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ORIGINAL RESEARCH ARTICLE

Inflammatory-Metabolic Burden and Depressive Symptom Phenotypes in US Adults: A Survey-Weighted Latent Class Analysis of NHANES 2021–2023

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ABSTRACT

Background. Depression is clinically heterogeneous, and total Patient Health Questionnaire-9 (PHQ-9) scores can conceal symptom configurations with different inflammatory and metabolic correlates. Evidence linking immune-inflammatory activity and insulin resistance to depression has mostly addressed total symptom burden or binary thresholds.

Objective. To identify latent PHQ-9 symptom phenotypes in US adults and to evaluate whether the systemic immune-inflammation index (SII), the triglyceride-glucose index (TyG), and their interaction were associated with phenotype membership.

Methods. This cross-sectional secondary analysis used the National Health and Nutrition Examination Survey (NHANES) August 2021–August 2023 fasting subsample (adults aged at least 20 years with complete PHQ-9, blood count, fasting glucose, and triglyceride data). Survey-weighted ordinal latent class models (two to five classes) were compared. Multinomial regression (modal class membership; jackknife repeated-replication variance) adjusted for age, sex, race and ethnicity, education, body mass index, current smoking, and diabetes.

Results. Among 2,427 adults, a three-class solution was chosen: Minimal (53.4%), Somatic-dominant (32.5%), and Mixed-severe (14.1%); entropy was 0.810 and average posterior probability 0.915. In the adjusted sample (n = 2,409), odds ratios for Mixed-severe versus Minimal membership per one-standard-deviation increase were 1.16 (95% confidence interval [CI] 0.94–1.42) for SII, 1.10 (95% CI 0.89–1.36) for TyG, and 1.08 (95% CI 0.93–1.24) for SII×TyG. The global interaction test was not significant (p = 0.470). Continuous-score analyses agreed.

Conclusion. PHQ-9 responses identified three well-separated symptom phenotypes. SII, TyG, and their interaction did not independently distinguish phenotype membership. Phenotyping may refine epidemiological description. Single-occasion biomarkers of this kind should not currently assign depressive subtypes.

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1. Introduction

Depression is not one uniform condition. Two people can reach the same total symptom score through very different combinations of affective, cognitive, somatic, and behavioral complaints, and those combinations may carry different functional, biological, and prognostic meanings. The Patient Health Questionnaire-9 (PHQ-9) is a validated and widely used measure of how often depressive symptoms occur. Its total score, however, treats every item as an interchangeable indicator of one severity dimension.[1] That suits screening. It can also hide whether a high score is driven mainly by sleep and energy complaints, by anhedonia and low mood, or by a broad co-occurrence of symptoms that includes thoughts of death or self-harm. A person-centered analysis can add to the total score by asking whether reproducible response patterns define subgroups within the population.

Latent class analysis (LCA) offers a probabilistic way to find such subgroups without fixing symptom domains in advance. Recent population studies of the PHQ-9 and related measures show, again and again, that

heterogeneity in depression involves both severity and qualitative differences in profile, and this holds across very different samples. Analyses of Japanese adults, community-dwelling older adults, young adults in Chile, and a large national sample in Peru all recovered distinguishable profiles instead of a single severity continuum.[2–5] These results support item-level modeling in varied populations. A caution follows. Class labels summarize conditional response probabilities. They are not diagnoses.

Inflammation and metabolic dysfunction are plausible contributors to some forms of depressive symptomatology. One hierarchical model fitted across five US population samples tied C-reactive protein to general depressive liability and to specific appetite and fatigue features.[6] Contemporary clinical and population studies have likewise related immunometabolic characteristics to the direction of appetite change, insomnia, fatigue, anhedonia, and wider energy-related symptom dimensions.[7–10] Family-based and prospective cohort studies add that inflammatory or metabolic risk can cluster with affective symptoms within families and across developmental periods, although these designs do not show a single pathway that fits every depressive presentation.[11,12] The picture is mixed. The observed associations are neither uniform nor causal by default. Symptom-cluster and network studies show that total-score pathways and symptom-specific pathways can coexist, and that findings may depend on the biomarker, the direction of the symptom, age, and clinical context.[6–12] Cross-sectional work is also open to reverse directionality. Sleep disruption, inactivity, smoking, diet, medication, and distress can alter inflammatory and metabolic physiology, while chronic disease and adiposity can influence both biomarker levels and symptom reporting. A single measurement may capture transient infection, fasting variation, medication effects, or chronic comorbidity as well as any process related to depression. The question is therefore not whether biomarker levels correlate with a PHQ-9 threshold. It is whether they distinguish multivariate symptom patterns once major demographic, behavioral, and metabolic covariates are taken into account.

The systemic immune-inflammation index (SII) combines platelet, neutrophil, and lymphocyte counts into an easily calculated marker of peripheral inflammatory-immune balance. Recent studies using the National Health and Nutrition Examination Survey (NHANES) report positive, nonlinear, or subgroup-dependent associations between SII, or related cellular indices, and depressive-symptom thresholds.[13–18] Associations have also been examined in adolescents, hemodialysis patients, stroke survivors, adults with sleep difficulties, and myocardial-infarction survivors.[19–24] Their size and shape differed by population, outcome definition, and adjustment set. So SII should be evaluated against symptom phenotypes. An association with total severity cannot simply be assumed to carry over to every presentation. The triglyceride-glucose index (TyG) is a practical surrogate for insulin resistance and is calculated from fasting triglyceride and glucose concentrations. Recent cross-sectional studies linked TyG, or TyG–body mass index composites, with depressive symptoms in hypertensive and general US adult populations.[25,26] A large prospective cohort tied higher TyG to later depression and anxiety.[27] A contemporary US analysis also found an association between a combined C-reactive protein–TyG index and depressive symptoms.[28] Clinical stratification, pooled trial, and machine-learning studies suggest that combinations of inflammatory, metabolic, and energy-related features may carry more information than any single domain. Their predictive performance and clinical meaning still depend on context.[29–31] Diet-related inflammation and insulin resistance may share pathways relevant to mood,[32] and longitudinal latent-profile research shows that patterns of depressive symptoms can follow distinct trajectories.[33] These observations motivate an interaction analysis. They do not establish synergy between inflammation and insulin resistance, nor which symptom pattern such synergy would affect most.

Most population evidence treats depression as a total PHQ-9 score or a binary threshold. Most phenotype-oriented studies have focused on C-reactive protein, diagnosed depression, or selected clinical cohorts. The post-pandemic NHANES August 2021–August 2023 cycle allows survey-weighted, item-level PHQ-9 phenotyping to be combined with two inexpensive indices that capture complementary inflammatory and metabolic information in a fasting subsample. The present study adds a joint person-centered and biomarker-oriented evaluation. It separates phenotype discovery from adjusted testing of SII, TyG, and their interaction, and it distinguishes descriptive co-occurrence from evidence of independent association. The primary aim was to identify the number, prevalence, and symptom profiles of latent PHQ-9 classes (hereafter, phenotypes) among US adults. Secondary aims were to estimate adjusted associations of SII and TyG with class membership, to test whether TyG modified the association between SII and phenotype membership, and to examine whether continuous total and domain scores led to the same conclusions.

2. Methods

2.1. Study design and setting

This study was a secondary cross-sectional analysis of the public-use NHANES August 2021–August 2023 cycle. NHANES uses a stratified, multistage probability design to represent the civilian, noninstitutionalized US population. The 2021–2023 cycle was the first full public release after the coronavirus disease 2019 interruption and used an updated sample design and modified field procedures.[34] Questionnaire, examination, and laboratory files were linked by the unique respondent sequence number (SEQN). The analysis used de-identified public data and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cross-sectional studies.[35]

The analytic question was specified in two stages. First, survey-weighted ordinal LCA was used to identify person-centered profiles across all nine PHQ-9 items. Second, assigned class membership was used as the outcome in survey-adjusted multinomial models evaluating SII, TyG, and their product interaction. The class-discovery stage was intended to characterize symptom heterogeneity; the regression stage was intended to assess association rather than prediction, diagnosis, mediation, or causality.

2.2. Participants

All 11,933 participants in the cycle were considered. Eligibility for this analysis required age at least 20 years, non-pregnant status at examination, valid responses of 0–3 for all nine PHQ-9 items, complete platelet, absolute neutrophil, and absolute lymphocyte measurements, positive fasting glucose and triglyceride values, a fasting duration of at least 8 hours but less than 24 hours, and a positive fasting-subsample weight. These criteria ensured that the symptom indicators and both derived exposures could be calculated in the same analytic population and that inference corresponded to the fasting subsample.

Sequential restriction yielded 7,809 adults aged at least 20 years; 7,768 were not pregnant; 5,175 had complete PHQ-9 data; 2,605 had the required complete blood-count, fasting-glucose, and triglyceride measurements; and 2,427 met the fasting-duration and positive-weight criteria. The adjusted model used complete cases for all prespecified covariates, leaving 2,409 participants. Because the analysis used a fixed public cycle rather than prospectively recruited participants, no prospective sample-size calculation determined enrolment. Precision was represented by 95% confidence intervals, and model complexity was constrained in view of the available fasting subsample and survey design degrees of freedom.

2.3. Variables and instruments

Depressive symptom indicators. NHANES administered the nine-item PHQ depression screener to eligible adults. Each item asked how often, during the previous two weeks, the respondent had been bothered by: little interest or pleasure; feeling down, depressed, or hopeless; sleep disturbance; tiredness or low energy; poor appetite or overeating; negative self-evaluation; concentration difficulty; psychomotor slowing or agitation; and thoughts of being better off dead or self-harm. Response categories were 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The public DPQ_L documentation and codebook defined the item wording, eligibility, and coding.[34] All nine ordinal items were used individually as LCA indicators; no threshold was applied during class estimation.

For sensitivity analyses, three continuous outcomes were derived: the PHQ-9 total score (range 0–27); a somatic-domain score comprising sleep, energy, appetite, and psychomotor items (items 3, 4, 5, and 8); and a cognitive-affective-domain score comprising anhedonia, depressed mood, negative self-evaluation, concentration, and thoughts of death or self-harm (items 1, 2, 6, 7, and 9). These domains were used to test whether conclusions depended on modal class assignment. They were not treated as diagnostic scales or as replacements for the item-level latent model.

Systemic immune-inflammation index. SII was calculated as SII = (platelet count × absolute neutrophil count) / absolute lymphocyte count. Platelet count was obtained from LBXPLTSI, absolute neutrophils from LBDNENO, and absolute lymphocytes from LBDLYMNO in the complete blood count with 5-part differential component. Values had to be positive and complete. Because SII was right-skewed, it was transformed on the base-2 logarithmic scale. The transformed value was then standardized using the analytic survey weights so that regression estimates represented a one-standard-deviation difference. A one-unit increase in $\log_2$ SII corresponds to a doubling of the unstandardized index before standardization, but the reported odds ratios refer to the standardized scale.

Triglyceride-glucose index. TyG was calculated as TyG = ln[(fasting triglycerides [mg/dL] × fasting glucose [mg/dL]) / 2]. Fasting triglycerides were taken from LBXTLG in the reference-method triglyceride file and fasting plasma glucose from LBXGLU. The formula and units follow recent primary studies of TyG and depression.[25–27] TyG was standardized using the analytic survey weights and entered per one standard deviation. The interaction term was the product of the standardized $\log_2$ SII value and the standardized TyG value, which allowed the main effects to be interpreted at the weighted mean of the other exposure and reduced nonessential collinearity.

Covariates. The adjustment set was chosen a priori to address major sources of demographic, behavioral, and metabolic confounding while preserving parsimony. Covariates were age, sex, race and ethnicity, education, body mass index (BMI), current smoking, and diabetes. Age and BMI were modelled as continuous variables. Race and ethnicity were grouped into three categories, and education into two categories, to avoid sparse cells given the fasting-subsample size and limited survey degrees of freedom. Current smoking reflected self-reported current cigarette use. Diabetes was based on self-report and survey variables. Age, sex, race and ethnicity, and education were taken from DEMO_L, BMI from BMX_L, current smoking from SMQ_L, and diabetes from DIQ_L. These variables can influence inflammatory cell counts, glucose and triglycerides, and depressive symptom expression, and were therefore retained regardless of bivariate significance.

2.4. Data collection and analytic preparation

NHANES interviews and examinations were conducted by trained National Center for Health Statistics (NCHS) personnel using standardized procedures. The PHQ-9 was administered by computer-assisted interview; laboratory measurements were obtained from mobile examination center specimens and processed under documented quality-control procedures.[34] The present secondary analysis did not alter field collection, contact

participants, or link public records to restricted identifiers.

Data files were merged by SEQN. The analytic preparation verified unique respondent identifiers, valid PHQ-9 ranges, positive biomarker components, fasting duration, weight eligibility, and complete exposure derivations. Pregnancy status was used only as an exclusion criterion. Participants missing any latent indicator or biomarker component were not entered into LCA because the source analysis defined a common complete-indicator population. Adjusted regression used complete covariates. The difference between the class-analysis and adjusted samples was documented explicitly rather than silently changing denominators.

2.5. Statistical analysis

The fasting-subsample two-year weight (WTSAF2YR) was used because the TyG calculation depended on fasting glucose and the reference triglyceride measurement. The masked variance units SDMVSTRA and SDMVPSU were retained. Estimates were therefore interpreted for adults represented by the eligible fasting subsample, not as unweighted characteristics of the observed participants. Survey design information was carried through descriptive analyses and association models.

Survey-weighted ordinal LCA models with two, three, four, and five classes were fitted to the nine four-category PHQ-9 items. Sixty random initializations were used for each candidate number of classes to reduce the possibility that the selected solution represented a local rather than global optimum. Model selection considered the Bayesian information criterion (BIC), entropy, average posterior probability (AvePP), minimum class proportion, interpretability, and stability. Lower BIC indicated better relative fit, whereas entropy and AvePP described separation and assignment certainty. A minimum class proportion of 5% was required to avoid selecting solutions dominated by very small, potentially unstable classes. The selected labels were assigned after inspecting weighted item-response probabilities and were descriptive rather than diagnostic.

Class prevalence was estimated with posterior-probability weighting. For the association stage, each participant was assigned to the class with the highest posterior probability. Survey-weighted multinomial logistic regression compared the Somatic-dominant and Mixed-severe classes with the Minimal class. The model included standardized $\log_2$ SII, standardized TyG, their product interaction, and the prespecified covariates. Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and two-sided p values were reported. The global interaction hypothesis was evaluated with a two-degree-of-freedom Wald test across both non-reference class contrasts.

Variance was estimated with jackknife repeated replication (JKn) replicate weights constructed from the masked stratum and primary sampling unit structure. This approach was used to propagate the complex design into the multinomial estimates. Sensitivity models treated the PHQ-9 total, somatic-domain, and cognitive-affective-domain scores as continuous outcomes within the complex survey design. Each model included SII, TyG, their interaction, and the same covariates, and reported the change in score per one-standard-deviation exposure difference. The analysis was exploratory: p values were interpreted together with effect magnitude, interval width, coherence across outcomes, and the global interaction test. No result was selected or described solely because it crossed a conventional significance threshold.

The analysis was conducted locally in R, and analytic outputs, figures, checksums, and session information were retained. Independent checks covered SEQN uniqueness, SII and TyG calculations, class prevalence totals, modal counts, the model-selection rule, classification quality, exponentiation of multinomial coefficients, confidence-interval arithmetic, the global interaction p value, and figure generation.

2.6. Ethical approval

The parent NHANES protocol obtained informed consent under NCHS institutional procedures, and the public-use files are de-identified. This secondary analysis involved no new recruitment, intervention, or participant contact. Ethical approval for the present analysis and manuscript was granted by the CMHC Research Center Ethics Committee Indonesia (No. 2026/018). The analysis was conducted in accordance with the ethical principles applicable to secondary use of de-identified human research data.

3. Results

3.1. Participant flow and analytic sample

Table 1 shows the participant flow and class-specific characteristics. Of 11,933 participants in the cycle, 7,809 were aged at least 20 years and 7,768 were non-pregnant. Complete responses to all nine PHQ-9 items were available for 5,175 adults. Requiring the complete blood-count components for SII and the fasting glucose and triglyceride measurements for TyG reduced the sample to 2,605. Application of the 8 to less than 24 hour fasting criterion and positive fasting-subsample weight yielded 2,427 participants for LCA. Eighteen additional participants lacked one or more model covariates, producing an adjusted regression sample of 2,409.

Across the modal classes, unweighted counts were 1,368 in the Minimal class, 732 in the Somatic-dominant class, and 327 in the Mixed-severe class. Weighted mean age was 52.4 years in the Minimal class, 45.5 years in the Somatic-dominant class, and 44.4 years in the Mixed-severe class. The weighted proportion of women was 45.8%, 54.4%, and 55.9%, respectively. Mean BMI increased from 29.0 kg/m^2 in the Minimal class to 30.1 kg/m^2 in the Somatic-dominant class and 31.8 kg/m^2 in the Mixed-severe class. Geometric mean SII was 478.1, 488.0, and 527.4 across the three classes, while mean TyG was 8.58, 8.53, and 8.65. These unadjusted values describe class composition and do not establish independent relationships.

Table 1. Participant flow and descriptive characteristics by modal latent class.

Panel / characteristic	Overall / stage	Minimal	Somatic-dominant	Mixed-severe
Panel A. Participant flow				
NHANES participants	11,933	—	—	—
Adults aged ≥20 years	7,809	—	—	—
Non-pregnant	7,768	—	—	—
Complete PHQ-9	5,175	—	—	—
Complete CBC, glucose, triglycerides	2,605	—	—	—
Fasting 8 to <24 h; positive WTSAF2YR	2,427	—	—	—
Complete adjusted-model covariates	2,409	—	—	—
Panel B. Class characteristics				
Unweighted n	2,427	1,368	732	327
Posterior-weighted prevalence, %	100.0	53.4	32.5	14.1
Age, weighted mean, years	—	52.4	45.5	44.4
Women, weighted %	—	45.8	54.4	55.9
BMI, weighted mean, kg/m^2	—	29.0	30.1	31.8
SII, weighted geometric mean	—	478.1	488.0	527.4
TyG, weighted mean	—	8.58	8.53	8.65
PHQ-9 total, weighted mean	—	1.0	4.9	12.4

Values are unweighted counts unless otherwise indicated. BMI, body mass index; CBC, complete blood count; PHQ-9, Patient Health Questionnaire-9; SII, systemic immune-inflammation index; TyG, triglyceride-glucose index; WTSAF2YR, fasting-subsample two-year weight.

3.2. Latent class selection and symptom profiles

Table 2 lists the fit and classification statistics. BIC decreased from 30,095.7 for two classes to 29,498.9 for three, 29,288.7 for four, and 29,254.5 for five. The four- and five-class solutions offered lower BIC values but produced minimum class proportions of 4.2% and 3.5%, below the prespecified 5% threshold. Entropy also declined from 0.881 in the two-class solution to 0.810, 0.806, and 0.788 as additional classes were added. The three-class model retained a minimum class proportion of 14.1%, entropy of 0.810, and AvePP of 0.915. It was selected as the most defensible balance of fit, separation, class size, stability, and interpretability.

Table 2. Comparison of candidate survey-weighted ordinal latent class models.

Classes	BIC	Entropy	AvePP	Minimum class, %	Decision
2	30,095.7	0.881	0.970	31.6	Not selected
3	29,498.9	0.810	0.915	14.1	Selected
4	29,288.7	0.806	0.880	4.2	Class <5%
5	29,254.5	0.788	0.865	3.5	Class <5%

Lower BIC indicates better relative fit. Selection considered BIC together with entropy, average posterior probability (AvePP), class size, stability, and interpretability. A prespecified minimum class proportion of 5% was required.

The class-specific symptom probabilities are shown in Figure 1. The Minimal phenotype had low probability (0–6%) of anhedonia, depressed mood, negative self-evaluation, concentration difficulty, psychomotor change, and thoughts of death or self-harm. Its residual symptoms were predominantly sleep disturbance (25%) and fatigue (29%), with appetite change at 12%.

The Somatic-dominant phenotype showed a more selective intermediate pattern led by fatigue and sleep disturbance. The probabilities of reporting each item at least several days were 50% for anhedonia, 54% for depressed mood, 63% for sleep disturbance, 81% for fatigue, 45% for appetite change, 50% for negative self-evaluation, 35% for concentration difficulty, 16% for psychomotor change, and 2% for thoughts of death or self-harm. Fatigue and sleep disturbance were therefore the defining high-frequency manifestations, accompanied by moderate affective symptoms but very low endorsement of the ninth PHQ-9 item.

The Mixed-severe phenotype displayed high probability across almost the entire symptom set: 92% for anhedonia, 94% for depressed mood, 91% for sleep disturbance, 98% for fatigue, 79% for appetite change, 83% for negative self-evaluation, 78% for concentration difficulty, 41% for psychomotor change, and 23% for thoughts of death or self-harm. The pattern was not merely somatic; it combined affective, cognitive, behavioral, and somatic symptoms. Mean total PHQ-9 scores were 1.0, 4.9, and 12.4 in the Minimal, Somatic-dominant, and Mixed-severe classes, respectively.

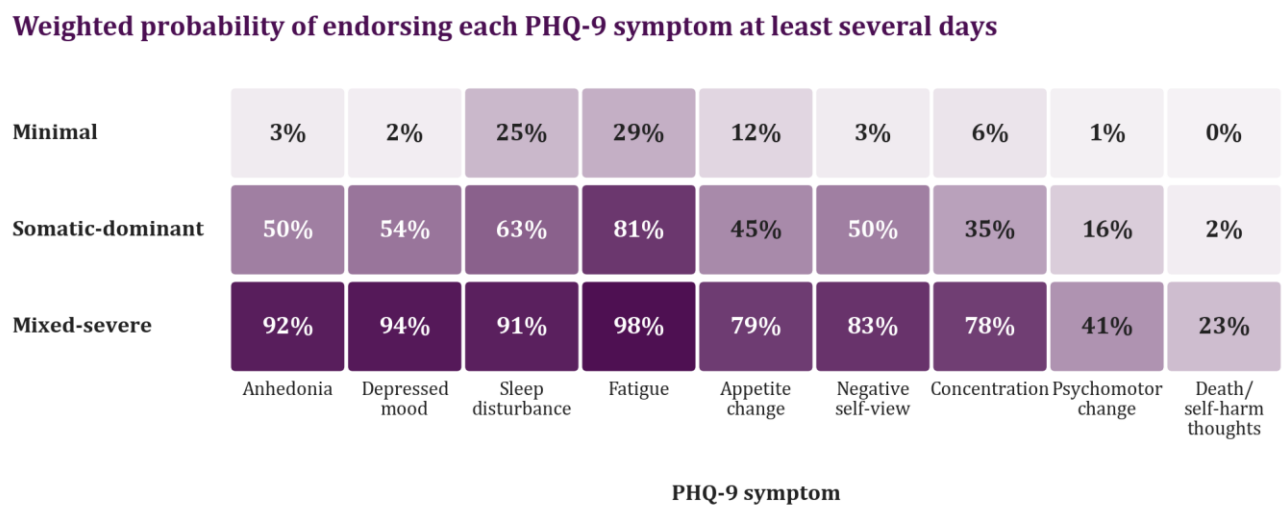


Figure 1. Posterior-weighted probability of endorsing each PHQ-9 symptom at least several days, by selected latent phenotype. Probabilities are class-specific descriptive estimates; labels are not clinical diagnoses.

Posterior-weighted class prevalence appears in Figure 2: 53.4% for the Minimal phenotype, 32.5% for the Somatic-dominant phenotype, and 14.1% for the Mixed-severe phenotype.

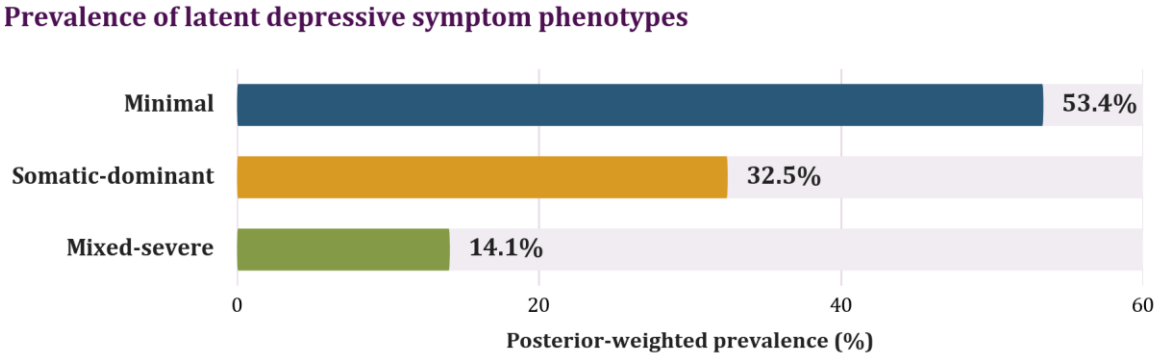


Figure 2. Posterior-weighted prevalence of the selected latent depressive symptom phenotypes in the NHANES August 2021–August 2023 fasting analytic sample (n = 2,427).

3.3. Adjusted associations of SII, TyG, and their interaction

Adjusted multinomial estimates are given in Table 3, and Figure 3 shows their confidence-interval patterns. For Somatic-dominant versus Minimal membership, the OR per one-standard-deviation increase in $\log_2$ SII was 1.03 (95% CI 0.89–1.18; p = 0.729), the OR for TyG was 0.98 (95% CI 0.86–1.11; p = 0.739), and the OR for the SII×TyG interaction was 0.96 (95% CI 0.86–1.08; p = 0.536). These estimates were close to the null value and the intervals included both modest inverse and positive associations.

For Mixed-severe versus Minimal membership, the point estimates were above one but remained imprecise: SII OR 1.16 (95% CI 0.94–1.42; p = 0.162), TyG OR 1.10 (95% CI 0.89–1.36; p = 0.390), and interaction OR 1.08 (95% CI 0.93–1.24; p = 0.325). The global Wald test for the SII×TyG interaction was χ^2 = 1.51 with 2 degrees of freedom (p = 0.470). Thus, the adjusted data did not support effect modification of the SII-phenotype association by TyG.

Table 3. Adjusted associations of SII, TyG, and their interaction with latent phenotype membership and continuous PHQ-9 outcomes.

Outcome / contrast	SII per 1 SD	TyG per 1 SD	SII×TyG
Panel A. Multinomial OR (95% CI); p			
Somatic-dominant vs Minimal	1.03 (0.89–1.18); 0.729	0.98 (0.86–1.11); 0.739	0.96 (0.86–1.08); 0.536
Mixed-severe vs Minimal	1.16 (0.94–1.42); 0.162	1.10 (0.89–1.36); 0.390	1.08 (0.93–1.24); 0.325
Panel B. Continuous β (95% CI); p			
PHQ-9 total	0.14 (−0.07 to 0.36); 0.200	0.12 (−0.13 to 0.36); 0.354	0.11 (−0.03 to 0.25); 0.132
Somatic domain	0.08 (−0.01 to 0.17); 0.066	0.10 (−0.04 to 0.24); 0.158	0.03 (−0.04 to 0.10); 0.391
Cognitive-affective domain	0.06 (−0.09 to 0.20); 0.445	0.01 (−0.11 to 0.14); 0.826	0.08 (−0.02 to 0.18); 0.124

Multinomial models used the Minimal phenotype as reference and adjusted for age, sex, race and ethnicity, education, BMI, current smoking, diabetes, both standardized exposures, and their product interaction. Global interaction test: χ^2 = 1.51, 2 df, p = 0.470. Variance used JKn replicate estimation. β is the adjusted score difference.

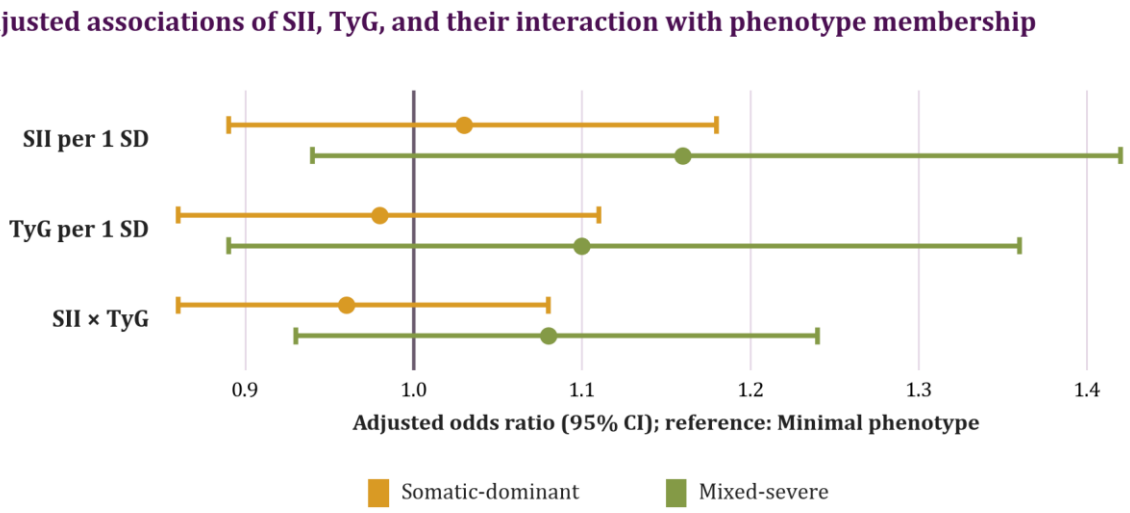


Figure 3. Adjusted odds ratios and 95% confidence intervals for Somatic-dominant and Mixed-severe phenotype membership versus the Minimal phenotype. Estimates are per one standard deviation of standardized $\log_2$ SII, TyG, or their product interaction.

3.4. Descriptive joint-burden pattern

When SII and TyG were each divided at their analytic-sample median for descriptive presentation, the Mixed-severe phenotype comprised 17.6% of the high-SII/high-TyG group and 12.0% of the low-SII/low-TyG group, an absolute difference of 5.6 percentage points. The other two joint categories showed intermediate compositions. Because these categories were unadjusted, median-based, and created for description, this pattern was not treated as evidence of biological interaction. The discrepancy between the descriptive proportions and the adjusted interaction test indicates that age, BMI, diabetes, demographic composition, sampling variability, or other covariate structure could account for at least part of the crude pattern.

3.5. Continuous-outcome sensitivity analyses

Continuous-outcome sensitivity estimates appear in Panel B of Table 3 and yielded conclusions consistent with the multinomial models. For total PHQ-9 score, coefficients per one-standard-deviation difference were 0.14 (95% CI −0.07 to 0.36; p = 0.200) for SII, 0.12 (95% CI −0.13 to 0.36; p = 0.354) for TyG, and 0.11 (95% CI −0.03 to 0.25; p = 0.132) for the interaction. For the somatic-domain score, the corresponding estimates were 0.08 (95% CI −0.01 to 0.17; p = 0.066), 0.10 (95% CI −0.04 to 0.24; p = 0.158), and 0.03 (95% CI −0.04 to 0.10; p = 0.391). For the cognitive-affective domain, estimates were 0.06 (95% CI −0.09 to 0.20; p = 0.445), 0.01 (95% CI −0.11 to 0.14; p = 0.826), and 0.08 (95% CI −0.02 to 0.18; p = 0.124). Every interval included zero. The somatic SII estimate was closest to conventional significance, but its small magnitude and interval remained compatible with little or no association.

4. Discussion

4.1. Principal findings

This survey-weighted analysis found three interpretable PHQ-9 symptom phenotypes in the NHANES 2021–2023 fasting subsample. The largest was a Minimal group. A sizable Somatic-dominant group was characterized mainly by fatigue and sleep disturbance, and a smaller Mixed-severe group showed broad affective, somatic, cognitive, and behavioral involvement. The three-class model had good average posterior assignment. It avoided the very small classes produced by the four- and five-class solutions. The person-centered result confirms that adults with similar or overlapping total scores need not share the same item configuration. It also shows that somatic symptoms can cluster at an intermediate level without the full Mixed-severe pattern.

The biomarker results were more restrained. After adjustment, SII, TyG, and their product interaction did not reliably separate either the Somatic-dominant or the Mixed-severe class from the Minimal phenotype. Point estimates for Mixed-severe membership were positive, particularly for SII, yet the confidence intervals included the null and covered values compatible with little association as well as a modest increase. The global interaction test and every continuous-score sensitivity analysis agreed. The descriptive enrichment of Mixed-severe membership in the high-SII/high-TyG group should therefore be treated as hypothesis-generating. It is not evidence of inflammatory-metabolic synergy.

A clear symptom structure alongside uncertain biomarker differentiation is useful. It suggests that PHQ-9 heterogeneity can be identified more reliably than it can be explained by two single-occasion peripheral indices in this fasting subsample. Null or imprecise adjusted associations do not invalidate the phenotypes. Class separation and biomarker association are separate questions. A recognizable class structure can arise from many biological, psychological, social, and measurement processes, and SII and TyG capture only some of them.

4.2. Comparison with the existing literature

The three-class structure broadly agrees with recent person-centered studies, which recover a low-symptom group, one or more intermediate patterns, and a high-severity group. The content of the intermediate classes

varies. Instrument and population both matter. Studies of Japanese adults, community-dwelling older adults, Chilean young adults, and Peruvian national survey respondents identified profiles that differed in severity and in quality.[2–5] Longitudinal latent-profile work has also shown that depressive symptom patterns can follow distinct trajectories.[33] The Somatic-dominant class found here fits the broader principle that intermediate symptom burden is not always a scaled-down copy of severe depression. Its fatigue and sleep probabilities were much higher than those for psychomotor change or thoughts of death or self-harm. A total score would flatten that profile.

The findings also complement recent item-level inflammatory research. A hierarchical model linked C-reactive protein at once to latent depression and to specific appetite and fatigue features.[6] Symptom-cluster work related a neurovegetative profile to higher C-reactive protein,[8] and a network analysis in older adults examined depressive symptoms together with inflammatory and metabolic markers over time.[10] The present study used a different person-centered method and a cellular index, so it did not test the same parameters. Still, all of these approaches treat symptom organization as a substantive outcome. None assumes a homogeneous total score. The adjusted SII results here imply that class-based heterogeneity was not clearly differentiated by SII in this sample, even though other inflammatory markers have been related to selected symptoms or to network structure.

Recent clinical and population studies of inflammatory depression have often emphasized somatic or energy-related symptoms. Individual-symptom analyses found associations of appetite direction and insomnia with BMI, waist circumference, insulin, glucose, triglycerides, and related metabolic features.[7] Metabolomic and inflammatory profiling separated immunometabolic symptom dimensions from melancholic and anxious dimensions.[9] Family-based, developmental, and treatment-outcome studies have likewise linked immunometabolic profiles to selected affective or energy-related features rather than to every depressive manifestation.[11,12,29,30] Machine-learning work suggests that immunometabolic markers can add to multivariable classification in selected clinical samples.[31] These patterns shaped our expectation. SII or TyG might preferentially identify the Somatic-dominant or Mixed-severe class.

The present results do not strongly support that expectation. Several differences may explain the divergence. First, SII is built from routine blood-cell counts and is not interchangeable with C-reactive protein, interleukin-6, or multi-analyte inflammatory profiles. Second, the PHQ-9 appetite and sleep items are bidirectional: decreased and increased appetite share one item, and so do insomnia and hypersomnia. Immunometabolic theories often predict stronger links with increased appetite, weight gain, and hypersomnia, but the public PHQ-9 responses do not separate those directions. Third, the analysis covered adults across the full symptom spectrum, not a clinically diagnosed major-depression sample enriched for immune dysregulation. Fourth, adjustment for BMI and diabetes may remove confounding but can also reduce associations that run through metabolic phenotype, depending on the causal structure. Fifth, biomarkers and symptoms were measured on one occasion. That adds random biological and temporal mismatch.

The SII literature in depression has produced generally positive but heterogeneous results. Large NHANES analyses reported modest, nonlinear, cardiovascular-stratified, or hypertension-specific associations between cellular inflammatory indices and binary depressive-symptom thresholds.[13–18] Studies in adolescents, hemodialysis patients, stroke survivors, adults with sleep difficulties, and myocardial-infarction survivors also reported positive associations in some settings.[19–24] These populations differ in inflammatory burden, comorbidity, medication, and outcome definition. The phenotype outcome used here is more demanding than a single PHQ-9 threshold. A modest average association with symptom severity can coexist with limited power to distinguish several latent classes, especially once classification uncertainty and the fasting-subsample design are considered.

The TyG results add some nuance to earlier work. Recent cross-sectional studies found associations of TyG or TyG–body mass index with depressive symptoms in hypertensive and general US adult populations,[25,26] and a large prospective cohort reported an association with incident depression and anxiety.[27] In the present study the TyG point estimate for Mixed-severe versus Minimal membership was above one but imprecise, while the Somatic-dominant estimate was near one. This does not refute a link between insulin resistance and depression incidence or total burden. TyG simply did not clearly partition PHQ-9 class membership after simultaneous adjustment and interaction modeling in this cycle.

The lack of a supported SII×TyG interaction deserves comment. Pragmatic stratification and pooled trial studies suggest that combined inflammatory, metabolic, and energy-related features can identify groups with broader immunometabolic dysregulation.[29,30] A composite C-reactive protein–TyG index was positively associated with depressive symptoms in a multi-cycle US analysis,[28] and machine-learning work has evaluated broader immunometabolic panels for clinical classification.[31] Those studies used different biomarkers, outcome definitions, and functional forms. The comparison is loose. Multiplying standardized SII and TyG tests one specific departure from additivity on the multinomial log-odds scale. It is not a universal test of biological convergence. The null interaction therefore narrows the conclusion to the model that was actually estimated.

4.3. Interpretation and plausible mechanisms

Inflammatory and metabolic processes could influence depressive symptoms through overlapping but distinct pathways. None of these pathways was measured in the present study. Peripheral immune activation may affect cytokine signalling, microglial activity, monoamine

synthesis, glutamate metabolism, reward processing, hypothalamic-pituitary-adrenal function, sleep, and fatigue. Insulin resistance may alter cerebral glucose utilization, vascular function, adipokine signalling, energy availability, and the inflammatory environment. Platelets, neutrophils, and lymphocytes also respond to infection, stress hormones, smoking, medication, and chronic disease. Triglycerides and glucose are sensitive to fasting adherence, recent behavior, metabolic disease, and treatment.

These mechanisms might be expected to align most closely with sleep, energy, appetite, and psychomotor symptoms. Yet the Somatic-dominant phenotype was not associated with SII or TyG in the adjusted model. One interpretation is that the somatic pattern is etiologically heterogeneous. Fatigue and sleep disturbance are common across mood, anxiety, pain, respiratory, endocrine, occupational, and social conditions. A latent class groups people with similar response patterns, but it does not mean that every member shares one mechanism. A symptom-defined class that contains several causal pathways can dilute biomarker associations.

A second interpretation is that the strongest immunometabolic signal may lie in directional symptom details that the PHQ-9 does not capture. Increased appetite and hypersomnia may carry different metabolic implications from appetite loss and insomnia, yet the combined items treat these opposite manifestations as equivalent response categories. Recent individual-symptom, metabolomic, familial, and clinical-stratification studies suggest that separating the directions could improve biological specificity.[7,9,11,29–31] Future surveys could keep PHQ-9 comparability and add directional follow-up questions.

A third interpretation concerns timing. The symptoms refer to the previous two weeks, whereas SII and TyG are laboratory values from a single examination. Chronic immunometabolic states may matter. One measurement also includes short-term biological variation. Repeated measurement of biomarkers and symptoms would let investigators separate stable between-person differences from within-person fluctuation. It would also allow them to test temporal ordering, and to determine whether changes in biomarkers precede, accompany, or follow changes in symptom configuration.

Residual confounding remains plausible. Physical activity, sleep duration and timing, diet, alcohol, medication, acute infection, chronic inflammatory disease, menstrual or hormonal status, and antidepressant use could influence both exposures and symptoms. Including every available covariate would be inappropriate for this sample size and could cause overfitting or adjustment for mediators. The parsimonious model addressed major confounders. It cannot rule out alternative explanations. Adjustment for BMI and diabetes may also partly control pathways through which insulin resistance relates to mood. Causal diagrams and longitudinal data are needed to define whether such variables act as confounders, mediators, or consequences for a specific research question.

Finally, statistical precision limits interpretation. The fasting-subsample requirement reduced the available adult sample from 7,809 to 2,427, and the smallest selected class contained 14.1% of the weighted sample and 327 observed participants. That exceeded the prespecified minimum, and classification quality was good. Even so, interaction tests generally need more information than main-effect tests, and the confidence intervals around the Mixed-severe estimates allow small-to-moderate associations. The appropriate conclusion is not proof of absence. It is a lack of sufficiently precise evidence for independent or interactive differentiation in this sample.

4.4. Implications for research and clinical interpretation

The immediate value of the phenotype result is descriptive. It is also hypothesis-generating. Population surveillance and etiological research may gain information by retaining item patterns, rather than reducing every respondent to a total score or binary cut-off. A Somatic-dominant pattern covering almost one third of the weighted analytic population suggests that sleep and energy complaints account for a large share of low-to-moderate symptom burden. Researchers studying work ability, sleep disorders, chronic disease, pain, or post-infectious symptoms may find the distinction useful when they specify outcomes or confounders.

The class labels are not clinical diagnoses. The PHQ-9 is a screener, the classes were derived in a general adult population, and modal membership is probabilistic. A clinician must still assess duration, functional impairment, differential diagnosis, bipolarity, substance use, medical causes, and context. The 23% item-9 endorsement probability in the Mixed-severe class describes the class at population level and cannot determine the risk of any individual. Any positive report of thoughts of death or self-harm needs a direct, timely safety assessment under local clinical protocols, whatever the class assignment, biomarker level, or total score.

The biomarker findings argue against using SII or TyG to assign depressive subtypes in routine practice. Both indices are inexpensive and may be useful for cardiometabolic or inflammatory assessment in appropriate settings, but the adjusted associations here were not precise or consistent enough to support psychiatric classification. Screening programs should not imply that a high SII or TyG explains a person's depressive presentation, and a low value should not reduce attention to severe or safety-relevant symptoms.

Future studies should state in advance whether their target is general depressive liability, a specific directional symptom, a latent phenotype, incident disorder, treatment response, or prognosis. These are different estimands. Pooling compatible NHANES cycles could improve precision. Care is needed, however: the post-pandemic cycle introduced design changes, and the

triglyceride method requires careful harmonization with earlier releases.[34] External replication should use cycle-appropriate weights, assess measurement invariance or class comparability, and document whether the same three profiles recur.

Longitudinal cohorts with repeated PHQ items, fasting biomarkers, C-reactive protein, cytokines, adipokines, medication, sleep, physical activity, and diet could test temporal and mechanistic hypotheses. Methods that build classification uncertainty directly into distal-outcome or covariate models would strengthen inference. Within-sample bootstrapping or split-sample validation could evaluate class stability. External validation could assess transportability across age, race and ethnicity, sex, and clinical comorbidity. Directional appetite and sleep measures are especially needed to test immunometabolic-depression models.

Intervention studies offer a further test. If a reproducible phenotype with inflammatory or metabolic enrichment can be identified prospectively, it may help stratify trials of lifestyle, metabolic, or anti-inflammatory interventions. That use requires evidence that the phenotype predicts differential treatment benefit beyond readily measured severity and comorbidity. The current study does not establish such utility. What it does is define a transparent phenotype structure and set an empirical boundary around what SII and TyG explained in one nationally representative cycle.

4.5. Strengths and limitations

The study has several strengths. It used a contemporary national probability survey and applied the fasting-subsample weight, masked strata, and primary sampling units. It analyzed all nine ordinal PHQ-9 items and did not impose a priori somatic and cognitive subscales during class discovery. Candidate models with two to five classes were compared using multiple random starts, and selection took class size, classification quality, and interpretability into account rather than BIC alone. The exposure definitions are reproducible, and the adjusted analysis considered SII and TyG jointly with a prespecified interaction and covariate set. Continuous total and domain-score analyses offered an alternative outcome formulation. Exact effect estimates and uncertainty were retained, null results included. Scientific importance was not equated with statistical significance.

Several limitations define the scope of inference. First, cross-sectional measurement cannot establish temporal direction or causality. Depressive symptoms may influence sleep, diet, activity, smoking, healthcare, and metabolic regulation, and those factors may in turn influence SII and TyG. Second, the fasting laboratory and complete-indicator requirements selected a subset of adult participants. Survey weights address the design and specified nonresponse but cannot guarantee removal of selection related to unmeasured variables. Complete-case adjustment excluded only 18 participants. Missingness at earlier selection stages was larger. It may limit generalizability.

Third, SII and TyG were measured once. SII can vary with acute infection, hematological conditions, medication, stress, and transient immune changes. TyG can vary with fasting adherence, glucose regulation, lipid treatment, and recent metabolic state. Neither index directly measures central neuroinflammation or brain insulin signalling. Fourth, PHQ-9 items combine opposite symptom directions for sleep, appetite, and psychomotor change, which limits the ability to isolate atypical energy-related manifestations. The instrument was designed for screening and severity assessment, not biological subtyping.

Fifth, class membership was assigned by the highest posterior probability for the multinomial model. Entropy and AvePP indicated good separation. Even so, modal assignment does not fully propagate classification uncertainty. It can attenuate associations. Posterior-weighted prevalence partly addresses this for class proportions, but a one-step model or an uncertainty-adjusted three-step approach would be preferable for replication. Sixth, the selected three-class model did not minimize BIC. The four- and five-class models had lower BIC but contained classes below 5%. Selection prioritized stability and practical interpretability, so finer rare profiles may exist and would need a larger sample.

Seventh, the parsimonious covariate set could not address every behavioral, pharmacological, medical, and social factor. Race and ethnicity and education were grouped to preserve design degrees of freedom, which may conceal heterogeneity within categories. Linear main effects may also miss thresholds or nonlinear relationships reported elsewhere. Eighth, the study was exploratory. It evaluated several class contrasts and sensitivity outcomes. Results were interpreted by magnitude, intervals, and coherence rather than by multiplicity-adjusted declarations, and isolated p values should not be overemphasized.

Finally, the numerical results could be checked for internal consistency but have not been independently reproduced from the participant-level data. External reproduction depends on the public NHANES files and on the analysis code being made available with sufficiently detailed derivations and package versions.

5. Conclusion

Survey-weighted PHQ-9 responses from US adults formed three well-separated phenotypes: Minimal, Somatic-dominant, and Mixed-severe. After adjustment, SII, TyG, and their interaction did not independently distinguish them, and the continuous-score sensitivity analyses supported the same reading. Phenotyping adds descriptive resolution beyond the PHQ-9 total score. Single-occasion SII or TyG cannot assign clinical subtypes. Longitudinal replication is warranted: repeated and broader immunometabolic measures, explicit handling of classification uncertainty, and directional appetite and sleep items would test the question properly.

Declarations

Generative AI use. None.

Author contributions. H.P.P.: conceptualization, methodology, software, formal analysis, investigation, data curation, visualization, writing – original draft. S.M., T.P.S.: validation, supervision. R.R.: resources, writing – review and editing. All authors approved the final manuscript.

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Informed consent. The parent NHANES obtained informed consent from participants under NCHS procedures. The present secondary analysis used de-identified public-use data and involved no new participant contact.

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