vs. 37.8%, $p < 0.001$). In addition, depression-related scores were consistently elevated in this group, including the PHQ-9 total score, somatic factor score, and cognitive factor score (all $p < 0.001$). Accordingly, the prevalence of clinically significant depression (PHQ-9 ≥10) was more than twice as high among participants with varicose veins compared with those without the condition (17.1% vs. 7.2%, $p < 0.001$).

With respect to inflammatory biomarkers, several indicators differed significantly between groups, including the SII and platelet count (both $p < 0.001$), whereas the NLR did not differ significantly between participants with and without varicose veins ($p = 0.848$).

Further distributional analyses were conducted in a subset of 36,121 participants with available laboratory inflammatory markers and complete PHQ-9 data (Fig. 2A–

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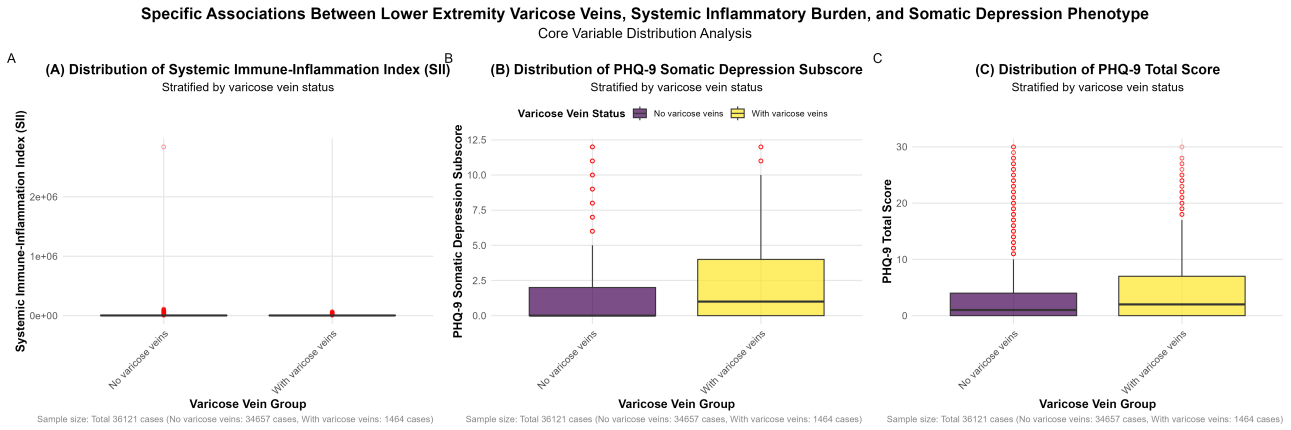

Fig. 2. Specific associations between lower extremity varicose veins, systemic inflammatory burden, and somatic depressive phenotype. (A) Distribution of the Systemic Immune-Inflammation Index (SII) by varicose vein status. (B) Distribution of the PHQ-9 Somatic Depression Subscore, and (C) Distribution of the PHQ-9 Total Score among participants with and without varicose veins. PHQ-9, Patient Health Questionnaire-9.

C).

Within this analytical subset, participants with varicose veins exhibited higher median SII values compared with the condition ($p < 0.05$). Similarly, both the PHQ-9 somatic subscore and total score were significantly higher in the varicose vein group. Distribution plots demonstrated a rightward shift in depressive symptom scores among participants with varicose veins, indicating a greater burden of somatic and overall depressive symptoms.

Taken together, these descriptive findings suggest consistent associations between lower extremity varicose veins, elevated systemic inflammatory markers, and increased depressive symptom burden across multiple analytical samples.

Associations Between Varicose Veins, Systemic Inflammation, and Depressive Symptoms

To further elucidate the potential relationships among varicose veins, systemic inflammation, and depressive symptomatology, a series of multivariable regression, interaction, and dose–response analyses were conducted (Figs. 3,4).

Fig. 3 presents the multivariable-adjusted associations between varicose veins, systemic inflammation, and depressive symptom scores. After adjustment for demographic, socioeconomic, and clinical covariates—including age, sex, race/ethnicity, body mass index, education level, income, smoking status, alcohol consumption, and comorbid conditions—participants with varicose veins exhibited significantly higher adjusted mean depressive symptom scores than those without the condition.

Specifically, the adjusted mean PHQ-9 somatic subscale score was 2.3 (95% CI: 2.18–2.42) among participants with varicose veins compared with 1.4 (95% CI: 1.4–1.5) among those without varicose veins ($p < 0.001$). Similarly, the adjusted mean PHQ-9 total score was 4.4 (95% CI: 4.2–4.6) in the varicose vein group versus 2.6 (95% CI: 2.5–2.7) in the non-varicose vein group ($p < 0.001$) (Fig. 3A).

In contrast, no statistically significant difference in the adjusted mean SII was observed between participants with and without varicose veins (3926.8 vs. 4294.4, $p > 0.05$). Nevertheless, further examination of continuous relationships revealed that SII was positively associated with PHQ-9 somatic depression scores in both groups. As illustrated in Fig. 3B, the association appeared steeper among participants with varicose veins, suggesting that higher levels of systemic inflammation may be more strongly related to somatic depressive symptom burden in this subgroup.

The interaction analysis (Fig. 4A) demonstrated a significant interaction between SII and varicose vein status (p for interaction <0.01). Across increasing tertiles of SII, PHQ-9 somatic depression scores showed a progressive upward trend in both groups; however, the slope was noticeably steeper among participants with varicose veins, indicating that a greater systemic inflammatory burden may amplify the association between varicose veins and somatic depressive symptoms.

The dose–response analysis (Fig. 4B) further supported this pattern. When SII and PHQ-9 somatic scores

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Table 1. Baseline characteristics of the study population.

Variable	Overall N = 39,668[1]	No varicose veins N = 38,084[1]	With varicose veins N = 1584[1]	*p*-value[2]
Age (years)				<0.001
Median (Q1, Q3)	49.0 (34.0, 64.0)	49.0 (34.0, 64.0)	57.0 (46.5, 66.0)	
Sex				<0.001
Male	19,203 (48.4%)	18,360 (48.2%)	843 (53.2%)	
Female	20,465 (51.6%)	19,724 (51.8%)	741 (46.8%)	
Age gGroup				<0.001
≥60 years	13,434 (33.9%)	12,738 (33.4%)	696 (43.9%)	
20–39 years	13,453 (33.9%)	13,240 (34.8%)	213 (13.4%)	
40–59 years	12,781 (32.2%)	12,106 (31.8%)	675 (42.6%)	
Race/Ethnicity				<0.001
Non-hispanic white	16,507 (41.6%)	15,858 (41.6%)	649 (41.0%)	
Non-hispanic black	8591 (21.7%)	8380 (22.0%)	211 (13.3%)	
Mexican american	6196 (15.6%)	5912 (15.5%)	284 (17.9%)	
Other race	4562 (11.5%)	4360 (11.4%)	202 (12.8%)	
Other hispanic	3812 (9.6%)	3574 (9.4%)	238 (15.0%)	
Education level				<0.001
<9th grade	4367 (11.0%)	4147 (10.9%)	220 (13.9%)	
9–11th grade	5693 (14.4%)	5446 (14.3%)	247 (15.6%)	
Some college or AA degree	11,545 (29.1%)	11,071 (29.1%)	474 (30.0%)	
College graduate or above	8924 (22.5%)	8613 (22.6%)	311 (19.7%)	
High school grad/GED or equivalent	9081 (22.9%)	8751 (23.0%)	330 (20.9%)	
Poverty income ratio (PIR)				<0.001
<1.0	7676 (21.4%)	7280 (21.1%)	396 (28.3%)	
≥3.0	13,047 (36.4%)	12,622 (36.6%)	425 (30.3%)	
1.0–1.9	9663 (26.9%)	9276 (26.9%)	387 (27.6%)	
2.0–2.9	5484 (15.3%)	5291 (15.4%)	193 (13.8%)	
Body mass index (kg/m^2)				<0.001
Median (Q1, Q3)	28.0 (24.3, 32.6)	28.0 (24.3, 32.5)	29.0 (25.0, 33.9)	
BMI category				<0.001
Overweight	12,389 (33.0%)	11,909 (33.0%)	480 (32.2%)	
Obese	14,266 (38.0%)	13,620 (37.8%)	646 (43.3%)	
Underweight	616 (1.6%)	596 (1.7%)	20 (1.3%)	
Normal	10,278 (27.4%)	9931 (27.5%)	347 (23.2%)	
PHQ-9 total score				<0.001
Median (Q1, Q3)	1.0 (0.0, 3.0)	0.0 (0.0, 3.0)	2.0 (0.0, 7.0)	
Somatic depression factor score				<0.001
Median (Q1, Q3)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	1.0 (0.0, 4.0)	
Cognitive depression factor score				<0.001
Median (Q1, Q3)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 3.0)	
Depression severity				<0.001
Mild	4776 (12.0%)	4534 (11.9%)	242 (15.3%)	
None/Minimal	31,887 (80.4%)	30,816 (80.9%)	1071 (67.6%)	
Moderate	1769 (4.5%)	1642 (4.3%)	127 (8.0%)	
Moderately severe/Severe	1236 (3.1%)	1092 (2.9%)	144 (9.1%)	
Clinically significant depression (PHQ-9 ≥10)				<0.001
No	36,663 (92.4%)	35,350 (92.8%)	1313 (82.9%)	
Yes	3005 (7.6%)	2734 (7.2%)	271 (17.1%)	

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Table 1. Continued.

Variable	Overall N = 39,668[1]	No varicose veins N = 38,084[1]	With varicose veins N = 1584[1]	*p*-value[2]
Systemic Immune-Inflammation Index (SII)				<0.001
Median (Q1, Q3)	3230.3 (2035.2, 5177.1)	3239.1 (2043.6, 5191.2)	2998.7 (1804.6, 4834.6)	
Neutrophil-to-lymphocyte ratio (NLR)				0.848
Median (Q1, Q3)	1.9 (1.5, 2.6)	1.9 (1.5, 2.6)	2.0 (1.4, 2.7)	
SII tertiles				0.003
Low	10,007 (27.7%)	9548 (27.5%)	459 (31.4%)	
High	13,691 (37.9%)	13,183 (38.0%)	508 (34.7%)	
Medium	12,423 (34.4%)	11,926 (34.4%)	497 (33.9%)	
NLR tertiles				0.067
Low	7350 (20.3%)	7030 (20.3%)	320 (21.9%)	
High	15,541 (43.0%)	14,893 (43.0%)	648 (44.3%)	
Medium	13,231 (36.6%)	12,735 (36.7%)	496 (33.9%)	
White blood cell count ($\times 10^3/\mu$L)				0.802
Median (Q1, Q3)	6.9 (5.7, 8.4)	6.9 (5.7, 8.4)	7.0 (5.6, 8.5)	
Lymphocyte percentage (%)				0.506
Median (Q1, Q3)	30.0 (24.7, 35.8)	30.0 (24.7, 35.8)	29.8 (24.1, 36.2)	
Neutrophil percentage (%)				0.486
Median (Q1, Q3)	58.4 (51.9, 64.4)	58.4 (51.9, 64.4)	58.7 (51.3, 64.4)	
Platelet count ($\times 10^3/\mu$L)				<0.001
Median (Q1, Q3)	240.0 (203.0, 284.0)	241.0 (204.0, 284.0)	227.0 (183.0, 275.0)	
Survey cycle				<0.001
2005–2006	4968 (12.5%)	4805 (12.6%)	163 (10.3%)	
2007–2008	5926 (14.9%)	5700 (15.0%)	226 (14.3%)	
2009–2010	6201 (15.6%)	6012 (15.8%)	189 (11.9%)	
2011–2012	5553 (14.0%)	5334 (14.0%)	219 (13.8%)	
2013–2014	5759 (14.5%)	5525 (14.5%)	234 (14.8%)	
2015–2016	5707 (14.4%)	5448 (14.3%)	259 (16.4%)	
2017–2018	5554 (14.0%)	5260 (13.8%)	294 (18.6%)	

[1] Continuous variables are presented as weighted medians (interquartile ranges), and categorical variables as unweighted frequencies with weighted percentages to account for the complex NHANES survey design. Owing to missing data for certain variables, the sums of subgroup observations for categorical variables may not equal the overall sample size. For PHQ-9 total score, median and interquartile range (Q1, Q3) are presented, reflecting the actual distribution of scores within the study sample. The theoretical score range for PHQ-9 is 0–27, but extreme values (e.g., 0 and 27) are not displayed because they were absent in most participants.

[2] *p*-values were calculated using survey-weighted Kruskal–Wallis tests for continuous variables and Rao–Scott adjusted chi-squared tests for categorical variables.

BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.

were integrated into a composite risk index, the prevalence of varicose veins demonstrated an overall increasing trend across risk quintiles, with a marked elevation in the highest quintile, despite a modest decrease between the first two quintiles (3.6%, 2.7%, 3.4%, 3.8%, and 6.4% for Q1–Q5, respectively; p for trend <0.001).

The correlation pattern heatmap (Fig. 4C) indicated modestly stronger correlations between inflammatory markers (SII and NLR) and depression measures—particularly PHQ-9 somatic scores—among individuals with varicose veins. In contrast, correlations between inflammatory markers and depressive symptoms were weaker in those without varicose veins.

Finally, effect size analyses (Fig. 4D) revealed small-to-moderate and statistically significant differences for depression-related outcomes (PHQ-9 total, cognitive, and somatic scores; Cohen's d approximately 0.35–0.45, $p < 0.05$), whereas effect sizes for inflammatory indices (SII and NLR) were small and not statistically significant.

Taken together, these findings indicate that varicose veins are consistently associated with greater burden of de-

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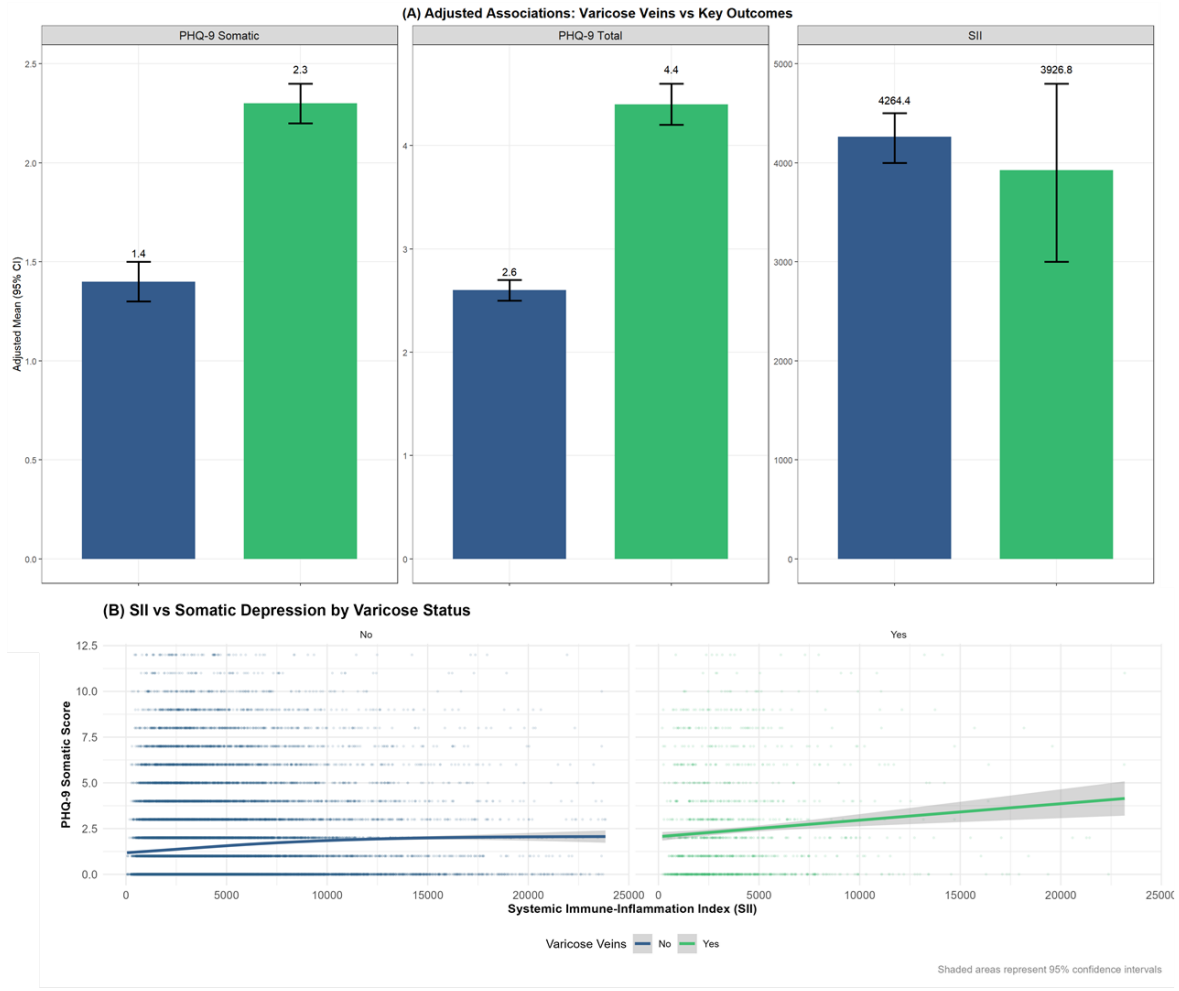

Fig. 3. Varicose veins, systemic inflammation, and somatic depression: adjusted associations and continuous relationships. (A) Panel A presents multivariable-adjusted associations between varicose vein status and key outcomes, including the PHQ-9 somatic subscore, PHQ-9 total score, and the SII. Values are shown as adjusted means with 95% confidence intervals derived from multivariable linear regression models. (B) Panel B depicts the continuous relationships between SII and PHQ-9 somatic depression score, stratified by varicose vein status. PHQ-9, Patient Health Questionnaire-9.

pressive symptoms, particularly those of the somatic subtype. Moreover systemic inflammation may function as a biological amplifier of this relationship. This results supports the hypothesis that chronic vascular inflammation may contribute to the development of somatic depressive phenotypes through inflammation–mood regulatory pathways, providing further insights into the psychophysiological comorbidity mechanisms of varicose veins.

Heterogeneity Analysis of the Association Between Varicose Veins and Somatic Depressive Symptoms

To examine potential demographic heterogeneity in the association between varicose veins and somatic depressive symptoms, stratified regression analyses were conducted across major subgroups defined by age, sex, and obesity status (Fig. 5).

Fig. 5 summarizes subgroup-specific associations between varicose veins and somatic depressive symptoms derived from multivariable-adjusted regression models. Stratified analyses were conducted according to predefined categories of age (<60 vs. ≥60 years), sex, and obesity status to evaluate the robustness and potential heterogeneity of the association.

As shown in Fig. 5A, the association between varicose veins and higher PHQ-9 somatic depression scores remained statistically significant across all examined subgroups ($p < 0.001$ for all), indicating consistency across major demographic and clinical strata. The overall pooled

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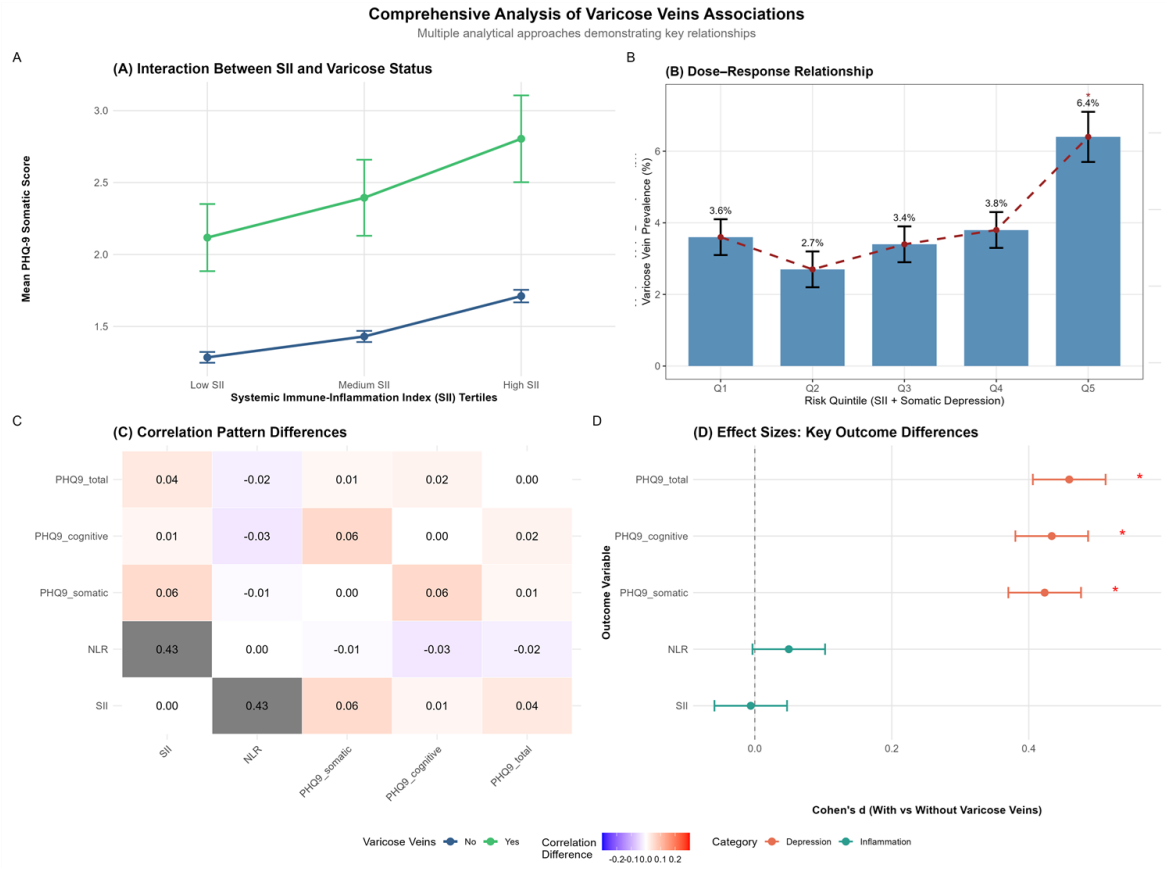

Fig. 4. Comprehensive analysis of varicose vein–inflammation–depression associations. (A) Panel A illustrates the interaction between Systemic Immune-Inflammation Index (SII) and varicose vein status in relation to somatic depressive symptoms. (B) Panel B demonstrates a dose–response relationship between the composite inflammation–depression risk quintiles (SII + somatic PHQ-9) and varicose vein prevalence. (C) Panel C compares the correlation pattern differences among key inflammatory and depressive variables by varicose vein status. (D) Panel D presents effect size estimates (Cohen's d) for key outcome differences. PHQ-9, Patient Health Questionnaire-9.

estimate demonstrated a positive association between varicose veins and somatic depressive symptoms (β = 0.84, 95% CI: 0.63–1.05).

Subgroup-specific effect estimates (Fig. 5B) suggested modest variation in the magnitude of the association. Relatively stronger associations were observed among women, non-obese individuals, and participants younger than 60 years, whereas the associations appeared somewhat attenuated among men, obese participants, and older adults. However, formal interaction tests were not statistically significant, indicating no evidence of effect modification by age, sex, or obesity status.

In addition, adjusted mean comparisons derived from the regression models (Fig. 5C) showed that participants with varicose veins had a significantly higher adjusted mean PHQ-9 somatic depression score (2.33, 95% CI: 2.22–2.44) compared with those without varicose veins (1.42, 95% CI: 1.40–1.44), corresponding to an adjusted mean difference of 0.91 points ($p < 0.001$). These findings indicate a consistently greater burden of somatic depressive symptoms among individuals with varicose veins after accounting for multiple confounding factors.

Nomogram Model for Predicting Somatic Depression Risk Based on Varicose Veins and Systemic Inflammation

To further evaluate the combined predictive effects of varicose veins and systemic inflammation on the risk of somatic depressive symptoms, an individualised nomogram model was developed based on the results of a multivariable logistic regression analysis (Fig. 6).

The model incorporated five statistically significant predictors, including varicose vein status, Logarithm-

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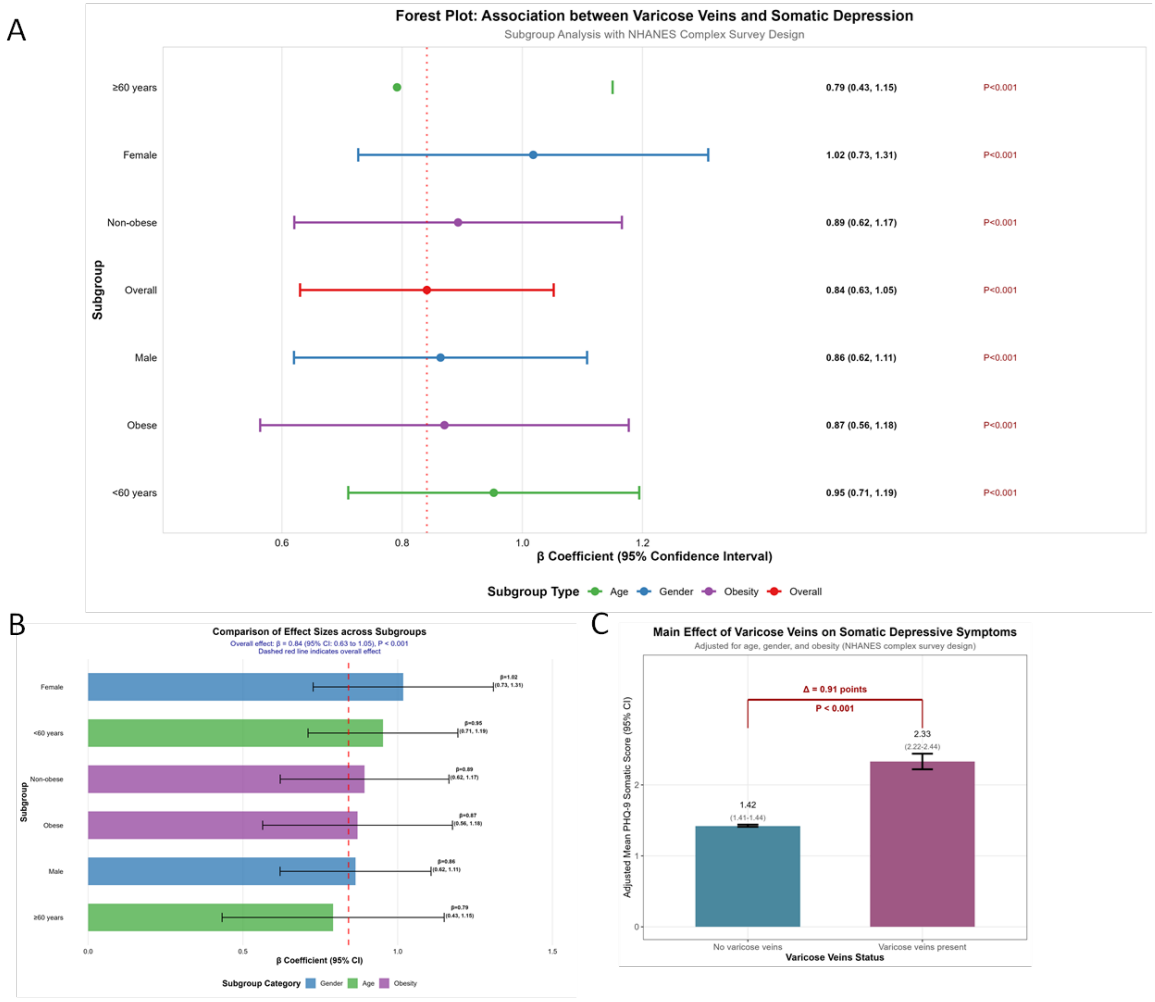

Fig. 5. Heterogeneity analysis of the association between varicose veins and somatic depressive symptoms. (A) Panel A presents subgroup analyses stratified by age, gender, and obesity status, showing standardized β coefficients with 95% confidence intervals. The red dashed line indicates the pooled overall estimate. Across all subgroups, the presence of varicose veins was consistently associated with higher PHQ-9 somatic depression scores (all $p < 0.001$), demonstrating robust associations irrespective of demographic characteristics. (B) Panel B displays the comparative effect sizes across subgroups. Stronger associations were observed in females ($\beta = 1.02$, 95% CI: 0.73–1.31), non-obese participants ($\beta = 0.89$, 95% CI: 0.62–1.17), and younger adults (<60 years; $\beta = 0.95$, 95% CI: 0.71–1.19), while relatively weaker effects were found among males, obese individuals, and older adults (≥60 years). (C) Panel C illustrates the adjusted mean difference in PHQ-9 somatic depression scores between participants with and without varicose veins. The adjusted mean score was 2.33 (95% CI: 2.22–2.44) in those with varicose veins, compared with 1.42 (95% CI: 1.40–1.44) in those without, representing a mean difference of 0.91 points ($p < 0.001$). Error bars represent 95% confidence intervals. PHQ-9, Patient Health Questionnaire-9.

transformed Systemic Immune-Inflammation Index (log-SII), age group, sex, and obesity status. Each variable was assigned a specific number of points according to its regression coefficient, and the sum of these scores generated a total score (Total Points), which corresponded to the predicted probability of somatic depressive symptoms.

The nomogram indicated that individuals with varicose veins, higher systemic inflammation levels, female sex, obesity, and middle to older age had a substantially greater predicted risk of somatic depressive symptoms. Among the predictors, varicose vein status and log-SII contributed the largest proportion of points, suggesting that these factors play particularly important roles in risk estimation.

As the total score increased, the predicted probability of somatic depression rose in an approximately linear fashion, indicating favourable discriminative ability and good clinical interpretability of the model.

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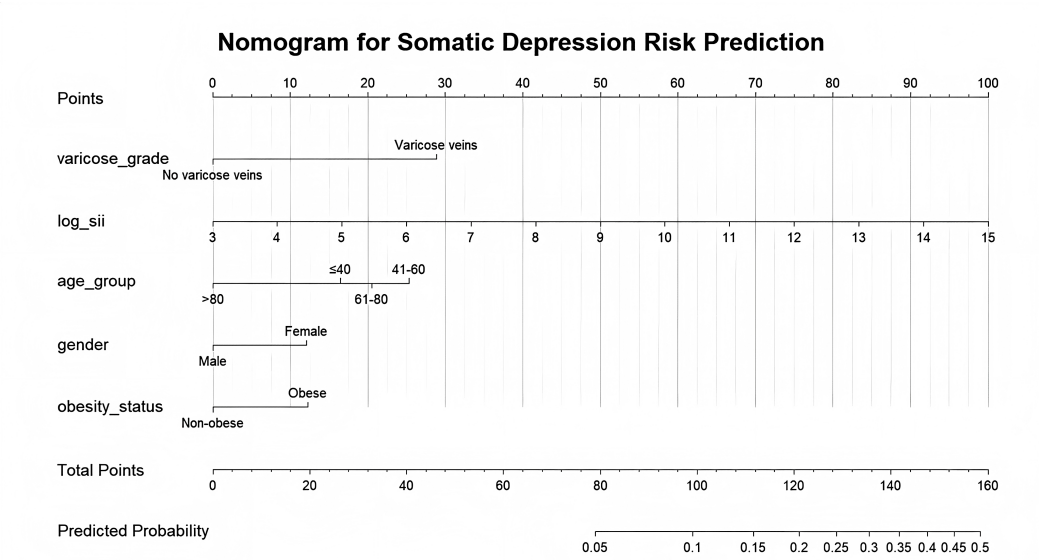

Fig. 6. Nomogram model for predicting somatic depression risk based on varicose veins and systemic inflammation. This figure presents an individualized risk prediction nomogram constructed using multivariable logistic regression analysis to estimate the probability of developing somatic depressive symptoms. The model incorporates five key predictors significantly associated with somatic depression risk: varicose vein status, systemic immune-inflammation index (log-SII), age group, gender, and obesity status. Each variable is assigned a corresponding score according to its regression coefficient, and the sum of these scores yields a total points value, which maps onto the lower scale to estimate the predicted probability of somatic depression for each individual.

This predictive framework integrates vascular, inflammatory, and demographic factors into a unified risk estimation framework, offering clinicians a simple yet effective tool for early identification and stratification of depression risk among individuals with varicose veins.

Overall, the findings emphasize a synergistic predictive contribution of varicose veins and systemic inflammation to somatic depressive symptoms, supporting the notion that incorporating inflammatory biomarkers alongside venous health indicators may improve early detection and targeted intervention for depression risk.

Performance Evaluation and Robustness Validation of the Clinical Prediction Model

To comprehensively assess the reliability and clinical applicability of the prediction model for somatic depressive symptoms, its discrimination, calibration, clinical utility, and robustness were evaluated multiple analytical approaches (Fig. 7 and **Supplementary Fig. 1**).

As shown in Fig. 7A, receiver operating characteristic (ROC) analysis demonstrated that the full prediction model, incorporating varicose vein status, SII, and demographic covariates, achieved an area under the curve (AUC) of 0.645. This performance was notably superior to the demographics-only model (AUC = 0.533) and the varicose-veins-only model, indicating that the inclusion of vascular and inflammatory factors improved predictive performance. These results suggest that the model has moderate discriminative ability to distinguish individuals at higher risk of somatic depressive symptoms from those at lower risk.

Calibration analysis (Fig. 7B) showed excellent agreement between predicted and observed probabilities, with a calibration slope of 1.000 and a Hosmer–Lemeshow test *p*-value of 0.645. The calibration curve closely followed the ideal 45° reference line, indicating good model fit without evidence of overfitting or systematic bias. This reflects the model's high interpretability and external generalizability.

The decision curve analysis (DCA, Fig. 7C) further demonstrated the model's clinical utility. Across a broad range of decision thresholds (0.05–0.40), the full model consistently provided a positive net benefit compared with both "treat-all" and "treat-none" strategies. This suggests that in clinical practice, the model could meaningfully improve decision-making by identifying individuals with varicose veins who are at increased risk of somatic depressive symptoms, thereby enabling more targeted screening and intervention.

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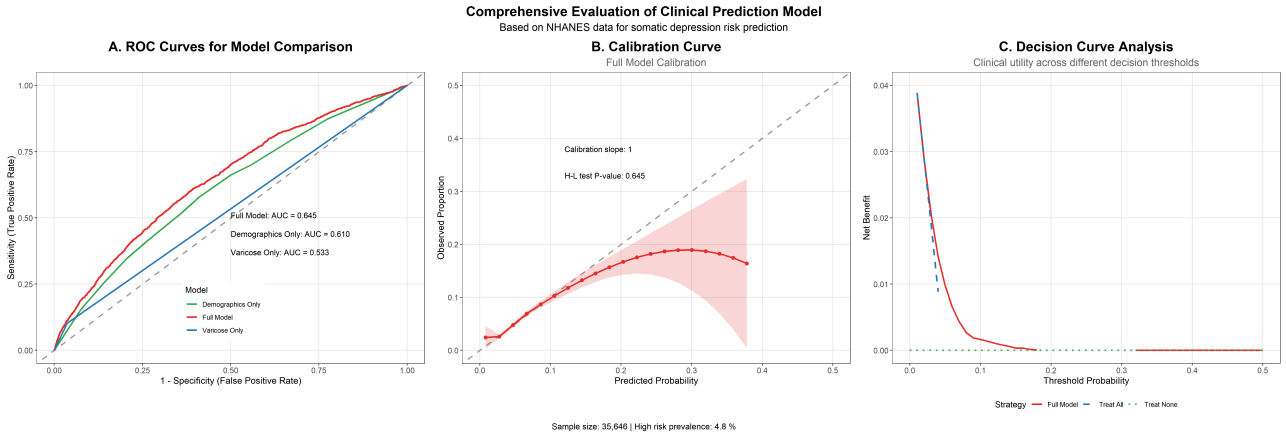

Fig. 7. Comprehensive evaluation of the clinical prediction model based on NHANES data for somatic depression risk prediction. (A) The ROC curves compare the discriminative performance of different models. (B) The calibration curve demonstrates good model fit, with a calibration slope of 1.000 and a Hosmer–Lemeshow test *p*-value of 0.645, suggesting strong agreement between predicted and observed probabilities without evidence of overfitting. (C) The decision curve analysis (DCA) evaluates the model's clinical utility across various threshold probabilities.

To assess the robustness and stability of the findings, several sensitivity analyses were conducted (**Supplementary Fig. 1**). In the main analysis, using a PHQ-9 somatic subscore threshold of ≥3, the presence of varicose veins was significantly associated with higher odds of somatic depressive symptoms (OR = 1.94, 95% CI: 1.73–2.17). This association remained consistent across all alternative scenarios. When individuals with extreme BMI values (<18.5 or >40) were excluded, the estimated odds ratio increased slightly (OR = 2.02, 95% CI: 1.79–2.28).

Similarly, applying a more stringent depression threshold (PHQ-9 ≥4) yielded a comparable association (OR = 2.12, 95% CI: 1.88–2.40), and after additional adjustment for education level, the relationship remained stable (OR = 1.92, 95% CI: 1.72–2.16). Across all analyses, both the direction and magnitude of the effect remained highly consistent, indicating that the observed association between varicose veins and somatic depressive symptoms was not driven by model specification or single covariate adjustments.

Taken together, the prediction model demonstrated moderate discrimination, good calibration, and potential clinical benefit, with results remaining stable across multiple sensitivity scenarios. These results suggest that the model may serve as a reliable and interpretable tool for the early identification and risk stratification of somatic depressive symptoms among individuals with varicose veins. Its stable performance across alternative analytical scenarios further supported the robustness of the vascular–inflammation–depression link, supporting its potential clinical utility for population screening and preventive management in vascular and mental health care.

Discussion

This large, nationally representative analysis of U.S. adults from the 2005–2018 NHANES cycles provides evidence of a significant association between varicose veins and somatic depressive symptoms, mediated in part by systemic inflammation. The study found that individuals with varicose veins exhibited significantly higher PHQ-9 somatic subscale scores, elevated SII, and increased levels of inflammatory biomarkers than those without venous disease. The prediction model integrating vascular, inflammatory, and demographic factors demonstrated acceptable discrimination (AUC = 0.645), good calibration, and meaningful clinical utility, with consistent findings across sensitivity analyses.

The observed association between varicose veins and somatic depressive symptoms is biologically plausible within the framework of chronic low-grade inflammation. CVD is characterized by endothelial dysfunction, leukocyte activation, and microvascular inflammatory processes, which are associated with persistent elevations in systemic inflammatory mediators, including CRP and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) [25,26]. Although IL-6 and TNF-α were not directly measured in the present study, the SII—which integrates neutrophil, lymphocyte, and platelet counts—serves as a composite marker

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reflecting the balance between innate immune activation and adaptive immune regulation and may capture a broader inflammatory milieu relevant to neuroimmune interactions.

Accumulating evidence suggests that peripheral inflammatory signals, reflected by markers such as CRP and composite indices of immune activation, may influence central nervous system function through neuroimmune pathways, including altered neurotransmitter metabolism, neuroendocrine regulation, and neural plasticity [27–29]. These processes have been linked to so-called "sickness behaviour" and somatic manifestations of depression, such as fatigue, sleep disturbance, and psychomotor slowing. In this context, the present findings that varicose veins were more strongly associated with somatic depressive symptoms than with cognitive or affective symptom domains are consistent with the hypothesis that chronic peripheral inflammatory states may preferentially affect somatic dimensions of depression rather than core mood symptoms.

Previous studies of chronic venous insufficiency have largely focused on physical discomfort and health-related quality-of-life impairment, with comparatively limited attention to mental health outcomes [30–32]. A small number of observational studies have examined pain profiles among patients with venous ulcers or chronic leg pain, primarily within clinical cohorts. However, these investigations have mainly focused on pain characteristics and often lacked evaluation of psychological symptoms or accompanying biological markers [33,34]. The present study extend this literature by situating venous disease within the broader inflammation–depression framework, which posits that sustained inflammatory activation may contribute to depressive symptomatology through cytokine-related alterations in monoaminergic signalling, neuroendocrine function, and brain plasticity [35–37]. Importantly, given the cross-sectional design of the present study, these findings should be interpreted as evidence of statistical association rather than as support for a specific causal or mechanistic pathway.

These findings carry significant clinical relevance, emphasizing several key aspects. Varicose veins may represent a vascular indicator of increased depression risk, particularly for depressive subtypes characterized by somatic or fatigue-related symptoms. Incorporating inflammatory indicators such as SII or CRP into venous health evaluations may further improve the identification of individuals with heightened psychological vulnerability, allowing for timely mental health interventions in vascular settings. Moreover, the nomogram-based prediction model developed in this study provides a practical and transparent framework for personalized assessment of depression risk among patients with venous disorders. From a broader public health standpoint, the coexistence of venous disease and depressive symptoms highlights the importance of integrated management strategies that combine vascular care with mental health support, including lifestyle modification, inflammation control, and psychosocial intervention.

This study benefits from a large, nationally representative NHANES sample, standardized assessments of depressive symptoms and inflammatory biomarkers, and a rigorous analytic framework incorporating multivariable modelling and predictive analyses, all of which enhance the robustness and generalizability of the findings. Several limitations should be acknowledged. First, elevated somatic depressive symptoms were defined using a PHQ-9 somatic subscale threshold of $\geq$3, selected based on prior psychometric evidence indicating sensitivity to clinically relevant symptom burden in population-based settings. However, this cutoff is inherently arbitrary, and alternative thresholds may yield different estimates, introducing potential symptom misclassification. Second, the nomogram-based prediction model demonstrated moderate discrimination (AUC = 0.645). While potentially useful for population-level risk stratification, it is not suitable as a standalone tool for individual-level clinical decision-making. Predictive performance may be improved by incorporating more specific inflammatory biomarkers, indicators of venous disease severity, psychosocial variables, and external validation in independent cohorts. Third, the cross-sectional design precludes causal inference, leaving temporal ordering, reverse causation, and shared or unmeasured confounding unresolved. Fourth, although decision curve analysis suggested modest net benefit over "treat-all" or "treat-none" strategies across certain thresholds, the magnitude and stability of this benefit were limited, indicating that the model currently has restricted clinical utility. Its primary value lies in the exploratory integration of venous disease status and inflammatory burden to characterize somatic depression risk rather than immediate clinical application. Fifth, lower extremity varicose vein diagnosis was not systematically collected across all NHANES cycles, resulting in design-related missingness rather than outcome-dependent nonresponse. While selection bias cannot be fully excluded, the findings are most applicable to adults with complete venous disease data, and validation in cohorts with systematic venous assessment is warranted. Finally, despite adjustment for multiple demographic, socioeconomic, lifestyle, and clinical covariates, residual confounding remains possible. Physical activity, sedentary behaviour, and use of anti-inflammatory or psychotropic medications may influence inflammation, venous function, and depressive symptoms but could not be comprehensively accounted for due

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to data limitations. Longitudinal studies with more detailed behavioral and medication data are needed to further clarify these relationships.

Conclusions

In summary, this study provides population-level evidence that varicose veins are significantly associated with somatic depressive symptoms, and this association is accompanied by higher levels of systemic inflammation. These findings support the concept of a vascular–inflammation–depression axis, whereby chronic peripheral inflammation associated with venous disease may contribute to somatic depressive manifestations. The predictive model developed in this study offers a practical framework for early identification, risk stratification, and preventive management of depression among individuals with varicose veins. Future longitudinal and interventional studies are warranted to elucidate causal pathways and to test whether targeting vascular inflammation could alleviate depressive symptoms and improve overall well-being in this population.

Availability of Data and Materials

The datasets used and/or analysed during the current study were available from the corresponding author on reasonable request.

Author Contributions

TW contributed to the study design, conceptualization, and critical revision of the manuscript. MM was responsible for literature research, data analysis, and drafting the manuscript. AA conducted data collection and performed statistical analysis. Additionally, all authors participated in the clinical and experimental research and reviewed and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

All NHANES protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and written informed consent was obtained from all participants. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. The present study used only de-identified public-use data and was therefore exempt from additional institutional review.

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This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.2158.

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