Association between C reactive protein and depression in a population of healthy adults: the Cooper Center Longitudinal Study

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ABSTRACT

The relationship between depression and inflammation is currently a topic of much interest. Previous studies have produced mixed results regarding the association between depression and high-sensitivity C reactive protein (hs-CRP). The aim of this report was to determine the association between hs-CRP and depression in a large sample of healthy adults. This is a cross-sectional study of 26,638 healthy adults seen for preventive medical examinations between December 2000 and August 2018 at the Cooper Clinic in Dallas, Texas. Multivariable logistic regression was used to evaluate the association between hs-CRP levels and depressive symptoms as measured by the 10-item Center for Epidemiologic Studies Depression Scale. Covariates included race, age, education, smoking history, alcohol use, menopausal status, body mass index (BMI), and medication use. The Hs-CRP level demonstrated a weakly positive association with depressive symptoms (OR 1.06 per mg/L, 95% CI 1.03 to 1.09 for women; OR 1.05 per mg/L, 95% CI 1.02 to 1.09 for men) that became insignificant when controlling for BMI in women (OR 1.02 per mg/L, 95% CI 0.98 to 1.05) and men (OR 1.02 per mg/L, 95% CI 0.98 to 1.05). Adjusting for antidepressant and statin use did not affect the association between hs-CRP and depressive symptoms in women (OR 0.99 per mg/L, 95% CI 0.96 to 1.03) or men (OR 1.01 per mg/L, 95% CI 0.97 to 1.05). Levels of hs-CRP were not associated with depression independent of BMI in a predominantly white, male population of higher socioeconomic status. This finding suggests that associations between hs-CRP and depression may be explained by obesity, which warrants further investigation into shared pathways between obesity and depression.

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INTRODUCTION

Depression is a leading cause of disability in the world.[1] In particular, depression is associated with chronic illnesses characterized by ongoing inflammation, including cardiovascular disease, diabetes mellitus, and cancer.[2] There is a critical need to understand what modifiable risk factors, including inflammation, might exist for depressive symptomatology.

While the causative mechanism of depression is unclear, inflammation is hypothesized as a central contributor to depressive symptom development.[3] Inflammation is frequently studied using a non-specific marker of low-grade inflammation, C reactive protein (CRP), which is an acute phase reactant produced by the liver in response to inflammation.[4] While the association between CRP and depression is extensively studied, the literature in this area is mixed. Several clinical and population-based studies as well as two meta-analyses have reported a positive association between CRP and depression.[5–9] Yet other large-scale studies found no association when controlling for covariates including body mass index (BMI), medical comorbidities and medication use.[10–18] Thus, the nature and strength of the association between inflammation and depressive symptoms remain uncertain. By using a generally healthy population, this study seeks to clarify the relationship between high-sensitivity CRP (hs-CRP) and depressive symptoms in the largest cross-sectional analysis to date.

METHODS

Population

Data were extracted from the Cooper Center Longitudinal Study, an observational study of generally healthy adults seen at the Cooper Clinic in Dallas, Texas for preventive medical examinations. The cohort consists of predominantly non-Hispanic white, middle-aged, well-educated adults of middle to high socioeconomic status.

The starting sample included 34,794 subjects who had preventive medical examinations including hs-CRP and depressive symptoms between December 2000 and August 2018. Men and women not between 18 and 80 years old (n=243), had prevalent disease (diabetes, heart attack, stroke, or cancer) (n=2414), had a BMI $<18.5\,kg/m^2$ (n=364), a diagnostic criterion for being underweight and possibly malnourished,[19 20] or hs-CRP ≥10 mg/L (n=1142) as a marker for chronic or acute illnesses associated with elevated levels of inflammatory markers (ie, infections) were excluded.[19–21] Finally, we excluded 582 subjects with unknown education,

7274 with unknown alcohol use, and 300 with unknown height or weight, to arrive at a sample of 26,638 men and women.

Demographic data and covariates

Demographic information as well as education level (years), medical history, behavioral health, and medication use were obtained with a self-administered questionnaire. Race was divided into the following categories: white, black, Hispanic, and Other (which includes Asian and American Indian). Where data for race were not available, the data were imputed as white.

Medical history included history of hypertension, insomnia, anxiety, depression and treatment for a nervous disorder. Menopausal status for women was divided into premenopausal and postmenopausal; where data were not available for menopause history, data for women over age 50 were imputed as postmenopausal. Medication use included data for the following medications: statins, steroids, anxiolytics, and antidepressants. Smoking history was divided into two categories: current smoker and non-smoker. Self-reported alcohol use history was reported in drinks per week and divided into heavy drinking history, >7 drinks for women or >14 drinks for men, based on the guidelines from the National Institute on Drug Abuse for drinking levels associated with a low risk of developing alcohol use disorder.[22] Covariates were chosen based on evidence from previous studies that support the association between these factors and elevations in inflammatory markers.[5 6 15 23]

Height and weight were measured and BMI was calculated as weight in kilograms divided by height in meters squared. Trained laboratory technicians followed a protocol to obtain blood pressure and anthropometric data. The Cooper Clinic laboratory performed blood chemistry analysis on venous blood samples, including hs-CRP, glucose, triglycerides, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. Levels of hs-CRP were measured using high-sensitivity assays over the 18-year period following standard procedures on Siemens Dimension, Ortho Vitros, or Abbott Architect diagnostic systems.

Center for Epidemiologic Studies Depression Scale

The 10-item Center for Epidemiologic Studies Depression Scale (CES-D) was self-administered by subjects and used to determine the presence or absence of depressive symptoms. The CES-D includes question items to assess depressed affect, positive affect and somatic retardation. Subjects are asked to respond to each item by rating the frequency of the symptom during the previous week on a 4-point scale. Previous studies have shown that the CES-D is a reliable and valid measure of depressive symptom burden.[24 25] The CES-D score ranges from 0 to 30. Conventionally, a cut-off score of greater than 10 is associated with clinically significant depressive symptomatology at a single moment.[24] We divided CES-D scores into two categories based on this cut-off score.[26]

Statistical analysis

Data were analyzed separately by sex. Categorical characteristics of the study sample were summarized by counts and percentages, and continuous characteristics were summarized by means and SD. We controlled for important demographic, anthropometric, substance-related and medication-related confounders to elucidate the independent relationship between hs-CRP and depression.

Multiple logistic regression analysis was used to identify predictors of CES-D ≥10. Models fit to women included hs-CRP and were adjusted for age, race, education, menopausal status, current smoking, heavy drinking, and BMI. Models fit to men were adjusted for the same variables without menopausal status. Multiple logistic regression analysis in the subgroup with recorded medication use included further adjustment for use of antidepressants and/or statins. All analyses were programmed in SAS/STAT V.9.4.

Table 1 Demographic, behavioral and medication use characteristics of included subjects (N=26,638)

	Female	Male
Characteristics	**n (%)**	**n (%)**
n	8114 (100.0)	18,524 (100.0)
Race/ethnicity		
White	7539 (92.9)	17,359 (93.7)
Black	132 (1.6)	261 (1.4)
Hispanic	266 (3.3)	491 (2.7)
Other	177 (2.2)	413 (2.2)
Current smoker	393 (4.8)	2473 (13.4)
Heavy alcohol use	2019 (24.9)	2522 (13.6)
Postmenopausal	3415 (42.1)	
Statin use*	533 (9.9)	2873 (24.3)
Antidepressant use*	912 (17.0)	700 (5.9)
CES-D ≥10	1124 (13.9)	1503 (8.1)
	Female	**Male**
Characteristics	**Mean (SD)**	**Mean (SD)**
Age (years)	49.2 (10.6)	50.0 (10.1)
Education (years)	15.8 (2.3)	16.5 (2.3)
Body mass index (kg/m²)	24.5 (4.5)	27.8 (4.1)
hs-CRP (mg/L)	1.9 (2.1)	1.5 (1.6)
CES-D	4.8 (4.8)	3.7 (3.9)

*n=17,195 subjects have data on antidepressant and statin use.
CES-D, Center for Epidemiologic Studies Depression Scale; hs-CRP, high-sensitivity C reactive protein.

RESULTS

The sample studied consists of 26,638 adults ranging from 18 years to 80 years old with a mean (SD) age of 49.2 (10.6) for women and 50.0 (10.1) for men. The characteristics of the included subjects are shown in table 1. Overall, this sample was 69% male with high levels of education. The mean (SD) BMI was 24.5 (4.5) kg/m^2 for women and 27.8 (4.1) kg/m^2 for men. The mean (SD) hs-CRP was 1.9 (2.1) mg/L for women and 1.5 (1.6) mg/L for men. The mean CES-D (SD) score was 4.8 (4.8) and 3.7 (3.9) for women and men, respectively.

Table 2 displays the OR and 95% CI of CES-D ≥10 in women and men. In women, a higher hs-CRP level was significantly associated with depressive symptoms when controlled for age, education, race, menopausal status, and

Table 2 CES-D ≥10 OR in women (n=8114) and men (n=18,524)

Covariates	Adjusted for demographic and behavioral characteristics excluding BMI OR (95% CI)	Adjusted for demographic and behavioral characteristics including BMI OR (95% CI)
Women		
hs-CRP (per mg/L)	1.06* (1.03 to 1.09)	1.02 (0.98 to 1.05)
Age (per year)	0.97* (0.96 to 0.97)	0.96* (0.96 to 0.97)
Black (vs white)	0.70 (0.40 to 1.23)	0.60 (0.34 to 1.07)
Hispanic (vs white)	0.89 (0.62 to 1.27)	0.88 (0.61 to 1.26)
Other (vs white)	1.12 (0.74 to 1.70)	1.12 (0.74 to 1.70)
Education (per year)	0.93* (0.91 to 0.96)	0.94* (0.91 to 0.96)
Postmenopausal	1.32* (1.11 to 1.59)	1.32* (1.10 to 1.58)
Current smoker	2.42* (1.92 to 3.05)	2.38* (1.89 to 3.01)
Heavy drinker	1.15 (0.99 to 1.33)	1.19* (1.03 to 1.38)
BMI (per kg/m^2)		1.05* (1.03 to 1.06)
Men		
hs-CRP (per mg/L)	1.05* (1.02 to 1.09)	1.02 (0.98 to 1.05)
Age (per year)	0.96* (0.96 to 0.97)	0.96* (0.96 to 0.97)
Black (vs white)	0.97 (0.62 to 1.52)	0.91 (0.58 to 1.42)
Hispanic (vs white)	1.02 (0.74 to 1.41)	0.98 (0.71 to 1.35)
Other (vs white)	0.94 (0.65 to 1.35)	0.98 (0.68 to 1.41)
Education (per year)	0.91* (0.89 to 0.93)	0.92* (0.90 to 0.94)
Current smoker	1.42* (1.23 to 1.63)	1.40* (1.22 to 1.61)
Heavy drinker	1.20* (1.04 to 1.39)	1.21* (1.05 to 1.40)
BMI (per kg/m^2)		1.04* (1.03 to 1.05)*

*P<0.05.
BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; hs-CRP, high-sensitivity C reactive protein.

smoking and drinking history (OR 1.06 per mg/L, 95% CI 1.03 to 1.09). However, after controlling for BMI, this association was no longer statistically significant (OR 1.02 per mg/L, 95% CI 0.98 to 1.05). Similarly in men, a significant association between hs-CRP and depressive symptom when controlling for age, education, race, smoking status and drinking history (OR 1.05 per mg/L, 95% CI 1.02 to 1.09) became non-significant when controlling for BMI (OR 1.02 per mg/dL, 95% CI 0.98 to 1.05).

Among the subgroup of subjects (n=17,195, with 5374 women and 11,821 men) with data on antidepressant and statin use, antidepressant use was significantly associated with CES-D ≥10 in women (OR 2.93, 95% CI 2.46 to 3.49) and men (OR 3.77, 95% CI 3.11 to 4.58). We also found that in women (OR 0.74, 95% CI 0.55 to 1.00) and men (OR 0.80, 95% CI 0.67 to 0.96), using statins was associated with a significantly lower odds of CES-D ≥10. However, adjusting for use of antidepressants and statins did not affect the association between hs-CRP and CES-D ≥10 in women (OR 0.99, 95% CI 0.96 to 1.03) or men (OR 1.01, 95% CI 0.97 to 1.05).

DISCUSSION

In the largest study to date, we found hs-CRP was not associated with depression among generally healthy adults after controlling for BMI. Our findings are consistent with prior population-based studies that found no significant association between CRP and depression independent of BMI.[12 15] Our findings also align with other studies that found no association between CRP and depression independent of other covariates related to depression, including antidepressant use and chronic illness.[10 11 13 16 27]

An association between obesity and depression has long been established,[28 29] but relationships between obesity, inflammation, and depression are less well defined. Shelton *et al*[12] found an association between obesity and depression mediated by elevations in inflammatory markers; however, only interleukin (IL)-6 was elevated, whereas tumor necrosis factor (TNF)-alpha and CRP were not. In the current study with a healthy adult population, after adjustment for BMI, CRP was not associated with depression. Based on the findings of Shelton *et al*,[12] it may be that other inflammatory markers besides CRP predominate in the pathophysiologic pathway.[30]

The findings of this analysis warrant further studies to evaluate alternative mechanisms in the pathophysiology of depression, with attention to those that may also contribute to increased BMI. One potential pathway is the hypothalamic pituitary adrenal axis, the dysregulation of which has been posited as a shared mechanism in depression and obesity.[31]

We must also consider the different features of melancholic, psychotic and atypical subtypes of depression in addition to differences in depressive symptoms, which may be somatic or affective. Inflammation may explain particular subtypes and symptoms of depression better than others, and previous studies have found a greater association between CRP and somatic symptoms of depression than with melancholic depression.[3 32–35]

The limitations of this study include the homogeneity of the study population with respect to a cohort that is 69% male, well educated and with middle to high socioeconomic status. Homogeneity in a cohort of this size, while potentially increasing the internal validity of the findings, may decrease their generalizability. Further limitations apply to measures of inflammation and obesity as well as exclusion criteria. We only measured obesity by BMI, which has limited ability to assess body fat distribution and to distinguish between lean body mass and fat body mass. Several studies have shown that measures of central obesity better predict visceral adiposity that is more detrimental to overall health and particularly associated with depression; however, BMI is highly correlated with this measure.[31 36] Another limitation is the sole use of hs-CRP to measure inflammation. Further, while some studies have looked at the role of other inflammatory markers, such as IL-6, IL-2, and TNF-alpha, in depression, CRP has been the most reproducible and widely used marker of inflammation in several studies of chronic disease.[5 6]

The cross-sectional nature of our study is limited to a one-time measure of CRP that may differ from a longitudinal analysis of CRP measures over time. However, the protocol used to measure and quantify CRP provides consistent quality of measurement free from errors attributable to differences in collection method, time and fasting duration prior to collection. Finally, the gold standard of evaluation for depression uses the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for

major depressive disorder, whereas the CES-D is a one-time screening tool for depressive symptoms that is not used for the diagnosis of depressive symptoms, which may not in all individuals correlate with depression. However, the validity and reproducibility of the CES-D in other studies suggest a strong association between a high CES-D score and clinically significant symptoms of depression in racially diverse populations.[25] In addition, CES-D-10 does not allow differentiation among the various types of depression.

The strengths of this study include a large sample size, validated assessment of depressive symptoms, inclusion of a broad age range from 18 to 80, and control for several demographic, psychosocial, substance, and medication-related covariates. Furthermore, the exclusion of patients with proinflammatory, chronic medical conditions and with hs-CRP >10 mg/L strengthens an analysis of the impact of low-grade inflammation on depressive symptoms independent of chronic disease and acute inflammation.

In conclusion, we found no significant association between hs-CRP and depressive symptoms independent of BMI. This study supports continued research to explore alternative pathophysiologic mechanisms of depression with attention toward a shared pathway underlying obesity and depression. Future studies are needed to evaluate the association between inflammatory markers, metabolic factors and immune regulators with depression, with consideration for the heterogeneity of depression as a disease and in the setting of a diverse base population more representative of the 'real world' regarding racial and socioeconomic distributions.

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