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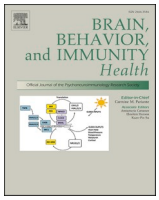

The association between depressive symptoms and high-sensitivity C-reactive protein: Is body mass index a moderator?

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ABSTRACT

Objective: Depression and obesity are highly comorbid conditions with shared biological mechanisms. It remains unclear how depressive symptoms and body mass index (BMI) interact in relation to inflammation. This cross-sectional study investigated the independent associations of depressive symptoms and BMI with high sensitivity C-reactive protein (hs-CRP), as well as the moderating role of BMI on the depressive symptoms-hs-CRP association.

Methods: Participants ($n = 8827$) from the 2015–2018 National Health and Nutrition Examination Surveys were aged ≥20 with a BMI ≥18.5 kg/m^2, completed the Depression Screener, and had hs-CRP data. Multivariable linear regression was used to analyze hs-CRP in relation to depressive symptoms and BMI. An interaction term was included to examine whether the depressive symptoms-hs-CRP relationship differs depending on BMI.

Results: There was a slight, albeit non-significant, increase in hs-CRP levels with each one-point increase in depressive symptoms (aCoef.Estm. = 0.01, 95% CI = −0.05, 0.06, $p = 0.754$). Participants with overweight (aCoef.Estm. = 1.07, 95% CI = 0.61, 1.53, $p < 0.001$) or obese (aCoef.Estm. = 3.51, 95% CI = 3.04, 3.98, $p < 0.001$) BMIs had higher mean hs-CRP levels than those with a healthy BMI. There were no significant interactions between depressive symptoms and overweight (aCoef.Estm. = 0.04, 95% CI = −0.04, 0.13, $p = 0.278$) or obese (aCoef.Estm. = 0.11, 95% CI = −0.01, 0.22, $p = 0.066$) BMI indicating a lack of difference in the depressive symptoms-hs-CRP association across participants in the healthy versus overweight and obese ranges.

Conclusions: This study suggests that BMI might not act as a moderator in the association between depressive symptoms and hs-CRP. Results should be replicated in larger samples. Further research is warranted to understand underlying mechanisms.

1. Introduction

Depression and obesity are global public health concerns, with rates that are on the rise (Liu et al., 2020), (Seidell and Halberstadt, 2015). Across 2017 and 2018, depression and obesity affected 8.7% (Daly et al., 2021) and 42.4% (Fryar et al., 2020) of adults in the United States (US), respectively. A meta-analysis reported a 37% increased risk of obesity in individuals with depression, as well as an 18% increased risk of depression in those with obesity (Mannan et al., 2016). In the presence of comorbidity, depression and obesity raise greater concern by heightening the risk of functional disability (Lin et al., 2022) and non-communicable diseases (Haregu et al., 2020).

The National Institute of Mental Health's Research Domain Criteria framework bolsters the search for alternative ways to characterize mental disorders based on their pathophysiological mechanisms (Insel et al., 2010). With respect to depression, the cytokine hypothesis posits that inflammatory processes contribute to its pathogenesis (Maes et al., 2009), (Schiepers et al., 2005). C-reactive protein (CRP) and its high-sensitivity form (hs-CRP), which can detect slight increases in inflammation, have been commonly studied as markers of inflammation

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in depression (Orsolini et al., 2022). A systematic review and meta-analysis reported that CRP levels were elevated >1 mg/L in 58% and >3 mg/L in 27% of individuals with depression (Osimo et al., 2019). Moreover, a meta-analysis of cross-sectional reports demonstrated a positive association between depression and CRP in clinical and community-based samples (Howren et al., 2009).

While there is increasing literature supporting the presence of inflammation in depression (Osimo et al., 2019), (Osimo et al., 2020), it remains unclear whether this may be related to the high prevalence of concurrent obesity in this population (McLaughlin et al., 2021). Elevated (hs-)CRP has been shown to be associated with obesity when obesity is defined using various body measures, including body mass index (BMI), waist circumference, and waist-to-hip ratio (Choi et al., 2013), (Brooks et al., 2010), (Koziarska-Rościszewska et al., 2021). Consequently, chronic low-grade inflammation has been examined as one of the shared biological mechanisms that could explain the complex and multifactorial relationship between depression and obesity (Milaneschi et al., 2019), (Milano et al., 2020), (Ouakinin et al., 2018), (Berk et al., 2013), (Chu et al., 2023), (Frank et al., 2022). While individuals with depression might present with increased inflammation regardless of body weight, some evidence suggests that elevated BMI contributes more to inflammation than depression (McLaughlin et al., 2021), (Ambrósio et al., 2018). As such, BMI may act as a moderator in the depression-inflammation relationship (Howren et al., 2009), such that the association is strongest in those with obesity (Cho et al., 2021).

Recently, efforts have been made to elucidate how depression and hs-CRP are linked while also considering BMI. To the authors' knowledge, it is not fully understood how depressive symptoms and BMI interact in relation to inflammation. Qin et al. (2017) found no significant relationship between depression and hs-CRP in healthy, overweight, or obese BMI. In addition, McLaughlin et al. (2021) reported that the odds of having elevated hs-CRP were significantly increased in participants with comorbid depression and overweight status, but not in those with depression- or overweight-only. Moreover, the odds of having elevated hs-CRP were significantly decreased in participants with neither condition (McLaughlin et al., 2021). Chae et al. (2022) found that the depression- and depressive symptoms-by-obesity interactions were not significant. However, their study (Chae et al., 2022) categorized participants into obese and non-obese groups, which may have oversimplified the contributions of BMI to hs-CRP by assuming that individuals in the healthy and overweight ranges have similar levels of inflammation. Related research (i.e., exploring associations, but not interactions) has focused on obesity only (Vetter et al., 2013), (Dixon et al., 2008) or combined participants with overweight and obese BMIs (McLaughlin et al., 2021). Thus, there is a need to examine how BMI modifies the association between depressive symptoms and inflammation in a more detailed way by using distinct healthy, overweight, and obese groups to enhance the understanding of where differences might lie. In addition, research may benefit from treating depressive symptom and hs-CRP values as continuous rather than binary or categorical measures – as has been done in previous work (McLaughlin et al., 2021), (Chae et al., 2022) – based on evidence suggesting that the association between depressive symptoms and CRP might be linear (Köhler-Forsberg et al., 2017).

This study investigated the independent associations of depressive symptoms and BMI with hs-CRP, as well as the moderating role of BMI in the depressive symptoms-hs-CRP association. We hypothesized that 1) levels of hs-CRP would increase with depressive symptoms; 2) participants with an overweight or obese BMI would have higher levels of hs-CRP compared to those with a healthy BMI; and 3) BMI would moderate the association between depressive symptoms and hs-CRP such that the association would be strongest in participants with an obese BMI.

2. Methods

2.1. Study population

This study used data from the 2015–2018 National Health and Nutrition Examination Surveys (NHANES). NHANES is conducted by the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC). This cross-sectional survey used a highly stratified multistage probability sampling design to assess the health and nutritional status of the noninstitutionalized civilian US population. The NHANES protocol was approved by the Research Ethics Review Board of the NCHS and informed consent was obtained from participants prior to data collection. Data were collected through home interviews and health examinations administered by trained personnel. Descriptions of the survey protocol, sampling procedures, and details of the laboratory tests conducted can be found on the CDC website (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#). Male and non-pregnant female participants ≥20 years of age with a BMI ≥18.5 kg/m^2 were included in this study if they completed the Mental Health - Depression Screener (DPQ) and had hs-CRP data. Participants <20 years of age were excluded from the study since some of the data used in the current analyses were only collected from those who were a minimum of 20 years old. Individuals with a BMI in the underweight range (i.e., <18.5 kg/m^2) were also excluded from analyses since the current study aimed to demonstrate an association between depressive symptoms and hs-CRP levels in participants with an elevated BMI based on research suggesting that this association is strongest in obesity (Cho et al., 2021).

2.2. Exposure variables

Data pertaining to depressive symptoms were collected through self-report and calculated by summing responses to items DPQ010 through DPQ090 from the DPQ, which are the nine questions of the Patient Health Questionnaire (PHQ-9). The PHQ-9 assesses the frequency of depressive symptoms over the past 2 weeks based on the *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition* major depressive disorder diagnostic criteria (Kroenke et al., 2001). Each symptom was scored on a 4-point scale ranging from 0 (experienced not at all) to 3 (experienced nearly every day). The PHQ-9 is a reliable and valid measure of depressive symptoms (Kroenke et al., 2001). Total PHQ-9 scores were kept as continuous values for all analyses.

BMI (kg/m^2) was calculated by NHANES (BMXBMI) using weight and height data that were objectively collected by trained personnel in the Mobile Examination Center (MEC) (National Health and Nutrition Examination Survey 2015–2016, 2016), (National Health and Nutrition Examination Survey 2017-2018, 2017). Values were categorized into healthy (≥18.5 to <25 kg/m^2), overweight (≥25 to <30 kg/m^2), and obese (≥30 kg/m^2) BMI (Centers for Disease Control and Prevention).

2.3. Outcome variable

The outcome of this study was inflammation measured by hs-CRP (mg/L). Laboratory details pertaining to hs-CRP collection are described elsewhere (National Health and Nutrition Examination Survey 2015–2016, 2019), (National Health and Nutrition Examination Survey 2017–2018, 2020). Due to a change in equipment from the 2015/2016 (DxC 660i) to 2017/2018 (Cobas 6000) NHANES cycles, values were adjusted using Equation (1) as recommended by NHANES (National Health and Nutrition Examination Survey, 2017). This adjustment was determined to be suitable for application to Cobas 6000 values ≤20 mg/L due to measurement sensitivity of devices at these values (National Health and Nutrition Examination Survey, 2017). hs-CRP levels were kept as continuous values for all analyses.

$$Y\ (DxC\ 660i) = 1.150\ (95\%CI: 1.114\ to\ 1.186) * X\ (Cobas\ 6000) - 0.3397\ (95\%CI: -0.3663\ to\ -0.3130) \quad (1)$$

As a sensitivity analysis, statistical analyses were rerun after excluding participants with hs-CRP >10.0 mg/L to account for potential acute infection or injury (Chae et al., 2022), (Pearson et al., 2003), (Mac Giollabhui et al., 2020), which may have skewed the results from the main analysis.

2.4. Statistical analysis

All statistical analyses were performed using R v 4.2.1 and the package "survey" to account for MEC survey weights. Survey weights were divided by two to account for the merging of two survey cycles, as recommended by NHANES. Categorical variables were described as raw frequency and weighted percent in the study population demographic characteristics table, while continuous variables were described as weighted mean and standard deviation (*SD*). A chi-square test of independence was used to check for statistically significant (p-value ≤ 0.05) differences in categorical demographic characteristics between the three BMI groups, and a t-test was used to test for differences in continuous variables. Multivariable linear regression was used to analyze the independent associations of depressive symptoms and BMI with the outcome of hs-CRP level. An interaction term between depressive symptoms and BMI was added to this model to examine whether the relationship between depressive symptoms and hs-CRP differs depending on the level of BMI. Individuals who "refused" to answer, responded "I don't know", or had missing data for variables of interest were excluded from analyses.

To control for confounding bias, age (continuous), sex (male, female), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other race - including multi-racial), and education (≤high school, >high school) were included as covariates in the model for partial adjustment. The fully adjusted model included the same covariates as the partially adjusted model with the addition of cardiovascular disease (i.e., coronary heart disease, angina, myocardial infarction, stroke, or congestive heart failure; yes, no), liver conditions (yes, no), chronic bronchitis (yes, no), emphysema (yes, no), rheumatoid arthritis (yes, no), human immunodeficiency virus (yes, no), hepatitis C (yes, no), kidney conditions (i.e., kidney disease, kidney stones, urinary incontinence, or nocturia; yes, no), and diabetes (yes, no). For the main effects analyses pertaining to depressive symptoms and BMI, the opposite exposure variable (i.e., BMI or depressive symptoms, respectively) was also adjusted for.

3. Results

3.1. Demographic characteristics

Data were collected from 19,225 participants during the 2015–2018 NHANES cycles. The study population included 8827 individuals (Fig. 1), with a mean hs-CRP measurement of 3.83 mg/L (*SD* = 6.74 mg/L). The mean PHQ-9 score of the total study population was 3.10 (*SD* = 4.06), and 6636 (weighted percent = 74.29%) participants had overweight or obese BMIs. The mean age of the study population was 48.74 years (*SD* = 17.00; range = 20 to 80), and 4458 participants (50.70%) were female. Significant differences across groups emerged for most of the covariates. Table 1 and Supplementary Table S1 present the demographic characteristics for the study population and the sensitivity analysis, respectively.

3.2. Independent associations of depressive symptoms and BMI with hs-CRP

Following partial adjustment for covariates, participants demonstrated a 0.11 mg/L increase in hs-CRP levels with each one-point increase in PHQ-9 score (adjusted coefficient estimate [aCoef.Estm.] = 0.11, 95% confidence interval [CI] = 0.05, 0.17, $p = 0.001$) (Table 2). After full adjustment for covariates, participants demonstrated a slight, albeit non-significant, increase in hs-CRP levels with each increase in PHQ-9 score (aCoef.Estm. = 0.01, 95% CI = −0.05, 0.06, $p = 0.754$) (Table 2). The sensitivity analysis showed similar results (Supplementary Table S2).

Participants with an overweight (aCoef.Estm. = 0.93, 95% CI = 0.58, 1.27, $p < 0.001$) or obese (aCoef.Estm. = 3.34, 95% CI = 2.94, 3.74, $p < 0.001$) BMI had higher mean hs-CRP levels compared to those with a healthy BMI after partial adjustment for covariates (Table 2). The fully adjusted model followed the same pattern of results (Table 2). The

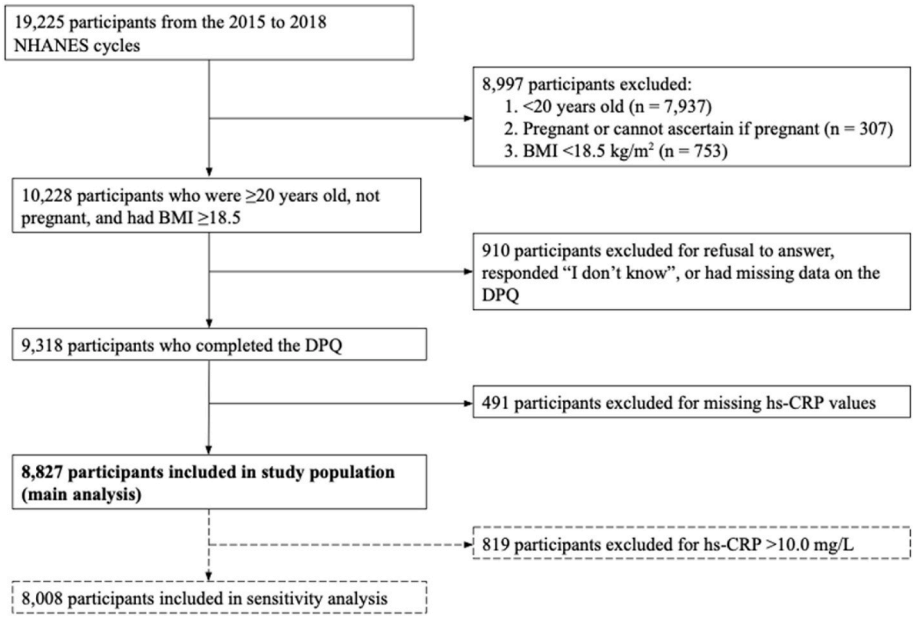

Fig. 1. Participant inclusion flowchart. Abbreviations: BMI = body mass index; DPQ = Mental Health - Depression Screener; hs-CRP = high-sensitivity C-reactive protein; NHANES = National Health and Nutrition Examination Survey.

Table 1
Demographic characteristics of study population ($n = 8827$).

Characteristic	Total	Healthy BMI	Overweight BMI	Obese BMI	*p*-value
Sample size	8827 (100.00)	2191 (25.72)	2875 (31.90)	3761 (42.39)	–
Age (mean, *SD*)	48.74 (17.00)	45.66 (17.82)	50.49 (17.07)	49.30 (16.16)	<0.001[a]
Sex - female	4458 (50.70)	1141 (56.80)	1248 (43.79)	2069 (52.20)	<0.001[a]
Race					<0.001[a]
Mexican American	1405 (8.83)	197 (5.23)	498 (9.31)	710 (10.64)	
Other Hispanic	992 (6.40)	186 (4.92)	386 (8.28)	420 (5.88)	
Non-Hispanic White	3122 (65.01)	805 (67.82)	987 (63.74)	1330 (64.25)	
Non-Hispanic Black	1885 (10.42)	407 (9.01)	520 (8.89)	958 (12.44)	
Other race - including multi-racial	1423 (9.34)	596 (13.03)	484 (9.77)	343 (6.79)	
Education - ≤ high school	3875 (36.31)	1294 (33.02)	1575 (36.12)	2077 (38.45)	0.015[a]
PHQ-9 (mean, *SD*)	3.10 (4.06)	2.90 (3.99)	2.71 (3.69)	3.52 (4.32)	<0.001[a]
hs-CRP (mg/L) (mean, *SD*)	3.83 (6.74)	2.11 (5.40)	2.93 (5.32)	5.56 (7.93)	<0.001[a]
Cardiovascular disease - yes	1009 (9.07)	181 (5.94)	320 (8.85)	508 (11.14)	<0.001[a]
Liver conditions - yes	463 (4.76)	103 (3.65)	134 (4.17)	226 (5.88)	0.029[a]
Chronic bronchitis - yes	562 (6.20)	107 (4.09)	142 (5.41)	313 (8.08)	<0.001[a]
Emphysema - yes	179 (1.62)	48 (1.68)	45 (1.33)	86 (1.79)	0.622
Rheumatoid arthritis - yes	517 (5.50)	87 (3.87)	159 (4.93)	271 (7.16)	0.001[a]
HIV - yes	28 (0.49)	8 (0.50)	11 (0.91)	9 (0.19)	0.109
Hepatitis C - yes	145 (1.47)	40 (1.79)	51 (1.52)	54 (1.24)	0.415
Kidney conditions - yes	4624 (47.68)	939 (38.50)	1445 (46.19)	2240 (54.39)	<0.001[a]
Diabetes - yes	1394 (11.63)	168 (4.41)	410 (9.72)	816 (17.45)	<0.001[a]

Abbreviations: BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein; PHQ-9 = Patient Health Questionnaire-9; HIV = human immunodeficiency virus; *SD* = standard deviation.
Categorical characteristics reported as unweighted frequency and weighted percent.
Continuous characteristics reported as weighted mean and standard deviation.
[a] Denotes statistical significance ($p \leq 0.05$).

sensitivity analysis demonstrated similar findings (Supplementary Table S2).

3.3. Interaction of depressive symptoms and BMI on hs-CRP

There were no significant interactions found between depressive symptoms and overweight BMI after both partial and full adjustment for covariates (fully adjusted aCoef.Estm. = 0.04, 95% CI = −0.04, 0.13, $p = 0.278$), indicating lack of evidence for a difference in the depressive symptoms-hs-CRP association between participants with healthy and overweight BMIs (Table 3). The interaction between depressive symptoms and obese BMI followed the same pattern of results (Table 3). The sensitivity analysis demonstrated similar findings (Table S3).

4. Discussion

The current study investigated the independent associations of depressive symptoms and BMI with hs-CRP, as well as the moderating role of BMI on the depressive symptoms-hs-CRP association, using a nationally representative sample of US adults. As part of a sensitivity analysis, participants with hs-CRP >10.0 mg/L were excluded from analyses to account for potential acute infection or injury (Chae et al., 2022), (Pearson et al., 2003), (Mac Giollabhui et al., 2020). After full adjustment for covariates, there was a slight increase in hs-CRP levels with each one-point increase in depressive symptoms, though this failed to reach statistical significance in both the total study population and when individuals with potential acute infection or injury were excluded from the sample. Participants with an overweight or obese BMI had significantly higher mean levels of hs-CRP compared to those with a healthy BMI. There were no significant interactions between depressive symptoms and overweight or obese BMI, indicating a lack of difference in the depressive symptoms-hs-CRP association between participants in the healthy and overweight or obese ranges.

The results of this study suggest a nuanced examination of the role of inflammation in the pathophysiology of depressive symptoms. Meta-analytic evidence has demonstrated a positive association between depression and CRP which persisted after adjustment for BMI (Howren et al., 2009). Similar to the current study, research has shown that this association is insignificant when adjusting for socio-demographic and health-related covariates, among others, in addition to BMI (Duivis et al., 2013), (Zhang et al., 2018), (Millar et al., 2024). Our results remained unchanged when individuals who presented with potential temporarily elevated hs-CRP levels (i.e., perhaps due to acute infection or injury) were excluded from analyses. There has been debate as to whether to remove these individuals from analyses, as has been done in previous research (Chae et al., 2022), particularly when studying depression (Mac Giollabhui et al., 2020). Some prior research has not specified whether participants with hs-CRP >10.0 mg/L were excluded from analyses (Duivis et al., 2013), and including these individuals allows for greater generalizability of results (Mac Giollabhui et al., 2020). To continue this line of work and further delineate the relationship

Table 2
Main effects models for associations of depressive symptoms and BMI with hs-CRP.

Variables	Coef.Estm (95% CI)	*p*-value	aCoef.Estm. (95% CI)	*p*-value	aCoef.Estm.[†] (95% CI)	*p*-value
Depressive symptoms (PHQ-9 score)[a]	0.13 (0.07, 0.19)	<0.001[c]	0.11 (0.05, 0.17)	0.001[c]	0.01 (−0.05, 0.06)	0.754
BMI - overweight[b]	0.85 (0.52, 1.17)	<0.001[c]	0.93 (0.58, 1.27)	<0.001[c]	1.07 (0.61, 1.53)	<0.001[c]
BMI - obese[b]	3.38 (3.00, 3.76)	<0.001[c]	3.34 (2.94, 3.74)	<0.001[c]	3.51 (3.04, 3.98)	<0.001[c]

Abbreviations: aCoef.Estm. = partially adjusted coefficient estimate (age, sex, race, and education); aCoef.Estm.[†] = fully adjusted coefficient estimate (age, sex, race, education, cardiovascular disease, liver condition, chronic bronchitis, emphysema, hepatitis C, kidney condition, rheumatoid arthritis, human immunodeficiency virus, and diabetes); BMI = body mass index; CI = confidence interval; Coef.Estm. = coefficient estimate; PHQ-9 = Patient Health Questionnaire-9.
Outcome variable: hs-CRP (mg/L).
[a] All models adjusted for BMI.
[b] All models adjusted for depressive symptoms.
[c] Denotes statistical significance ($p \leq 0.05$).

Table 3
Models for interaction of depressive symptoms and BMI on hs-CRP.

Variables	Coef.Estm. (95% CI)	*p*-value	aCoef.Estm. (95% CI)	*p*-value	aCoef.Estm.† (95% CI)	*p*-value
Depressive symptoms (PHQ-9 score)[a]	0.10 (0.02, 0.18)	0.020[c]	0.09 (0.00, 0.18)	0.043[c]	−0.05 (−0.11, 0.01)	0.105
BMI – overweight[b]	0.91 (0.57, 1.26)	<0.001[c]	1.04 (0.67, 1.40)	<0.001[c]	0.94 (0.38, 1.51)	0.005[c]
BMI – obese[b]	3.14 (2.66, 3.62)	<0.001[c]	3.15 (2.68, 3.63)	<0.001[c]	3.20 (2.57, 3.84)	<0.001[c]
Depressive symptoms x BMI overweight	−0.03 (−0.11, 0.05)	0.518	−0.04 (−0.12, 0.04)	0.305	0.04 (−0.04, 0.13)	0.278
Depressive symptoms x BMI obese	0.07 (−0.07, 0.21)	0.286	0.06 (−0.09, 0.20)	0.428	0.11 (−0.01, 0.22)	0.066

Abbreviations: aCoef.Estm. = partially adjusted coefficient estimate (age, sex, race, and education); aCoef.Estm.† = fully adjusted coefficient estimate (age, sex, race, education, cardiovascular disease, liver condition, chronic bronchitis, emphysema, hepatitis C, kidney condition, rheumatoid arthritis, human immunodeficiency virus, and diabetes); BMI = body mass index; CI = confidence interval; Coef.Estm. = coefficient estimate; PHQ-9 = Patient Health Questionnaire-9.
Outcome variable: hs-CRP (mg/L).
[a] All models adjusted for BMI.
[b] All models adjusted for depressive symptoms.
[c] Denotes statistical significance ($p \leq 0.05$).

between depressive symptoms and chronic inflammation, specifically, future studies may consider subsetting participants based on their hs-CRP levels (e.g., ≤3.0 mg/L, >3.0 mg/L to ≤10.0 mg/L, and >10.0 mg/L (Cho et al., 2021), (Zhang et al., 2018)). Nevertheless, evidence suggests that the depressive symptom-hs-CRP association is dependent on the covariates included in analyses (Figueroa-Hall et al., 2022). Importantly, causal pathways in the depressive symptom-inflammation relationship could not be established from the current study due to its cross-sectional nature. As such, it is possible that this relationship is bidirectional. Psychological stress has been proposed to increase proinflammatory cytokine activity, which signals the central nervous system and elicits depressive symptoms (Slavich and Irwin, 2014). On the contrary, pre-existing depression may increase stress reactivity, including cytokine changes (Maydych, 2019). In fact, there is evidence for positive associations between CRP levels and future depressive symptoms, as well as between depressive symptoms and future CRP levels (Valkanova et al., 2013), (Mac Giollabhui et al., 2021).

Similar to depressive symptoms, existing research suggests that overweight and obese BMI are associated with CRP (Choi et al., 2013). A prior investigation reported that the association between BMI values in the obese range and CRP is independent of depressive symptoms (Dixon et al., 2008). Our results revealed that the positive association between BMI and inflammation persists after adjustment for depressive symptoms not only in obese, but also in overweight BMI, when BMI values are categorized based on the established cut-offs (Centers for Disease Control and Prevention). Though the directionality of this relationship could not be confirmed by our analyses, research suggests that inflammation may be a consequence rather than a predictor of weight gain (van Zuydam et al., 2018), (Tuomisto et al., 2019). In fact, abdominal adiposity, a strong correlate of BMI (Pasanta et al., 2021), contributes to metabolic abnormalities, and causes cytokines to be released (Brooks et al., 2010). In line with this, weight loss has been shown to decrease inflammation in obesity (Capuron et al., 2017).

Similar to prior research using cross-sectional data from a nationally representative sample of German adults (Chae et al., 2022), this study suggests that BMI does not moderate the relationship between depressive symptoms and hs-CRP. While the previous German study demonstrated that, among participants with depressive symptoms, those with an obese BMI had higher levels of hs-CRP than participants with a non-obese BMI, the authors suggested that an additive effect of depressive symptoms and obese BMI was lacking, potentially due to a ceiling effect (Chae et al., 2022). Other research has likewise demonstrated that, in participants with depression, the odds of having hs-CRP ≥3 mg/L were of greater magnitude in participants with a BMI ≥25 kg/m^2 than in those with a healthy BMI, although the authors did not conduct statistical comparisons across groups (McLaughlin et al., 2021). Furthermore, while Cho et al. (2021) found that the depressive symptoms-hs-CRP association was strongest in individuals with an obese BMI, the authors did not test the interaction between depressive symptoms and BMI. In the present investigation, the absence of a moderating effect of BMI on the depressive symptoms-hs-CRP association may be explained by "collider" bias, which occurs when two variables (i.e., an exposure and outcome) are related to a third variable which is controlled for (e.g., by stratification or inclusion as a covariate) in analyses (Holmberg and Andersen, 2022). BMI is associated with depressive symptoms (Tassone et al., 2023) and hs-CRP (as demonstrated by the current study) and may act as a collider variable, thus skewing their association.

4.1. Strengths and limitations

This study is strengthened by the use of a nationally representative sample, removal of participants with potential acute infection or injury in the sensitivity analysis, and the objective measurement of BMI which was used to distinctly group participants. However, it is not without limitations. Due to constraints of the NHANES dataset, measurement of depressive symptoms was collected through self-report, rather than clinical judgment, subjecting responses to recall or social desirability bias. Moreover, despite research showing that hs-CRP is elevated in treatment resistant, but not treatment responsive, depression (Chamberlain et al., 2019), the heterogeneity of depression in those with the disorder could not be accounted for. The cross-sectional survey data used in the present investigation are subject to non-response bias and limit our results to correlation. As such, findings from this study cannot be used to infer cause and effect.

4.2. Conclusions and future directions

This study suggests that BMI might not moderate the depressive symptoms-hs-CRP relationship. The results presented here should be replicated in larger samples, and further research is warranted to understand the mechanisms underlying this phenomenon. Longitudinal data could establish temporality in the independent associations of depressive symptoms and BMI with hs-CRP and their interaction. Future studies should consider whether participants who present with elevated inflammatory markers are experiencing infection or injury to further elucidate the relationship between depressive symptoms and acute versus chronic inflammation. Moreover, research should examine if a similar pattern of associations exists when using measures of abdominal adiposity, rather than BMI.

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CRediT authorship contribution statement

Vanessa K. Tassone: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Michelle Wu: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Shakila Meshkat:** Writing – review & editing. **Sophie F. Duffy:** Writing – review & editing. **Smia Baig:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Hyejung Jung:** Methodology, Supervision, Writing – review & editing. **Wendy Lou:** Supervision, Writing – review & editing. **Venkat Bhat:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100773.

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