
Beyond inflammation and cholesterol: atherogenic index of plasma mediates the link between hsCRP/HDL-C ratio and depression in US adults NHANES 2015–2020

Received: 20 July 2025

Accepted: 29 December 2025

Published online: 21 January 2026

Cite this article as: Ma# J., Hu J., Tang F. et al. Beyond inflammation and cholesterol: atherogenic index of plasma mediates the link between hsCRP/HDL-C ratio and depression in US adults NHANES 2015–2020. *Ann Gen Psychiatry* (2026). <https://doi.org/10.1186/s12991-025-00624-3>

Jing-Ying Ma#, Jue Hu, FaDan Tang, YiLin Meng, Fa Ye, Lin-Lin Hu & Yong-Hua Zhang

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

Beyond Inflammation and Cholesterol: Atherogenic Index of Plasma Mediates the Link between hsCRP/HDL-C Ratio and Depression in US Adults NHANES 2015-2020

Jing-Ying Ma¹, Jue Hu², FaDan Tang¹, YiLin Meng¹, Fa Ye¹, Lin-Lin Hu^{1*}, Yong-Hua Zhang^{1*}

1.Jing-Ying Ma¹: Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou 310007, China; majingyingg@163.com

2. Jue Hu²:First Clinical School, Zhejiang Chinese Medical University, Hangzhou 310053, China; 347717480@qq.com

3. FaDan Tang¹: Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou 310007, China; tdfly187818@163.com

4.YiLin Meng¹: Hangzhou Hospital of Traditional Chinese Medicine; Hangzhou, 310004, China; 402548973@qq.com.

5. Fa Ye¹: Hangzhou Hospital of Traditional Chinese Medicine; Hangzhou, 310004, China; yefaa0311@126.com.

6.Lin-Lin Hu^{1*}: Hangzhou Hospital of Traditional Chinese Medicine; Hangzhou, 310004, China; hulinlin1028@126.com.

7.Yong-Hua Zhang^{1*}: Hangzhou Hospital of Traditional Chinese Medicine; Hangzhou 310004, China; 1341983510@qq.com

*Correspondence:

Yong-Hua Zhang: 1341983510@qq.com

Lin-Lin Hu: hulinlin1028@126.com

ABSTRACT

Background: Dyslipidemia and inflammation play key roles in the pathophysiology of depression and are significantly associated with the plasma atherogenic index (AIP). However, a reliable biomarker for diagnosing depression remains elusive. The hsCRP/HDL-C ratio, combining C-reactive protein (hs-CRP) and high-density lipoprotein cholesterol (HDL-C), may serve as a potential composite indicator.

Objective: This study aims to explore the relationship between the hsCRP/HDL-C ratio and depression.

Methods: NHANES data (2015-2020) from 10,357 participants were analyzed. Depression was assessed using the PHQ-9, and dyslipidemia with AIP. Participants were grouped based on their hsCRP/HDL-C ratio. Statistical

methods included Student's t-test, chi-square test, logistic regression, restricted cubic spline (RCS) model, and mediation analysis.

Results: RCS regression analysis showed a nonlinear relationship between the hsCRP/HDL-C ratio and depression. The two-piece logistic regression model was used to calculate the threshold effect, and the likelihood ratio test ($p < 0.05$) indicated that the inflection point for hs-C/H was 11.608. When the hsCRP/HDL-C ratio was below this threshold, a positive correlation with depression was observed (OR: 1.04, 95% CI: 1.01-1.07). When the hsCRP/HDL-C ratio was equal to or greater than the threshold, a negative correlation was found (OR: 0.99, 95% CI: 0.97-1.00). Subgroup analysis showed consistent results, with marital status being the only factor that significantly influenced this relationship. Mediation analysis revealed that AIP partially mediated the relationship between hsCRP/HDL-C ratio and depression, explaining 11.2% of the total effect (95% CI: 2.26%-27.00%).

Conclusions: A higher hsCRP/HDL-C ratio is associated with increased depression risk. Interventions targeting CRP levels and lipid abnormalities may help reduce this risk.

Keywords: plasma atherogenic index, depression, hsCRP/HDL-C ratio, C-reactive protein, high-density lipoprotein cholesterol

1. Introduction

Depression is a common mental health disorder with significant social impacts, primarily characterized by persistent low mood, typically accompanied by symptoms such as anhedonia, fatigue, sleep and appetite disturbances, feelings of worthlessness, cognitive impairments, and suicidal ideation or actions (Marx, Penninx et al. 2023)(Malhi and Mann 2018).

Depression not only severely affects patients' social functioning and quality of life, leading to substantial personal, familial, and societal burdens, but also increases susceptibility to other conditions, such as cardiovascular diseases and metabolic syndrome(Siskind and Kisely 2019)(Wang, Li et al. 2020).

Although treatment methods are diverse, including pharmacotherapy, psychotherapy, and physical therapies, individual differences and treatment duration limitations affect the effectiveness and applicability of pharmacotherapy in specific populations, such as adolescents, pregnant women, and postmenopausal women(Weavers, Heron et al. 2021). Thus, early diagnosis and management in depression are essential, requiring the

creation of dependable, accurate, and readily available biomarkers in clinical environments to track the start and course of the condition.

Recent research has increasingly examined the relationship between metabolic illnesses and mental health issues, especially emphasizing the crucial role of chronic inflammation in these processes (Apweiler, Saliba et al. 2024). A critical challenge in this field involves determining the direction of this association: does depression lead to metabolic disturbances (e.g., through changes in diet and lifestyle), or do metabolic disorders predispose individuals to depression? Evidence supports both pathways, creating a complex bidirectional relationship that merits further investigation. A wealth of studies has revealed the complexity of the pathophysiological mechanisms underlying this relationship (Dregan, Matcham et al. 2019)(Apweiler, Saliba et al. 2024). According to previous studies, persons who suffer from depression often display certain abnormalities in their blood lipid profiles, such as variations in HDL levels, higher levels of LDL and triglycerides, and irregular changes in total cholesterol (TC) levels. The intensity of depression symptoms is strongly correlated with these lipid abnormalities, particularly when suicidal thoughts are present (Enko, Brandmayr et al. 2018)(Bharti, Bhardwaj et al. 2021). In adolescents with depression, individuals with more severe symptoms typically exhibit more pronounced lipid metabolic abnormalities, such as elevated LDL, triglycerides, and total cholesterol levels, as well as reduced HDL levels (Khalfan, Campisi et al. 2023). These findings further confirm the strong link between lipid metabolism dysregulation and depression. Biomarkers reflecting lipid profile changes may therefore serve as valuable indicators for depression. High-sensitivity C-reactive protein (hs-CRP), a common tool for assessing inflammatory risk, is a highly sensitive measure of low-grade immune inflammation and has been shown to be significantly associated with cardiovascular events (Denegri and Boriany 2021). However, during the acute phase response, HDL-C proteins are susceptible to oxidation and may transition from anti-inflammatory to pro-inflammatory particles through protein modifications (Navab, Reddy et al. 2011). Meta-analyses have indicated that CRP levels are generally elevated in individuals with depression (Osimo, Baxter et al. 2019). Consequently, the hsCRP/HDL-C ratio, as a composite marker, is increasingly recognized as a valuable clinical indicator, praised for its simplicity, practicality, and

relevance to cardiovascular diseases (Gao, Wang et al. 2024). Although this marker has been widely used, its relationship with depression remains incompletely understood. An in-depth investigation of the association between the hsCRP/HDL-C ratio and depression may provide important insights for future research and aid in identifying potential biomarkers.

Previous research has demonstrated that dyslipidemia is a key factor in the development and progression of depression (Valkanova and Ebmeier 2013). The Atherogenic Index of Plasma (AIP), initially proposed by Dobiásová, is a novel marker used to assess lipid metabolism disturbances. AIP serves not only as a biomarker for predicting atherosclerosis but also shows significant association with cardiovascular risk (Qu, Fang et al. 2024)(Dobiásová 2006). Recent studies have shown a significant association between AIP levels and the occurrence of depression (Zhang, Zhang et al. 2024)(Kong and Zou 2024)(Nunes, Piccoli de Melo et al. 2015). Since lipids and AIP can serve as potential markers for pharmacological intervention and help evaluate depression risk in individuals with elevated hsCRP/HDL-C ratio, investigating the mediating role of AIP between the hsCRP/HDL-C ratio and depression holds significant academic and clinical importance.

Based on this background, our study aims to examine the association between depression and the hsCRP/HDL-C ratio in American adults, as well as the potential mediating role of AIP in this relationship.

2. Methods

2.1 Research population

This study utilized data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional, nationally representative survey of the non-institutionalized U.S. population conducted by the National Center for Health Statistics (NCHS). The survey employs a complex, multistage probability sampling design and collects data through interviews, physical examinations, and laboratory tests. Further information about NHANES is available on its official website (<https://www.cdc.gov/Nchs/Nhanes/>).

Data from two NHANES cycles (2015-2016 and 2017-2020) were analyzed. The study focused on adults aged 20 years or older with complete data on hs-CRP, high-density lipoprotein cholesterol (HDL-C), cardiovascular disease (CVD) status, and Patient Health Questionnaire-9 (PHQ-9) scores. The

age threshold of 20 years was selected in accordance with the NHANES protocol, which defines its adult study population as participants aged 20 and above. From an initial pool of 25,531 participants, the following exclusion criteria were applied: (1) age under 20 years ($n = 10,580$); (2) pregnancy ($n = 157$); (3) missing CRP or HDL-C data ($n = 1,938$); (4) incomplete PHQ-9 scores ($n = 1,031$); and (5) missing CVD data or insufficient covariate information ($n = 1,468$). After these exclusions, 10,357 participants comprised the final analytical cohort (Fig 1).

2.2 Lab measurements and the determination of the hsCRP/HDL-C Ratio

Serum hs-CRP levels were measured using a high-sensitivity near-infrared particle immunoassay approach on the Beckman Coulter UniCel DxC 600 Synchron and UniCel DxC 660i Synchron Access chemistry analyzers. During the 2017-2018 cycle, a dual-reagent immunoturbidimetric system based on the Roche Cobas 6000 was used to assess serum hs-CRP levels. As the instrumentation differed between the two cycles, hs-CRP readings from the 2015-2016 cycle were standardized by the NHANES laboratory to ensure comparability with subsequent cycles, a process that aligns with rigorous quality assurance protocols. Nevertheless, the use of different analytical platforms should be acknowledged as a potential limitation of the study. Furthermore, the analysis did not include higher hs-CRP readings [https://www.cdc.gov/Nchs/Nhanes/2017-2018/HSCRP_J.htm].

Serum high-density lipoprotein cholesterol (HDL-C) levels were tested using the Cobas 6000 fully automated biochemical analyzer. The exposure indicator ratio (hsCRP/HDL-C ratio) was calculated by dividing HDL-C levels (mmol/L) by hs-CRP levels (mg/L). Participants were categorized into tertiles based on this ratio, with the first tertile serving as the reference group: Low ratio group (T1): <2.35 ; Moderate ratio group (T2): 2.35-2.90; and High ratio group (T3): ≥2.90 .

2.3 Evaluation of Depression

Based on DSM-IV criteria, the nine-item Patient Health Questionnaire (PHQ-9) was used to assess depressive symptoms. The total score ranged from 0 to 27, with each item scored from 0 ("not at all") to 3 ("nearly every day"). PHQ-9 scores of ≥10 were considered indicative of depression, with 88% sensitivity and 88% specificity (Kroenke, Spitzer et al. 2001).

2.4 Determining the AIP

Triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) markers of blood levels are used to compute the AIP. The following formula is used to determine AIP: $\log_{10}[\text{TG (mmol/L)} / \text{HDL-C (mmol/L)}]$ (Dobiásová and Frohlich 2001).

2.5 Assessment of covariates

Several variables were selected as covariates for adjustment based on previous research. Demographic information was collected via questionnaires, including age, gender, race/ethnicity, marital status, educational attainment, and the household income-to-poverty ratio (PIR). **PIR data were based on self-reported income. This metric, defined by the U.S. Census Bureau, is calculated as the ratio of family income to the federal poverty threshold, serving as an indicator of a family's relative socioeconomic status.** Following the classification scheme used in NHANES methodology, participants were categorized into three socioeconomic strata: low income ($\text{PIR} < 1.30$), middle income ($\text{PIR} = 1.30\text{-}3.49$), and high income ($\text{PIR} \geq 3.50$). This categorization accounts for the well-documented association between lower socioeconomic status and increased depression risk, establishing PIR as a key potential confounder (Zhang, Zhang et al. 2024)(Wang, Tian et al. 2025).

Race was categorized as Hispanic, Mexican American, Non-Hispanic White, Non-Hispanic Black, and Other Races. Educational levels were classified as: less than 9th grade; 9th-11th grade (including 12th grade without diploma); high school graduate or GED or equivalent; some college or associate degree; and college graduate or above. Body mass index (BMI) was measured at the Mobile Examination Center. Additionally, information on medical history, physical activity, smoking status, alcohol use, and physician-diagnosed diseases—including hypertension, diabetes, hyperlipidemia, chronic kidney disease (CKD), and CVD—was collected. CVD status was determined by an affirmative response to having ever been diagnosed by a physician or other health professional with coronary heart disease (CHD), heart attack (myocardial infarction, MI), angina, congestive heart failure (CHF), or stroke.

2.6 Statistical Analysis

Demographic data were recorded for all participants; participants were then categorized according to PHQ-9 scores using the predefined cut-offs. The normality of continuous variables was assessed using the

Kolmogorov-Smirnov test. Data are presented as mean±standard deviation for normally distributed variables, median (interquartile range) for non-normally distributed variables, and frequency (percentage) for categorical variables. Group comparisons were performed using one-way ANOVA, the Kruskal-Wallis H test, or the chi-square test, as appropriate. The association between depression and tertiles of the hs-CRP/HDL-C ratio was evaluated using multivariable logistic regression, with the lowest tertile serving as the reference group. A series of four models with progressive adjustments were fitted to address potential confounding, with full details provided in the notes to Table 2. Briefly, Model 1 was unadjusted; Model 2 adjusted for basic demographics; and Model 3 constituted a fully adjusted model for confounding. Critically, Model 4 included all covariates from Model 3 plus the AIP to specifically explore its potential role as a mediator.

The dose-response relationship was examined using a restricted cubic spline (RCS) model. If a nonlinear association was detected, we identified the threshold point (inflection point) at which the relationship changed. Subsequently, two separate logistic regression models were fitted for values below and above this threshold. Subgroup analyses were conducted to assess the stability of the primary association. Furthermore, a formal mediation analysis was performed to quantify the mediating effect of AIP. This involved first establishing the associations between the hs-CRP/HDL-C ratio and AIP, and between AIP and depression, using fully adjusted regression models. The RMediation package in R was then used to decompose the total effect into direct and indirect effects, calculating the proportion mediated. The 95% confidence interval for the mediation effect was estimated using a non-parametric bootstrap approach with 1000 iterations. All analyses were two-tailed, with a P-value < 0.05 considered statistically significant. Data processing and statistical analyses were performed using R software (version 4.4.0).

3. Results

3.1 Baseline characteristics of participants

Table 1 displays the baseline characteristics of the participants in this study. Out of 10,357 individuals, 9,470 (91.44%) had a PHQ-9 score below 10, while 887 (8.56%) had a score of 10 or higher. The median hsCRP/HDL-C ratio was 2.25 in the depressed group compared to 1.44 in the non-depressed group (P

< 0.05). Several baseline characteristics showed significant differences between participants with and without depression ($P < 0.05$), including gender, race, education level, marital status, smoking status, income-to-poverty ratio (PIR), physical activity level, BMI, CVD, hypertension, diabetes, hyperlipidemia, and CKD. However, age and alcohol use did not differ significantly ($P > 0.05$). Comorbidities—including cardiovascular disease, stroke, hypertension, diabetes, hyperlipidemia, and chronic kidney disease—were more prevalent among participants with PHQ-9 scores ≥ 10 compared to those with scores < 10 . Individuals with depression also had higher proportions of being female, non-Hispanic White, divorced or widowed, current smokers, high school education only, and belonging to lower-income groups with less physical activity.

3.2 Association between hsCRP/HDL-C Ratio and Depression

We used multivariable logistic regression models to analyze the association between the hsCRP/HDL-C ratio and depression (Table 2). The results showed that in both the unadjusted model (β coefficient: 0.06, 95% CI: 0.05-0.07) and the covariate-adjusted models, the hsCRP/HDL-C ratio was significantly positively correlated with depression occurrence, whether treated as a continuous or categorical variable. RCS analysis visually demonstrated a nonlinear relationship between the hsCRP/HDL-C ratio and depression (Fig. 2A). We therefore employed a piecewise logistic regression model to further evaluate this association and calculated the threshold effect of the hsCRP/HDL-C ratio (Fig. 5, Table 3). Likelihood ratio tests indicated $P < 0.05$, supporting the superiority of the two-piecewise logistic regression model over the single logistic regression model. The inflection point for the hsCRP/HDL-C ratio was 11.608. Below this threshold, each unit increase in hs-C/H was associated with a 4% increase in depression prevalence (OR: 1.04, 95% CI: 1.01-1.07). However, in the fully adjusted model that included all covariates (Model 3), we did not find a significant nonlinear dose-response relationship between the hsCRP/HDL-C ratio and depression risk (P nonlinearity = 0.226, Fig. 2B).

When the hsCRP/HDL-C ratio was categorized into tertiles, the association changed as covariates were progressively adjusted. In Model 1, moderate and high levels of hs-C/H were significantly associated with depression risk. In Model 2, which adjusted for gender, race, marital status, and BMI, moderate

(OR = 1.32, 95% CI = 1.09-1.60, $P = 0.004$) and high (OR = 1.58, 95% CI = 1.29-1.92, $P < 0.001$) levels of hs-C/H remained significantly associated with depression risk. In Model 3, after further adjustment for smoking, education level, physical activity, BMI, CKD, hypertension, diabetes, and hyperlipidemia, only the high level (OR = 1.25, 95% CI = 1.01-1.54, $P = 0.036$) was significantly associated with depression risk, while the moderate level ($P = 0.101$) was no longer significant. However, after adjusting for AIP in Model 4, the association between moderate and high levels of hs-C/H and depression risk was no longer significant, suggesting that AIP may play a potential mediating role in this relationship.

3.3 Subgroup and Sensitivity Analyses

Using age, gender, race, education level, smoking status, physical activity, PIR, BMI, marital status, history of hypertension, diabetes, and CVD as stratification variables, we examined trends in effect sizes across subgroups and constructed a forest plot to visualize the association between the hsCRP/HDL-C ratio and depression (Fig. 3). In all subgroups, the hsCRP/HDL-C ratio was positively correlated with depression. However, a significant interaction ($P < 0.05$) was observed between marital status and the hsCRP/HDL-C ratio on depression risk. For every unit increase in the hsCRP/HDL-C ratio, the probability of depression increased by 2.0% (OR: 1.02, 95% CI: 1.01-1.03) in the married group and by 1.0% (OR: 1.01, 95% CI: 1.05-1.14) in the cohabiting group. No significant interactions were observed with other factors.

3.4. Mediation analysis

Using the established multivariable logistic regression model, we found that after incorporating AIP into the analysis, AIP mediates the relationship between the hsCRP/HDL-C Ratio and depressive symptoms. The mediation model and pathways are illustrated in Fig. 4.

According to the findings, there was a significant correlation between AIP and depression ($\beta = 0.313$, $P = 0.036$) and the hsCRP/HDL-C Ratio and AIP ($\beta = 0.008$, $P < 0.001$). Subsequent investigation revealed that hsCRP/HDL-C Ratio had an indirect impact size of 11.2% ($P = 0.04$) on depression via AIP, which was significant. This implies that AIP, which accounts for around 4% of the overall impact (95% CI: 2.26%-27.00%), partly mediates the association between hsCRP/HDL-C Ratio and depression. These results suggest that the

hsCRP/HDL-C Ratio may indirectly affect the onset of depressive symptoms by modulating the metabolic marker AIP. This finding further emphasizes the potential mechanisms involving chronic inflammation and metabolic disturbances in the onset of depressive symptoms.

4. Discussion

To the best of our knowledge, this is the first study to investigate the association between the hsCRP/HDL-C ratio and depression in a nationally representative population. Our analysis yields three principal findings: first, a higher hsCRP/HDL-C ratio is associated with an increased risk of depression; second, this relationship is characterized by a nonlinear, threshold effect; and third, a significant portion of this association is mediated by the AIP. The observed threshold effect is of particular clinical relevance. It indicates that the depression risk escalates with increasing ratio levels primarily within a lower-to-moderate range, suggesting the existence of a critical window where interventions targeting inflammation and lipid metabolism might be most impactful for prevention. The robustness of the primary association across extensive adjustments for confounders and most subgroup analyses underscores its stability. An intriguing exception was the significant interaction with marital status, where the association was stronger in married or cohabiting individuals. This points to a complex interplay whereby intimate partner relationships—whether through shared lifestyle, stress, or support dynamics—may modulate an individual's biological vulnerability to depression.

Although direct comparisons are limited due to the novelty of the hsCRP/HDL-C ratio, the association we observed is mechanistically consistent with prior research. Previous work has independently linked both elevated inflammatory markers and adverse lipid profiles to depression (Milton, Ward et al. 2021) (Zainal and Newman 2023). Our findings synthesize these two established pathophysiological pathways by demonstrating that their confluence, captured by a single composite biomarker, is associated with depression. The ratio serves as an integrated indicator of chronic low-grade inflammation and metabolic dysfunction. Suboptimal levels of chronic peripheral proinflammatory proteins and lipid indicators may theoretically serve as risk factors or repercussions associated with an increased incidence of depression (Penninx 2017). The clinical relevance of this ratio is

underscored by its association with conditions characterized by both metabolic and inflammatory burden, such as cardiovascular diseases (Gao, Wang et al. 2024). Our results align with and extend previous findings, like the observed link between hs-CRP and depression in adolescents (Jung and Kang 2019), by proposing that the interplay between inflammation and lipid metabolism, rather than either factor alone, may be critical. The biological plausibility of our findings can be conceptualized through a synergistic model. Chronic inflammation, indicated by the hsCRP component, can directly contribute to depression by altering neurotransmitter systems and impairing emotional regulation circuits. This phenomenon can be explained from several perspectives. First, the hsCRP/HDL-C ratio serves as an indicator of chronic low-grade inflammation, particularly in the context of metabolic abnormalities. Chronic inflammation may induce depression by modifying neurotransmitter systems (e.g., serotonin and norepinephrine) and by impacting the brain circuits responsible for emotional regulation, eventually precipitating the development of depression (Pan, Xia et al. 2018)(Bolijn and Lucassen 2015). Secondly, elevated hsCRP/HDL-C ratio are often associated with insulin resistance and glucocorticoid secretion abnormalities, which could impact neural plasticity and neurotrophic factor synthesis, thus promoting the development of depression. Elevated cortisol levels are significantly associated with the development of depression, and cortisol may intensify depressed symptoms by suppressing the release of neurotrophic factors (Świątkiewicz, Wróblewski et al. 2023)(Masi and Brovedani 2011). Moreover, hormonal fluctuations significantly influence the regulation of the brain's reward system. Elevated hsCRP/HDL-C ratio often correlate with alterations in cortisol, insulin, and several other hormones. These imbalances in hormones may influence the brain's reward system, leading to anhedonia and worsening depressive symptoms (Krogh, Nordentoft et al. 2010). In clinical practice, depressive symptoms are common among individuals with physical illnesses, including cardiovascular diseases, diabetes, end-stage renal disease, and postmenopausal women (Bucciarelli, Caterino et al. 2020)(Li, Yang et al. 2024)(Zhou, Liu et al. 2024). Therefore, considering the strong link between hsCRP/HDL-C ratio and depression, it is essential to conduct thorough assessments of individuals with elevated hs-C/H levels, evaluate associated risk factors, and implement suitable interventions to

mitigate the risk of depression.

A key mechanistic insight from our study is the demonstration that the AIP partially mediates the relationship between the hsCRP/HDL-C ratio and depression. According to mediation research, the association between depression and the hsCRP/HDL-C ratio is partly mediated by AIP. An essential indicator for determining blood lipid levels and atherosclerosis risk is AIP (Huang, Liu et al. 2023). Elevated AIP typically reflects enhanced systemic inflammation and lipid metabolism disturbances, which may further exacerbate a vicious cycle of chronic inflammation and lipid metabolic abnormalities. Previous research has demonstrated a significant link between lipid metabolism abnormalities and depression (Douglass, Dorfman et al. 2017)(Amin, Liu et al. 2023). Therefore, In those with high hsCRP/HDL-C ratio, controlling AIP levels may help lower the incidence of depression. This observed association may be attributable to the role of AIP in improving lipid metabolism and reducing inflammation, which are potential mechanisms implicated in the pathogenesis of depression. Consequently, our findings suggest that monitoring AIP levels in patients with elevated hsCRP/HDL-C ratio warrants further investigation. If validated, the assessment of AIP could potentially aid in identifying high-risk individuals and inform the development of personalized strategies for depression prevention and management.

Our research has a number of advantages that improve the reliability and validity of the findings. First, we specifically investigated the understudied association between depressive symptoms and the hsCRP/HDL-C ratio, a novel biomarker with clinical relevance. Second, our analysis utilized nationally representative data from two NHANES cycles, providing a diverse sample that enhances the generalizability of results. Depression was assessed using the validated PHQ-9 instrument, ensuring measurement reliability. Laboratory measurements of hs-CRP and HDL-C followed standardized NHANES protocols with rigorous quality control, guaranteeing data accuracy. Furthermore, we extended the analytical framework by examining AIP as a potential mediator, offering mechanistic insights. Finally, we employed robust statistical approaches including multivariable regression with comprehensive confounder adjustment, subgroup analyses to assess effect modification, and restricted cubic splines to evaluate nonlinear relationships, all of which strengthen the validity and depth of our

conclusions.

The caveats of our research must be carefully considered, however. Firstly, although several studies have shown the reliability of the PHQ-9 questionnaire, it is important to consider that characteristics like as participants' age, cultural background, and educational level may add bias into the findings. Furthermore, the biomarkers used as independent variables might change over time, and this study only used a single blood sample to evaluate them. As such, a single sample may not provide an accurate representation of the participants' long-term or overall levels. The use of psychiatric drugs, individual lifestyle characteristics, and other health issues are all possible confounding variables that might affect the accuracy and interpretation of the findings. Unfortunately, we couldn't account for all of them. Additionally, this study was conducted solely among U.S. adults, and it remains uncertain whether these findings are applicable to populations in other regions. Therefore, future research should expand to other geographic areas to assess the generalizability and relevance of these findings. Lastly, being a cross-sectional study, this research cannot establish causality but instead highlights correlations. Although our work presents strong evidence linking the hsCRP/HDL-C ratio to depression, more longitudinal research is needed to determine the exact associations.

5. Conclusion

In conclusion, our study, based on a nationally representative cohort of the U.S. population, reveals a significant positive correlation between the hsCRP/HDL-C ratio and depression. Through RCS analysis, we observed a positive nonlinear association between hs-C/H and depression, which was further confirmed by piecewise logistic regression analysis in a partially adjusted model, identifying an important inflection point at 11.608. Below this threshold, hs-C/H levels were associated with an increased risk of depression. Our findings suggest that the hsCRP/HDL-C ratio can serve as an effective indicator for assessing the depression risk in individuals with lipid metabolism disorders or chronic low-grade inflammation. Furthermore, AIP plays a crucial mediating role in this association. Therefore, the association between hsCRP/HDL-C ratio, AIP, and depression revealed in this study may provide useful insights for identifying individuals at elevated risk. These findings highlight the potential of these biomarkers in improving risk

stratification and could represent a valuable area for future investigative and interventional studies.

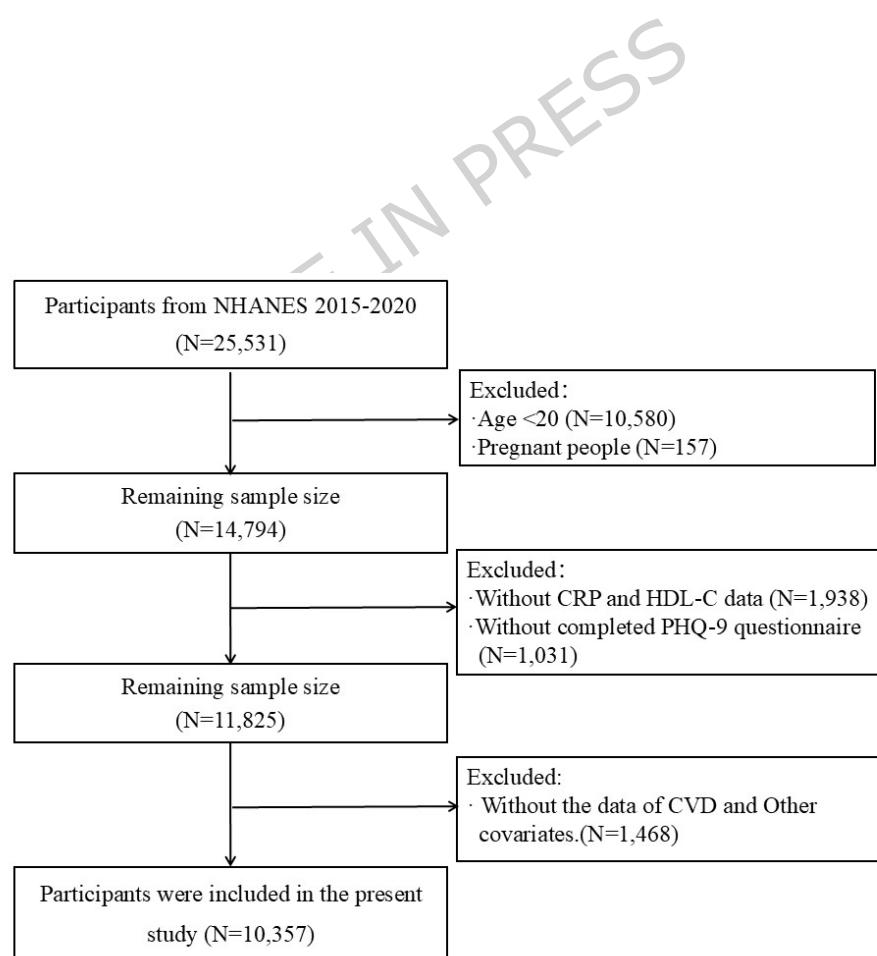


Fig 1. Flowchart of the sample selection from NHANES 2015-2020.

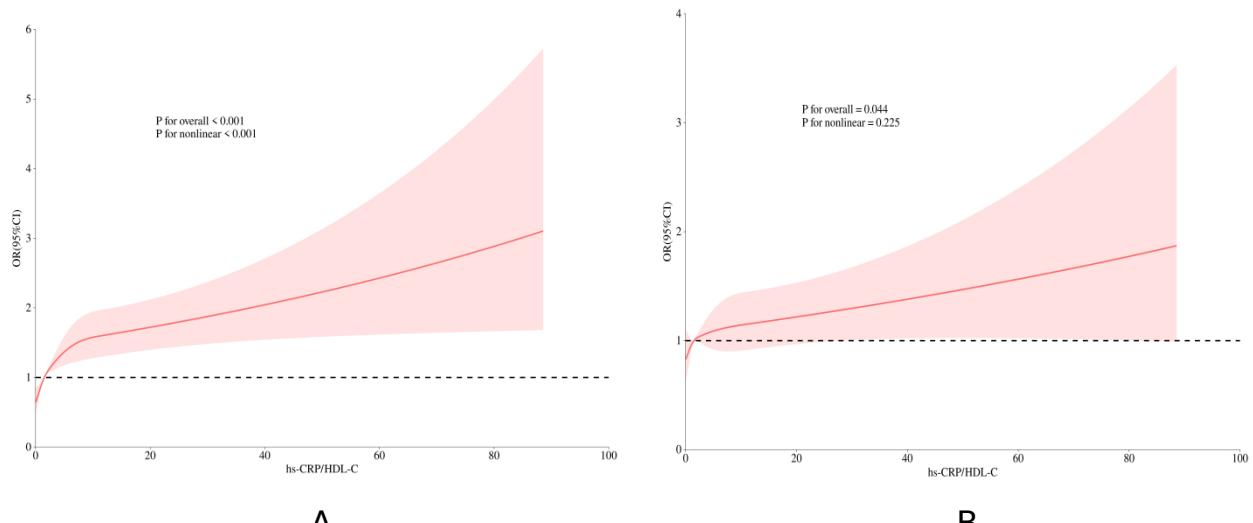


Fig 2.A. The dose-response relationship between hsCRP/HDL-C Ratio and PHQ-9 score;

Fig 2.B.The dose-response relationship between hsCRP/HDL-C Ratio and depression. The associations were adjusted for gender, race, marital status, smoke, education level, physical activity level, BMI, CKD, hypertension, diabetes and Hyperlipidemia.

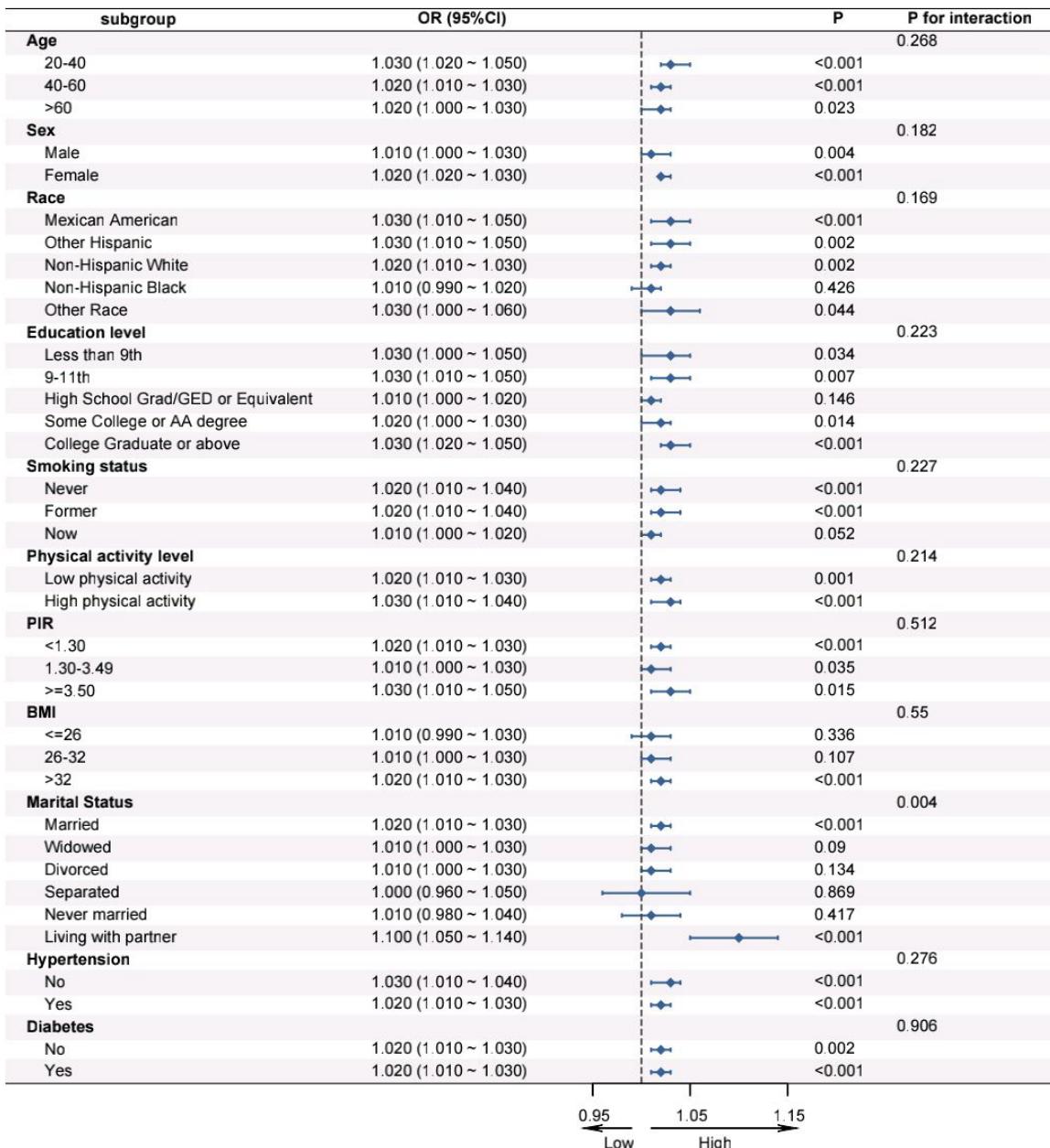


Fig 3. Verification of the association between RAR and Insomnia by subgroup analyses.

OR,Odds Ratio, CI,Confidence Interval;PIR, poverty-income ratio;DN,diabetic nephropathy;

MetS,metabolic syndrome;CKD,chronic kidney disease ;CVD, cardiovascular disease.

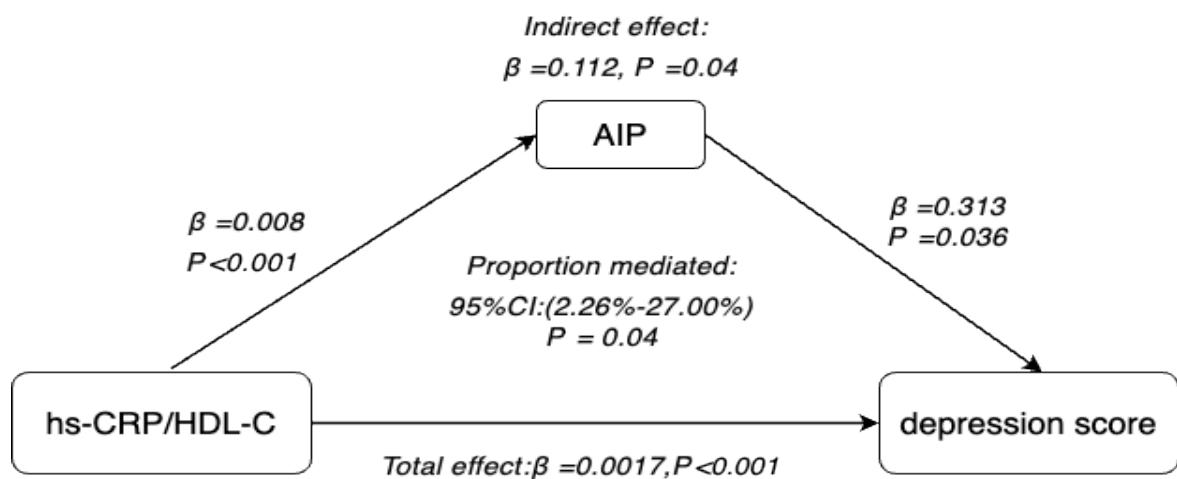


Fig 4. Estimated proportion of the association between hsCRP/HDL-C ratio and depression mediated by AIP.

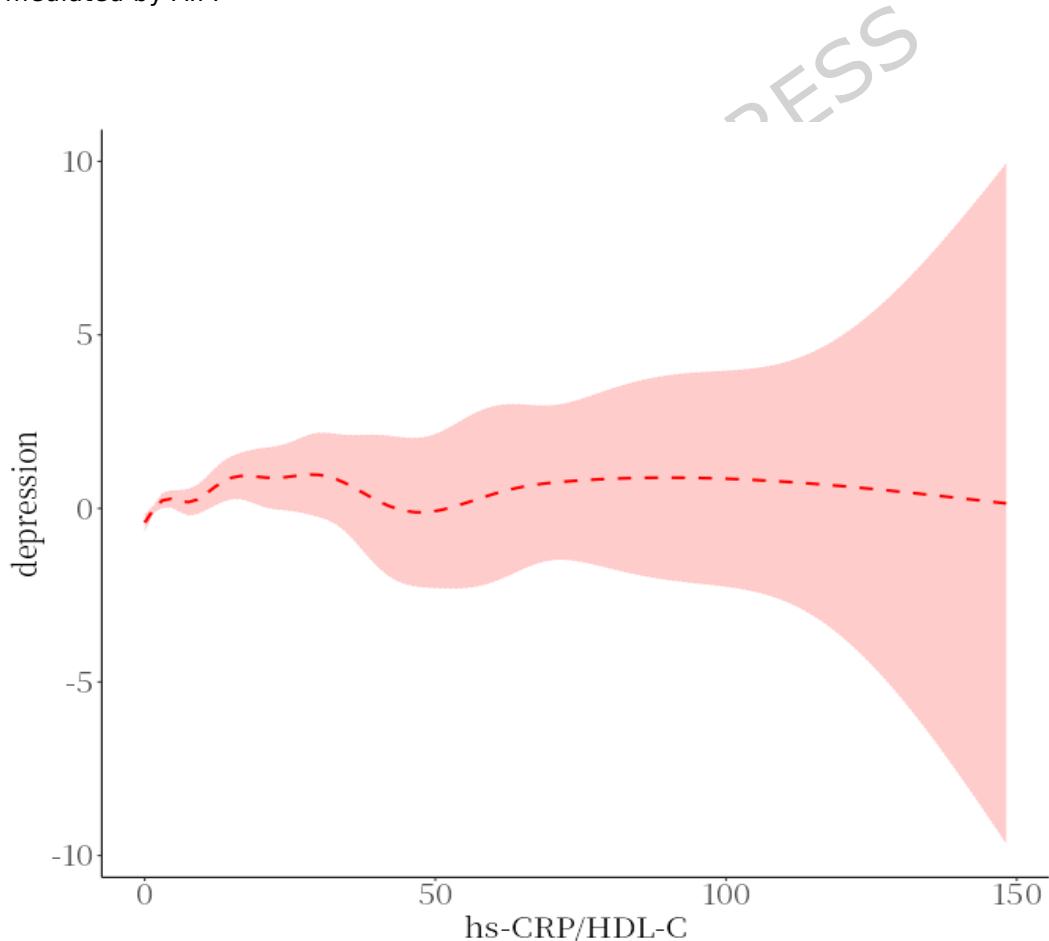


Fig 5. Results of two-piecewise logistic-regression model.

The red dashed line indicates the best fit, and the difference between the pink shaded areas represents the 95% confidence interval. The data were adjusted for all covariates in "model 3."

Table 1. Baseline characteristics of participants according to the PHQ-9 scores.

Characteristics	Total (n=10357)	PHQ-9<10	PHQ-9≥10	P
BMI, kg/m²	29.98 ± 7.41	29.80 ± 7.27	31.85 ± 8.57	<.001
Age, years	50.33 ± 17.31	50.40 ± 17.38	49.54 ± 16.50	0.141
Gender, n(%)				<.001
Male	5090 (49.15)	4746 (50.12)	344 (38.78)	
Female	5267 (50.85)	4724 (49.88)	543 (61.22)	
Race, n(%)				0.001
Mexican American	1442 (13.92)	1331 (14.05)	111 (12.51)	
Other Hispanic	1132 (10.93)	1009 (10.65)	123 (13.87)	
Non-Hispanic White	3848 (37.15)	3495 (36.91)	353 (39.80)	
Non-Hispanic Black	2353 (22.72)	2160 (22.81)	193 (21.76)	
Other Race	1582 (15.27)	1475 (15.58)	107 (12.06)	
Education level, n(%)				<.001
Less Than 9th Grade	817 (7.89)	726 (7.67)	91 (10.26)	
9-11th Grade	1111 (10.73)	968 (10.22)	143 (16.12)	
High School Grad/GED or Equivalent	2420 (23.37)	2183 (23.05)	237 (26.72)	
Some College or AA degree	3377 (32.61)	3076 (32.48)	301 (33.93)	
College Graduate or above	2632 (25.41)	2517 (26.58)	115 (12.97)	
Marital Status, n(%)				<.001
Married	5764 (55.65)	5403 (57.05)	361 (40.70)	
Widowed	1689 (16.31)	1498 (15.82)	191 (21.53)	
Divorced	1616 (15.60)	1427 (15.07)	189 (21.31)	
Separated	139 (1.34)	114 (1.20)	25 (2.82)	
Never married	746 (7.20)	660 (6.97)	86 (9.70)	
Living with partner	403 (3.89)	368 (3.89)	35 (3.95)	
Smoking status, n(%)				<.001
Never	5894 (56.91)	5521 (58.30)	373 (42.05)	
Former	2555 (24.67)	2340 (24.71)	215 (24.24)	
Now	1908 (18.42)	1609 (16.99)	299 (33.71)	
Drinking, n(%)				0.121
No	1240 (30.26)	1150 (30.59)	90 (26.55)	
Yes	2858 (69.74)	2609 (69.41)	249 (73.45)	
Physical activity level, n(%)				<.001
Low physical activity	3748 (36.19)	3381 (35.70)	367 (41.38)	
High physical activity	6609 (63.81)	6089 (64.30)	520 (58.62)	
PIR, n(%)				<.001
0-1.30	3404 (32.87)	2944 (31.09)	460 (51.86)	
1.30-3.49	3527 (34.05)	3249 (34.31)	278 (31.34)	
≥3.50	3426 (33.08)	3277 (34.60)	149 (16.80)	
CVD, n(%)				<.001
No	9150 (88.35)	8445 (89.18)	705 (79.48)	
Yes	1207 (11.65)	1025 (10.82)	182 (20.52)	
Strok, n(%)				<.001
No	9902 (95.70)	9099 (96.14)	803 (90.94)	
Yes	445 (4.30)	365 (3.86)	80 (9.06)	
Hypertension, n(%)				<.001
No	5769 (55.75)	5354 (56.58)	415 (46.89)	
Yes	4579 (44.25)	4109 (43.42)	470 (53.11)	
Hyperlipidemia, n(%)				<.001
No	3173 (30.64)	2945 (31.10)	228 (25.70)	
Yes	7184 (69.36)	6525 (68.90)	659 (74.30)	
Diabetes, n(%)				<.001
No	8003 (78.61)	7375 (79.27)	628 (71.69)	
Yes	2177 (21.39)	1929 (20.73)	248 (28.31)	
CKD, n(%)				<.001
No	8398 (81.61)	7727 (82.13)	671 (75.99)	
Yes	1893 (18.39)	1681 (17.87)	212 (24.01)	

Table 2. Association between hs-CRP/HDL-C and depression.

hs-CRP/HDL-C categorical	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR(95%CI)	P
Low	1.00 (Reference)	—	1.00 (Reference)	—	1.00 (Reference)	—	1.00 (Reference)	—
Middle	1.42 (1.18~1.70)	<0.01	1.32 (1.09~1.60)	0.004	1.18 (0.97~1.43)	0.101	1.05 (0.79~1.38)	0.757
High	1.95 (1.63~2.32)	<0.01	1.58 (1.29~1.92)	<0.001	1.25 (1.01~1.54)	0.036	1.02 (0.75~1.39)	0.897

Abbreviations: BMI, body mass index, CKD, chronic kidney disease, AIP: Atherogenic Index of Plasma.

Model 1: no covariates were adjusted.

Model 2: adjusted for gender, race, marital status and BMI.

Model 3: Further adjusted for behavioral and clinical confounders: smoking status, education level, physical activity level, CKD, hypertension, diabetes, and hyperlipidemia. This fully adjusted model aimed to isolate the independent association between the hs-CRP/HDL-C ratio and depression by accounting for a wide range of potential confounders.

Model 4: Included all covariates from Model 3 plus the AIP. The inclusion of AIP in this model served a distinct purpose from mere confounding control. As AIP is a composite marker of atherosclerotic dyslipidemia and is hypothesized to lie on the potential causal pathway between the hs-CRP/HDL-C ratio and depression, its addition allows for an initial assessment of mediation. The attenuation of the hs-CRP/HDL-C odds ratio from Model 3 to Model 4 provides insight into the extent to which the association may be mediated through atherosclerotic lipid pathways.

Table 3. Results of two-piecewise logistic-regression model.

hs-CRP/HDL-C	Depression OR (95%CI)	<i>P</i>
Model 1 Fitting model by standard linear regression	1.01 (1.00 - 1.02)	0.103
Model 2 Fitting model by two-piecewise linear regression		
Inflection point	11.608	
<11.608	1.01 (0.98 - 1.04)	0.577
≥11.608	0.99 (0.97 - 1.01)	0.185
P for likelihood test		0.122

The model adjusted for factors such as gender, race, marital status, BMI, smoking status, education level, physical activity level, CKD, hypertension, diabetes, hyperlipidemia, and CKD.

ARTICLE IN PRESS

Abbreviations

- BMI□Body Mass Index
- CVD□Cardiovascular Disease

AIP□Atherogenic Index of Plasma

NHANES□National Health and Nutrition Examination Survey

PHQ-9□Patient Health Questionnaire-9

PIR□Poverty income ratio

CKD□Chronic Kidney Disease

hs-CRP□high-sensitivity C-reactive protein

HDL-C□High-density lipoprotein cholesterol

Authorship contribution statement:

Jing-Ying Ma: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jue Hu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – review & editing. **Fa-Dan Tang:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **YiLin Meng:** Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

FaYe: Validation, Visualization□Supervision.

Lin-Lin Hu: Methodology, Project administration, Supervision. **Yong-Hua Zhang:** Conceptualization, Project administration, Supervision. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate: The National Health and Nutrition Examination Survey (NHANES) is a publicly available database, approved by the National Center for Health Statistics Institutional Review Board (IRB). All participants provided written informed consent during their participation in the national survey in the United States. Ethical review and approval were waived for this secondary analysis, as no additional institutional review board approval was required, in accordance with the Declaration of Helsinki.

Funding: None

Declaration of competing interest: None.

Data availability: Data used for this study are available on the NHANES website: <https://www.cdc.gov/nchs/nhanes/>. The datasets presented in this article are not readily available. □Requests to access the datasets should be

directed to majingyingg@163.com.

Acknowledgments We would like to extend our sincere gratitude to the professionals involved in the collection, management, and dissemination of the NHANES data, whose efforts have been invaluable to this research. Additionally, we acknowledge the contributions of the authors in the preparation and development of this manuscript.

References

- Marx, W., B. Penninx, M. Solmi, T. A. Furukawa, J. Firth, A. F. Carvalho and M. Berk (2023). "Major depressive disorder." *Nat Rev Dis Primers* 9(1): 44.
- Malhi, G. S. and J. J. Mann (2018). "Depression." *Lancet* 392(10161): 2299-2312.
- Siskind, D. and S. Kisely (2019). "Balancing body and mind: selecting the optimal antipsychotic." *Lancet* 394(10202): 900-902.
- Wang, Y. H., J. Q. Li, J. F. Shi, J. Y. Que, J. J. Liu, J. M. Lappin, J. Leung, A. V. Ravindran, W. Q. Chen, Y. L. Qiao, J. Shi, L. Lu and Y. P. Bao (2020). "Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies." *Mol Psychiatry* 25(7): 1487-1499.
- Weavers, B., J. Heron, A. K. Thapar, A. Stephens, J. Lennon, R. Bevan Jones, O. Eyre, R. J. Anney, S. Collishaw, A. Thapar and F. Rice (2021). "The antecedents and outcomes of persistent and remitting adolescent depressive symptom trajectories: a longitudinal, population-based English study." *Lancet Psychiatry* 8(12): 1053-1061.
- Apweiler, M., S. W. Saliba, L. Sun, J. Streyczek, C. Normann, S. Hellwig, S. Bräse and B. L. Fiebich (2024). "Modulation of neuroinflammation and oxidative stress by targeting GPR55 - new approaches in the treatment of psychiatric disorders." *Mol Psychiatry* 29(12): 3779-3788.
- Dregan, A., F. Matcham, L. Harber-Aschan, L. Rayner, A. Brailean, K. Davis, S. Hatch, C. Pariante, D. Armstrong, R. Stewart and M. Hotopf (2019). "Common mental disorders within chronic inflammatory disorders: a primary care database prospective investigation." *Ann Rheum Dis* 78(5): 688-695.

Enko, D., W. Brandmayr, G. Halwachs-Baumann, W. J. Schnedl, A. Meinitzer and G. Kriegshäuser (2018). "Prospective plasma lipid profiling in individuals with and without depression." *Lipids Health Dis* 17(1): 149.

Bharti, V., A. Bhardwaj, K. Hood, D. A. Elias, A. W. S. Metcalfe and J. S. Kim (2021). "A systematic review and meta-analysis of lipid metabolomic signatures of Major Depressive Disorder." *J Psychiatr Res* 139: 197-205.

Khalfan, A. F., S. C. Campisi, R. F. Lo, B. W. McCrindle and D. J. Korczak (2023). "The association between adolescent depression and dyslipidemia." *J Affect Disord* 338: 239-245.

Denegri, A. and G. Boriani (2021). "High Sensitivity C-reactive Protein (hsCRP) and its Implications in Cardiovascular Outcomes." *Curr Pharm Des* 27(2): 263-275.

Navab, M., S. T. Reddy, B. J. Van Lenten and A. M. Fogelman (2011). "HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms." *Nat Rev Cardiol* 8(4): 222-232.

Osimo, E. F., L. J. Baxter, G. Lewis, P. B. Jones and G. M. Khandaker (2019). "Prevalence of low-grade inflammation in depression: a systematic review and meta-analysis of CRP levels." *Psychol Med* 49(12): 1958-1970.

Gao, Y., M. Wang, R. Wang, J. Jiang, Y. Hu, W. Wang, Y. Wang and H. Li (2024). "The predictive value of the hs-CRP/HDL-C ratio, an inflammation-lipid composite marker, for cardiovascular disease in middle-aged and elderly people: evidence from a large national cohort study." *Lipids Health Dis* 23(1): 66.

Valkanova, V. and K. P. Ebmeier (2013). "Vascular risk factors and depression in later life: a systematic review and meta-analysis." *Biol Psychiatry* 73(5): 406-413.

Qu, L., S. Fang, Z. Lan, S. Xu, J. Jiang, Y. Pan, Y. Xu, X. Zhu and J. Jin (2024). "Association between atherogenic index of plasma and new-onset stroke in individuals with different glucose metabolism status: insights from CHARLS." *Cardiovasc Diabetol* 23(1): 215.

Dobiášová, M. (2006). "[AIP--atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice]." *Vnitr Lek* 52(1): 64-71.

Kong, D. and W. Zou (2024). "Association between atherogenic index of plasma and post-stroke depression: a cross-sectional study." *Eur J Psychotraumatol* 15(1): 2429266.

Nunes, S. O., L. G. Piccoli de Melo, M. R. Pizzo de Castro, D. S. Barbosa, H. O. Vargas, M. Berk and M. Maes (2015). "Atherogenic index of plasma and atherogenic coefficient are increased in major depression and bipolar disorder, especially when comorbid with tobacco use disorder." *J Affect Disord* 172: 55-62.

Kroenke, K., R. L. Spitzer and J. B. Williams (2001). "The PHQ-9: validity of a brief depression severity measure." *J Gen Intern Med* 16(9): 606-613.

Dobiásová, M. and J. Frohlich (2001). "The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL))." *Clin Biochem* 34(7): 583-588.

Zhang, H., L. Zhang, J. Li, H. Xiang, Y. Liu, C. Gao and X. Sun (2024). "The influence of Life's Essential 8 on the link between socioeconomic status and depression in adults: a mediation analysis." *BMC Psychiatry* 24(1): 296.

Wang, M., J. Tian, Y. Gao, N. An and Q. Wang (2025). "Mediating role of the ratio of family income to poverty in the association between depressive symptoms and stroke: Evidence from a large population-based study." *J Affect Disord* 379: 100-108.

Milton, D. C., J. Ward, E. Ward, D. M. Lyall, R. J. Strawbridge, D. J. Smith and B. Cullen (2021). "The association between C-reactive protein, mood disorder, and cognitive function in UK Biobank." *Eur Psychiatry* 64(1): e14.

Zainal, N. H. and M. G. Newman (2023). "Prospective network analysis of proinflammatory proteins, lipid markers, and depression components in midlife community women." *Psychol Med* 53(11): 5267-5278.

Penninx, B. W. (2017). "Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms." *Neurosci Biobehav Rev* 74(Pt B): 277-286.

Jung, Y. E. and K. Y. Kang (2019). "Elevated hs-CRP level is associated with depression in younger adults: Results from the Korean National Health and Nutrition Examination Survey (KNHANES 2016)." *Psychoneuroendocrinology* 109: 104397.

Pan, J. X., J. J. Xia, F. L. Deng, W. W. Liang, J. Wu, B. M. Yin, M. X. Dong, J. J. Chen, F. Ye, H. Y. Wang, P. Zheng and P. Xie (2018). "Diagnosis of major depressive disorder

based on changes in multiple plasma neurotransmitters: a targeted metabolomics study." *Transl Psychiatry* 8(1): 130.

Bolijn, S. and P. J. Lucassen (2015). "How the Body Talks to the Brain; Peripheral Mediators of Physical Activity-Induced Proliferation in the Adult Hippocampus." *Brain Plast* 1(1): 5-27.

Świątkiewicz, I., M. Wróblewski, J. Nuszkiewicz, P. Sutkowy, J. Wróblewska and A. Woźniak (2023). "The Role of Oxidative Stress Enhanced by Adiposity in Cardiometabolic Diseases." *Int J Mol Sci* 24(7).

Masi, G. and P. Brovedani (2011). "The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression." *CNS Drugs* 25(11): 913-931.

Krogh, J., M. Nordentoft, M. Mohammad-Nezhad and A. Westrin (2010). "Growth hormone, prolactin and cortisol response to exercise in patients with depression." *J Affect Disord* 125(1-3): 189-197.

Bucciarelli, V., A. L. Caterino, F. Bianco, C. G. Caputi, S. Salerni, S. Sciomer, S. Maffei and S. Gallina (2020). "Depression and cardiovascular disease: The deep blue sea of women's heart." *Trends Cardiovasc Med* 30(3): 170-176.

Li, S., D. Yang, X. Zhou, L. Chen, L. Liu, R. Lin, X. Li, Y. Liu, H. Qiu, H. Cao, J. Liu and Q. Cheng (2024). "Neurological and metabolic related pathophysiologies and treatment of comorbid diabetes with depression." *CNS Neurosci Ther* 30(4): e14497.

Zhou, J., W. Liu, X. Liu, J. Wu and Y. Chen (2024). "Independent and joint influence of depression and advanced lung cancer inflammation index on mortality among individuals with chronic kidney disease." *Front Nutr* 11: 1453062.

Huang, Q., Z. Liu, M. Wei, Q. Huang, J. Feng, Z. Liu and J. Xia (2023). "The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China." *Cardiovasc Diabetol* 22(1): 125.

Douglass, J. D., M. D. Dorfman, R. Fasnacht, L. D. Shaffer and J. P. Thaler (2017). "Astrocyte IKK β /NF- κ B signaling is required for diet-induced obesity and hypothalamic inflammation." *Mol Metab* 6(4): 366-373.

Amin, N., J. Liu, B. Bonnechere, S. MahmoudianDehkordi, M. Arnold, R. Batra, Y. J. Chiou, M. Fernandes, M. A. Ikram, R. Kraaij, J. Krumsiek, D. Newby, K. Nho, D. Radjabzadeh, A. J. Saykin, L. Shi, W. Sproviero, L. Winchester, Y. Yang, A. J. Nevado-Holgado, G. Kastenmüller, R. Kaddurah-Daouk and C. M. van Duijn (2023). "Interplay of Metabolome and Gut Microbiome in Individuals With Major Depressive Disorder vs Control Individuals." *JAMA Psychiatry* 80(6): 597-609.

ARTICLE IN PRESS