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Race/ethnicity moderates the relationship between depressive symptom severity and C-reactive protein: 2005–2010 NHANES data

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ABSTRACT

Because few studies have examined depression facets or potential moderators of the depression–inflammation relationship, our aims were to determine whether particular depressive symptom clusters are more strongly associated with C-reactive protein (CRP) levels and whether race/ethnicity moderates these relationships. We examined data from 10,149 adults representative of the U.S. population (4858 non-Hispanic White, 1978 non-Hispanic Black, 2260 Mexican American, 1053 Other Hispanic) who participated in the cross-sectional National Health and Nutrition Examination Survey between 2005 and 2010. Depressive symptoms were assessed by the Patient Health Questionnaire-9, and high-sensitivity serum CRP was quantified by latex-enhanced nephelometry. Total ($p < .001$), somatic ($p < .001$), and nonsomatic ($p = .001$) depressive symptoms were each positively related to serum CRP in individual models. However, in the simultaneous model that included both symptom clusters, somatic symptoms ($p < .001$), but not nonsomatic symptoms ($p = .98$), remained associated with serum CRP. Evidence of moderation by race/ethnicity was also observed, as six of the nine depressive symptoms × race/ethnicity interactions were significant ($ps < .05$). Among non-Hispanic Whites, the pattern of results was identical to the full sample; only somatic symptoms ($p < .001$) remained related to serum CRP in the simultaneous model. No relationships between total, somatic, or nonsomatic symptoms and serum CRP were observed among the non-Hispanic Black, Mexican American, or Other Hispanic groups. Our findings indicate that the link between depressive symptoms and systemic inflammation may be due to the somatic symptoms of sleep disturbance, fatigue, appetite changes, and psychomotor retardation/agitation and may be strongest among non-Hispanic Whites.

1. Introduction

Considerable evidence suggests that depression is an independent risk factor for atherosclerotic cardiovascular disease (CVD), including coronary artery disease and cerebrovascular disease (Van der Kooy et al., 2007). The longitudinal relationship between depression and incident CVD is consistent, as it has been observed in both genders and in various age and racial/ethnic groups (Rosengren et al., 2004; Van der Kooy et al., 2007). Because depression is a multidimensional construct or disorder composed of affective, cognitive, behavioral, and somatic symptoms (Davidson et al., 2005), recent investigations have compared the relative importance of these symptom clusters in predicting CVD risk. Findings of these studies have been contradictory; some investigators have reported that the somatic symptoms are stronger predictors of CVD risk markers or outcomes (Deverts et al., 2010; Stewart et al., 2007, 2009), whereas others have observed similar results for the affective and cognitive symptoms (Everson et al., 1996; Kubzansky et al., 2001; Matthews et al., 2004; Stewart et al., 2012). Consequently, whether or not certain depressive symptoms clusters are more cardiotoxic than others remains an open question.

Systemic inflammation is one mechanism that might explain how depression promotes the development of CVD (Kop and Gottdiener, 2005). A recent meta-analysis revealed that various inflammatory markers – i.e., the proinflammatory cytokines, interleukin (IL)-1 and IL-6, and the acute phase reactant, C-reactive protein (CRP) – are upregulated in individuals with depressive disorders or elevated symptoms, although substantial heterogeneity was observed across studies (Howren et al., 2009). In addition, some investigations (Boyle et al., 2007; Stewart et al., 2009), but not all (Gimeno et al., 2009; Kiecolt-Glaser et al., 2003), have found

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that depression predicts increases in inflammatory marker levels over periods of up to 10 years. Notably, systemic inflammation is thought to play a role in all phases of atherosclerosis (Epstein and Ross, 1999), and several of the inflammatory markers elevated in depression, such as CRP, are predictive of incident CVD after adjustment for conventional cardiovascular risk factors (Kaptoge et al., 2012).

Despite the substantial literature on the depression–inflammation relationship, only four studies have examined whether the strength of this association varies across depressive symptom clusters. In a sample of 263 healthy, older adults most of whom were non-Hispanic White, we found that the somatic-vegetative symptoms of depression, but not cognitive-affective symptoms, predicted increases in IL-6 over six years (Stewart et al., 2009). Neither symptom cluster, however, predicted 6-year change in CRP. In a sample of 2544 healthy, middle-aged adults over 40% of whom were non-Hispanic Black, Deverts et al. (2010) observed that race moderated the prospective association between depressive symptoms and CRP. Among non-Hispanic Blacks, the somatic and positive affect subscales of the depression measure, but not depressed affect and interpersonal problems subscales, were independent predictors of 5-year increases in CRP. In contrast, none of the symptom clusters predicted change in CRP among non-Hispanic Whites. In a population-based sample of 5000 adults aged 35–74 years, Michal and colleagues (2013) found that only somatic depressive symptoms were cross-sectionally associated with various inflammatory markers, including CRP, in age- and sex-adjusted analyses. These relationships, however, did not persist after further adjustment for traditional CVD risk factors. Finally, Duivis et al. (2013) recently reported that, after adjustment for demographic and health factors, the somatic but not the cognitive symptoms were positively related to CRP, IL-6, and tumor necrosis factor-α levels in 2861 Dutch community members aged 18–65 years. Collectively, the available results suggest that the somatic symptoms may be more strongly related to systemic inflammation than other depressive symptom clusters; however, the small number of studies still renders this a tenuous conclusion. In addition, the intriguing findings of Deverts et al. (2010) highlight the need for additional studies examining race/ethnicity as a potential moderator of the depression–inflammation relationship.

Accordingly, the aims of the present study were (1) to determine whether particular depressive symptom clusters are more strongly associated with serum CRP, a nonspecific marker of systemic inflammation predictive of incident CVD (Pearson et al., 2003), and (2) to test whether race/ethnicity is a moderator of the depression–CRP relationship. To achieve these aims, we examined data from a large sample of adults, representative of the U.S. population, who participated in cross-sectional National Health and Nutrition Examination Survey (NHANES) between 2005 and 2010. These survey years provided a good opportunity to accomplish our aims because most of the respondents completed a multidimensional measure of depressive symptoms and underwent a blood draw to quantify high-sensitivity serum CRP. Furthermore, the 2005–2010 sample consists of large numbers of individuals of African American and Latino descent.

2. Methods

2.1. Study design and sample

We examined cross-sectional data from the 2005–2010 NHANES survey years. These data were collected by the National Center for Health Statistics of the Centers for Disease Control and Prevention from a nationally representative sample of civilian, non-institutionalized adults and children to assess the health and nutritional status of the U.S. population. Detailed descriptions of the survey design (a stratified, multistage, probability sample) and procedures are available at the study website (www.cdc.gov/nchs/nhanes.htm). Briefly, approximately 5000 people were recruited each survey year, and non-Hispanic Blacks and Hispanics were among the groups oversampled to ensure accurate estimates. Individuals who were selected and agreed to participate completed a computer-assisted interview conducted by trained personnel in their homes. Additional interviews (including the depressive symptoms assessment) and all examinations (including the blood draw) were conducted at Mobile Examination Centers (MEC) after the home interview. This archival study was approved by the institutional review board at Indiana University-Purdue University Indianapolis.

From the total sample for the 2005–2010 survey years ($N = 31,034$), we selected all respondents aged 18 years and older ($n = 18,318$), of whom 15,136 had complete data for CRP and answered eight or more of the nine depression items. We then excluded 3397 adults who reported a history of one or more of the following conditions due to their likely influence on CRP levels: cardiovascular disease (coronary heart disease, angina, myocardial infarction, stroke, or congestive heart failure) (Casas et al., 2008; Pearson et al., 2003), chronic bronchitis (Gan et al., 2004), emphysema (Omori et al., 2009), rheumatoid arthritis (Sokka and Pincus, 2009), human immunodeficiency virus (Tien et al., 2010), hepatitis C (Kessel et al., 2007), liver conditions (Tilg et al., 1992), and kidney conditions (Abraham et al., 2009). Next, we excluded 1043 adults with CRP levels $\geqslant$10 mg/L, as values above this cut point are likely due to acute infection, trauma, or another non-cardiovascular cause (Pearson et al., 2003). Finally, we excluded the 547 respondents in the Other Race group (see Section 2.2.3 below). Thus, our final sample consisted of 10,149 adults (see Table 1 for characteristics).

2.2. Measures and procedures

2.2.1. Depressive symptoms

The Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001) was administered during the MEC examination to assess depressive symptom severity during the past two weeks. Using a 4-point scale (0 = not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day), respondents indicated the frequency with which they had experienced the following nine symptoms of major depressive disorder: (1) anhedonia, (2) depressed mood, (3) sleep disturbance, (4) fatigue, (5) appetite changes, (6) low self-esteem, (7) concentration problems, (8) psychomotor retardation/agitation, and (9) suicidal ideation. Total scores range from 0 to 27, with scores $\geqslant$10 being indicative of clinically significant depressive symptoms (Kroenke and Spitzer, 2002). The PHQ-9 has been shown to be a reliable and valid questionnaire in community samples, as indicated by its high internal consistency and good sensitivity and specificity for identifying cases of major depressive disorder (Kroenke and Spitzer, 2002; Kroenke et al., 2001; Manea et al., 2012; Patten and Schopflocher, 2009; Wittkampf et al., 2007).

For 70 respondents missing one PHQ-9 item, we imputed the missing value using the mean of the other eight items for that individual. We then calculated PHQ-9 Total (sum of all items) and two subscale scores. The PHQ-9 Somatic subscale score was computed by summing the sleep disturbance, fatigue, appetite changes, and psychomotor retardation/agitation items (Items 3, 4, 5, and 8), and the PHQ-9 Nonsomatic subscale score was computed by summing the remaining five items (Items 1, 2, 6, 7, and 9). Although prior studies have reported support for a one-factor model with all nine items loading on a single depression factor (Cameron et al., 2011; Huang et al., 2006), recent confirmatory factor analyses have found that a two-factor model provided a better fit to the

Table 1
Characteristics of respondents.

	Full Sample (N = 10,149)	Non-Hispanic White (n = 4858)	Non-Hispanic Black (n = 1978)	Mexican American (n = 2260)	Other Hispanic (n = 1053)
Age, years	44.3 (18.4)	48.2 (18.5)	42.4 (17.9)	39.7 (17.1)	39.7 (17.6)
Female, %	49.2	49.4	47.7	48.1	53.8
Education level, %					
Less than 9th Grade	10.8	3.4	3.4	29.9	18.0
9–12th Grade (no diploma)	17.2	11.3	21.0	23.8	23.2
High School Graduate/GED	24.3	25.3	27.1	21.2	21.4
Some College or Associates Degree	27.8	30.6	32.7	18.5	25.1
College Graduate or Above	19.9	29.4	15.8	6.6	12.3
Diabetes, %	7.3	5.8	10.5	7.6	7.8
Antihypertensive medication use	17.7	20.5	22.3	10.5	11.8
Lipid-lowering medication use	11.8	14.5	10.6	8.3	9.5
Oral contraceptive use	3.7	4.6	3.1	2.6	3.0
Hormone replacement therapy use	1.4	2.1	0.9	0.6	0.7
Body mass index, kg/m^2	28.3 (5.9)	27.8 (5.9)	29.2 (6.7)	28.7 (5.3)	28.1 (5.3)
Current smoking, %	20.6	22.0	24.3	16.0	15.9
Alcohol group					
Abstain, %	29.0	24.8	34.7	33.6	30.8
Moderate use, %	62.8	65.5	58.5	59.2	64.5
Heavier use, %	8.2	9.7	6.7	7.2	4.7
PHQ-9 Total (possible range: 0–27)	2.7 (3.7)	2.6 (3.5)	2.7 (3.9)	2.8 (3.8)	3.1*† (3.9)
Somatic symptoms (possible range: 0–9)	1.7 (2.1)	1.7 (2.0)	1.6 (2.2)	1.6 (2.2)	1.8 (2.2)
Nonsomatic symptoms (possible range: 0–18)	1.1 (2.0)	1.0 (1.9)	1.1 (2.1)	1.1* (2.0)	1.3* (2.1)
High-sensitivity serum C-reactive protein, mg/L	2.3 (2.2)	2.2 (2.2)	2.6*‡ (2.4)	2.4*‡ (2.3)	2.2 (2.1)

Note. Continuous variables are presented as mean (standard deviation), and categorical variables are presented as percentage. Only significant differences in Patient Health Questionnaire-9 (PHQ-9) scores are flagged.
* Significantly greater than non-Hispanic White group ($p < .05$).
† Significantly greater than non-Hispanic Black group ($p < .05$).
‡ Significantly greater than Other Hispanic group ($p < .05$).

data (Chilcot et al., 2013; Krause et al., 2008). Others have reported a slightly different two-factor model with Item 8 (psychomotor retardation/agitation) loading on the somatic factor (de Jonge et al., 2007). To facilitate comparisons between our investigation and prior studies, we computed our subscales scores based on the two-factor model reported by de Jonge and colleagues (2007), which is more commonly used in the depression–CVD literature.

2.2.2. C-reactive protein

Whole blood samples were collected from respondents who were asked to abstain from food, beverages (other than water), and certain over-the-counter medications for at least nine hours prior to their MEC examination. A questionnaire was administered to confirm fasting status at the start of this visit. Venipuncture was then performed using standard phlebotomy techniques by NHANES trained personnel. Serum specimens were frozen at −20 °C until the time of assay at University of Washington Medical Center. Serum CRP was quantified by latex-enhanced nephelometry using a Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics Inc., Somerville, NJ). Monoclonal antibodies were used to detect serum CRP, and N Rheumatology Standard SL was used as the standard measurement, given that this material is an internationally recognized source of purified human C-reactive protein. This high-sensitivity assay allowed for a minimum detection of 0.02 mg/dL and does not have a maximum reportable limit. Further details can be found on the website (http://www.cdc.gov/nchs/data/nhanes). Because the skewness (1.36) and kurtosis (1.21) values for the CRP variable were within acceptable ranges (Kline, 2010), it was not necessary to perform any transformations.

2.2.3. Other factors

The following variables were included as covariates in the statistical models: age (years), sex (0 = male, 1 = female), race/ethnicity (see below), education level (see Table 1), diabetes (0 = no, 1 = yes), antihypertensive medication use (0 = no, 1 = yes), lipid-lowering medication use (0 = no, 1 = yes), oral contraceptive use (0 = no, 1 = yes), and hormone replacement therapy use (0 = no, 1 = yes). The primary NHANES race/ethnicity variable has five levels: non-Hispanic White, non-Hispanic Black, Mexican American, Other Hispanic, and Other Race including Multi-Racial. For this report, we excluded the 547 respondents in the Other Race group because it was much smaller and heterogeneous than the other racial/ethnic groups, rending interpretation difficult. Of note, NHANES recommends not combining the Mexican American and Other Hispanic groups (http://www.cdc.gov/nchs/data/nhanes/analyticnote_2007-2010.pdf). We then created three race/ethnicity dummy variables comparing the non-Hispanic White group to the non-Hispanic Black group (d1), the Mexican American group (d2), and the Other Hispanic group (d3). Respondents reported the highest level of education completed during the household interview. For respondents aged 20+ years, the categories were less than 9th grade, 9–12th grade with no diploma, high school diploma or GED, some college or associates degree, and college graduate or above, whereas respondents aged 18–19 years were asked to indicate the highest grade level from 1st to 12th grade, if they had graduated high school or had a GED, and if they completed some college. We reclassified the education level of respondents aged 18–19 years using the categories for respondents 20+ years. During the household interview, respondents reported if they had ever been diagnosed with diabetes by a health professional. Respondents were also asked about their current use of antihypertensive and lipid-lowering medication during the Blood Pressure and Cholesterol interview in the home, and women were asked about their current use of oral contraceptives and hormone replacement therapy (pills and patches) during the Reproductive Health interview at the MEC (men were coded as 0).

The following variables were examined as potential mediators/confounders of observed depressive symptoms-CRP relationships: body mass index (BMI; kg/m^2), current smoking (0 = no, 1 = yes), and alcohol group (see below). BMI was computed from height

and weight measurements obtained during the physical examination at the MEC. The smoking assessment for respondents aged 18–19 years (MEC) was not identical to that for respondents aged 20+ years (household interview). For respondents aged 20+ years, we classified those who reported smoking at least 100 cigarettes during their lifetime and indicated that they now smoke cigarettes every day or some days as current smokers. For respondents aged 18–19 years, we classified those who reported smoking 15 or more days in the last 30 days as current smokers. To create the alcohol groups, we used data obtained during the Alcohol Use interview at the MEC. First, we calculated the number of days drinking alcohol during the past year. This value was then multiplied by the average number of drinks consumed per drinking day during the past 12 months, yielding the total number of drinks consumed during the past year. Next, we divided this value by 365 to compute drinks per day during the past year. From this variable, we created three alcohol groups: abstainer (0 drinks/day), moderate user (men: 0.1–2.0 drinks/day, women: 0.1–1.0 drinks/day), and heavier user (men: >2.0 drinks/day, women: >1.0 drinks/day). Finally, we created two dummy variables comparing abstainers to moderate users and to heavier users.

2.3. Data analysis

One-way analyses of variance (ANOVAs) with Tukey's post hoc tests were performed to examine differences in PHQ-9 scores and high-sensitivity serum CRP among the racial/ethnic groups. We evaluated the internal consistencies of the depressive symptom measures (Cronbach α) and their interrelationships (Pearson correlations) in the full sample and each race/ethnicity group. To determine whether particular depressive symptom clusters were more strongly associated with CRP levels, we constructed two sets of linear regression models with serum CRP as the criterion variable using the full sample. In the first set (individual models), the PHQ-9 Total, Somatic, or Nonsomatic score was entered as the predictor variable into separate models containing age, sex, race/ethnicity, education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, and hormone replacement therapy use as covariates. In the second set (simultaneous model), the Somatic and Nonsomatic scores were entered into the same model containing the aforementioned covariates.

We then examined BMI, smoking, and alcohol group as potential mediators/confounders of any observed relationships. First, from our final sample of 10,149 adults, we excluded the 889 respondents with missing data on any of these three factors, leaving a mediation/confounder sample of 9260. Next, we reran the simultaneous model. Finally, we added BMI, smoking, and alcohol group (two dummy variables), one at a time, to the simultaneous model. These behavioral factors were not included in the initial set of covariates, as they are among the candidate mediators of the depression–inflammation relationship (Hamer et al., 2009; Miller and Blackwell, 2006; Miller et al., 2003) and adjusting for them from the outset could mask relationships of interest. In addition, because BMI (Luppino et al., 2010) and smoking (Korhonen et al., 2007) have been found to predict future depression, they could also be operating as confounders. To quantify the effect of BMI, smoking, and alcohol group on any observed relationships, percent change in the effect size was computed as $[(B_{mediator/confounder} - B_{simultaneous})/B_{simultaneous}] \times 100$, where $B_{mediator/confounder}$ is the unstandardized coefficient for the PHQ-9 score from the simultaneous model with the selected mediator/confounder, and $B_{simultaneous}$ is the unstandardized coefficient for the PHQ-9 score from the simultaneous model without the selected mediator/confounder.

To test whether race/ethnicity moderated the relationship between depressive symptoms and serum CRP, we first computed 9 cross-product interaction terms by multiplying the PHQ-9 Total, Somatic, and Nonsomatic (first converted to *z* scores) by each of the race/ethnicity dummy variables (d1, d2, and d3). The three PHQ-9 Total interaction terms were entered into a linear regression model, with serum CRP as the criterion variable, that also contained age, sex, d1, d2, d3, education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, and hormone replacement therapy use, and the PHQ-9 Total *z* score. Parallel models were constructed for the Somatic and Nonsomatic scores. Because evidence of moderation was observed, we reran all models after stratifying by race/ethnicity. Of note, we conducted exploratory analyses to test depressive symptoms × age (all $ps > .10$) and depressive symptoms × sex (all $ps > .55$) interactions, none of which were significant. We also tested nine depressive symptoms × sex × race/ethnicity interactions, only one of which (PHQ-9 nonsomatic score × sex × d2) was significant ($p = .015$). Because we did not have any *a priori* hypotheses about these interactions and the one significant result may reflect a type I error, we decided against probing and interpreting the lone three-way interaction.

All estimates from the linear regression models were weighted using NHANES sample weights, which account for the complex survey design, survey nonresponse, and post-stratification (CDC, 2005). Analyses utilizing sample weights provide estimates representative of the U.S. civilian noninstitutionalized population. We conducted our analyses with SAS statistical software (version 9.3) using the survey linear regression procedure.

3. Results

3.1. Descriptive statistics and correlations

The mean PHQ-9 Total score for the full sample and each race/ethnicity group (see Table 1) fell in the minimal depression range; however, 645 (6.4%) respondents had a score ($\geqslant 10$) indicative of clinically significant depressive symptoms (Kroenke et al., 2001). One-way ANOVAs revealed that the PHQ-9 Total score [F (3, 10,145) = 4.55, $p = .003$] and Nonsomatic score [F (3, 10,145) = 8.30, $p < .001$] differed across the racial/ethnic groups, with the Other Hispanic group having a higher Total mean than the non-Hispanic White group ($p = .002$) and the non-Hispanic Black group ($p = .044$) and with the Mexican American group ($p = .005$) and the Other Hispanic group ($p < .001$) having a higher Nonsomatic mean than the non-Hispanic White group. No racial/ethnic differences in the Somatic score were observed [F (3, 10,145) = 2.25, $p = .08$].

The mean high-sensitivity serum CRP for the full sample and each race/ethnicity group (see Table 1) fell in the average CVD risk category range of 1.0–3.0 mg/L (Pearson et al., 2003). A one-way ANOVA [F(3, 10,145) = 11.65, $p < .001$] also indicated that serum CRP differed across the groups, with the non-Hispanic Black group having a higher mean serum CRP than the non-Hispanic White group ($p < .001$) and the Other Hispanic group ($p < .001$) and with the Mexican American group having a higher serum CRP than the non-Hispanic White group ($p = .004$) and the Other Hispanic group ($p = .044$). It should be noted that, although statistically significant differences were detected, the absolute differences in PHQ-9 scores and CRP levels between the racial/ethnic groups were small and likely not meaningful.

The PHQ-9 Total and Nonsomatic scores had at least adequate internal consistency (Cronbach's $\alpha \geqslant .70$) in the full sample and each race/ethnicity group, but the Somatic score tended to fall just short of this cut point (see Table 2). As was expected, the Nonsomatic and Somatic scores were moderately correlated in the full sample and each race/ethnicity group.

Table 2
Internal consistencies of and correlations among the depressive symptom measures.

Measure	Full Sample (N = 10,149)		Non-Hispanic White (n = 4858)		Non-Hispanic Black (n = 1978)		Mexican American (n = 2260)		Other Hispanic (n = 1053)	
	α	Subscales r	α	Subscales r	α	Subscales r	α	Subscales r	α	Subscales r
PHQ-9 Total	0.82		0.81		0.84		0.82		0.82	
Somatic symptoms	0.67		0.65		0.71		0.70		0.67	
Nonsomatic symptoms	0.76	0.65	0.78	0.62	0.76	0.68	0.73	0.67	0.75	0.66

Note. All correlations between the PHQ-9 Somatic and Nonsomatic scores are significant ($p < .05$).

3.2. Association of depressive symptoms with C-reactive protein: full sample

As is shown in Table 3, results of the individual models for the full sample revealed that the PHQ-9 Total ($p < .001$, partial $r = .05$), Somatic ($p < .001$, partial $r = .06$), and Nonsomatic ($p = .001$, partial $r = .03$) scores were each positively associated with serum CRP after adjustment for demographic factors, diabetes, and medication use. These effect sizes (rs) fall in the small range (Cohen, 1988). In the simultaneous model which included both PHQ-9 subscale scores, the Somatic score ($p < .001$), but not the Nonsomatic score ($p = .98$), remained positively related to serum CRP. As an illustration of this effect, the percentage of respondents across the Somatic score tertiles with CRP levels in the high CVD risk category of >3.0 mg/L (Pearson et al., 2003) were 25.8%, 27.6%, and 32.0%, respectively.

To examine BMI, smoking, and alcohol group as potential mediators/confounders of the somatic symptoms-CRP association, we first reran the simultaneous model in the mediation/confounder sample ($n = 9260$), which yielded similar results (Somatic score: $B = .08$, $SEB = .02$, $p < .001$; Nonsomatic score: $B = .00$, $SEB = .02$, $p = .98$). Adjusting for BMI reduced the somatic symptoms effect size by 44.7% ($B = .05$, $SEB = .01$, $p = .001$); however, adjusting for smoking reduced this effect size by only 2.3% ($B = .08$, $SEB = .02$, $p < .001$), and adjusting for alcohol group (two dummy variables) reduced it by only 0.5% ($B = .08$, $SEB = .02$, $p < .001$). BMI ($B = .16$, $SEB = .00$, $p < .001$) and smoking ($B = .17$, $SEB = .06$, $p = .01$) were positively associated with serum CRP, whereas both alcohol group dummy variables (abstainers vs. moderate drinkers: $B = -.24$, $SEB = .07$, $p = .002$; abstainers vs. heavier drinkers: $B = -.24$, $SEB = .08$, $p = .004$) were negatively related to CRP.

3.3. Association of depressive symptoms with C-reactive protein: stratified by race/ethnicity

The model testing the PHQ-9 Total by race/ethnicity interaction terms revealed that the Total × d1 (non-Hispanic White vs. non-Hispanic Black) interaction ($B = -.20$, $SEB = .07$, $p = .005$) and the Total × d2 (non-Hispanic White vs. Mexican American) interaction ($B = -.18$, $SEB = .06$, $p = .004$) were significant. The Total × d3 (non-Hispanic White vs. Other Hispanic) interaction was not ($B = -.15$, $SEB = .09$, $p = .11$). As can be seen in Table 3, individual models stratified by race/ethnicity indicated that PHQ-9 Total was more strongly associated with serum CRP among non-Hispanic Whites ($p < .001$) than among non-Hispanic Blacks ($p = .68$) or Mexican Americans ($p = .30$).

The same pattern of results was observed for the Somatic and Nonsomatic score. The Somatic × d1 (non-Hispanic White vs.

Table 3
Linear regression analyses examining associations of depression symptoms with high-sensitivity serum C-reactive protein.

	Full Sample (N = 10,149)		Non-Hispanic White (n = 4,858)		Non-Hispanic Black (n = 1,978)		Mexican American (n = 2,260)		Other Hispanic (n = 1,053)	
	IND Models[a] *B* (*SEB*)	SIM Model[b] *B* (*SEB*)	IND Models[c] *B* (*SEB*)	SIM Model[d] *B* (*SEB*)	IND Models[c] *B* (*SEB*)	SIM Model[d] *B* (*SEB*)	IND Models[c] *B* (*SEB*)	SIM Model[d] *B* (*SEB*)	IND Models[c] *B* (*SEB*)	SIM Model[d] *B* (*SEB*)
PHQ-9 Total	.04* (.01)		.06*†‡ (.01)		.01 (.01)		.01 (.01)		.01 (.02)	
Somatic Symptoms	.08* (.01)	.08* (.01)	.11*†‡ (.02)	.10* (.02)	.02 (.03)	---	.04 (.02)	---	.00 (.03)	---
Nonsomatic Symptoms	.05* (.02)	.00 (.02)	.08*†‡ (.02)	.01 (.02)	-.01 (.03)	---	.00 (.02)	---	.02 (.03)	---

Note: Shaded cells signify significant associations ($p < .05$). IND = individual. SIM = simultaneous. B = unstandardized regression coefficient. *SEB* = standard error of B. PHQ-9 = Patient Health Questionnaire-9.
[a]Adjusted for age, sex, race/ethnicity (3 dummy variables), education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, and hormone replacement therapy use.
[b]Adjusted for age, sex, race/ethnicity (3 dummy variables), education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, hormone replacement therapy use, and the other PHQ-9 subscales score.
[c]Adjusted for age, sex, education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, and hormone replacement therapy use.
[d]Adjusted for age, sex, education level, diabetes, antihypertensive medication use, lipid-lowering medication use, oral contraceptive use, hormone replacement therapy use, and the other PHQ-9 subscales score.
*Significantly greater than zero ($p < .05$).
†Significantly greater than B for non-Hispanic Black group ($p < .05$).
‡Significantly greater than B for Mexican American group ($p < .05$).

non-Hispanic Black) interaction ($B = -.18$, $SEB = .07$, $p = .010$) and Somatic × d2 (non-Hispanic White vs. Mexican American) interaction ($B = -.15$, $SEB = .06$, $p = .011$), but not the Somatic × d3 (non-Hispanic White vs. Other Hispanic) interaction ($B = -.19$, $SEB = .10$, $p = .06$), were significant. The Somatic score was more strongly related to serum CRP among the non-Hispanic Whites ($p < .001$) than among non-Hispanic Blacks ($p = .33$) and Mexican Americans ($p = .09$; see Table 3). The Nonsomatic × d1 (non-Hispanic White vs. non-Hispanic Black) interaction ($B = -.17$, $SEB = .07$, $p = .018$) and Nonsomatic × d2 (non-Hispanic White vs. Mexican American) interaction ($B = -.16$, $SEB = .07$, $p = .017$) interactions were significant, although the Nonsomatic × d3 (non-Hispanic White vs. Other Hispanic) interaction was not ($B = -.06$, $SEB = .09$, $p = .52$). The Nonsomatic score was more strongly related to serum CRP among the non-Hispanic Whites ($p = .002$) than among non-Hispanic Blacks ($p = .86$) and Mexican Americans ($p = .99$; see Table 3). Because of the relatively smaller sample size of the Other Hispanic group, we had less statistical power to detect differences in the magnitude of the depressive symptoms-CRP relationships between the non-Hispanic White and Other Hispanic groups (i.e., interactions involving the d3 variable).

We constructed a simultaneous model for the non-Hispanic White group only because that was the racial/ethnic group in which we observed depressive symptom-CRP associations (see Table 3). Results of this model revealed that the Somatic score ($p < .001$), but not the Nonsomatic score ($p = .66$), remained positively related to serum CRP. To illustrate this effect among non-Hispanic Whites, the percentage of respondents across the Somatic score tertiles with CRP levels in the high CVD risk category of >3.0 mg/L (Pearson et al., 2003) were 23.2%, 24.9%, and 31.7%, respectively.

In models examining potential mediators/confounders among non-Hispanic Whites ($n = 4719$ after excluding respondents with missing mediator/confounder data), we found that adjusting for BMI reduced the somatic symptoms effect size by 37.1% ($B = .06$, $SEB = .02$, $p < .001$). In contrast, adjusting for smoking reduced this effect size by only 2.1% ($B = .10$, $SEB = .02$, $p < .001$), and adjusting for alcohol group (two dummy variables) reduced it by only 1.2% ($B = .10$, $SEB = .02$, $p < .001$). BMI ($B = .16$, $SEB = .01$, $p < .001$), but not smoking ($B = .17$, $SEB = .08$, $p = .052$), was positively associated with serum CRP. Both alcohol group dummy variables (abstainers vs. moderate drinkers: $B = -.24$, $SEB = .10$, $p = .018$; abstainers vs. heavier drinkers: $B = -.32$, $SEB = .10$, $p = .003$) were negatively related to CRP.

4. Discussion

In a large sample of adults representative of the U.S. population, we found that the cross-sectional relationship between depressive symptom severity and high-sensitivity serum CRP was largely due to the somatic symptoms of depression. The PHQ-9 Somatic and Nonsomatic scores were both positively related to CRP levels in individual models, with effect sizes falling in the small range. Only the somatic score, however, remained associated in the simultaneous model that included both symptom clusters. This pattern of results indicates that the unique variance of the somatic subscale and the shared variance of both PHQ-9 subscales were associated with serum CRP, but the unique variance of the nonsomatic subscale was not. We also observed evidence of moderation by race/ethnicity, as six of the nine PHQ-9 × race/ethnicity interactions were significant. Total depressive symptoms, as well as somatic and nonsomatic symptoms, were more strongly associated with serum CRP among non-Hispanic Whites than among non-Hispanic Blacks and Mexican Americans. In the non-Hispanic White group, the pattern of results was identical to that of the full sample. Conversely, no relationships between total, somatic, or nonsomatic symptoms and CRP levels were observed in the non-Hispanic Black group, Mexican American group, or Other Hispanic group.

Altogether, our results indicate that the link between depressive symptom severity and systemic inflammation may be due to the somatic symptoms of sleep disturbance, fatigue, appetite changes, and psychomotor retardation/agitation and may be strongest among non-Hispanic Whites. In addition, our findings suggest that (a) the heterogeneity in depression–inflammation effect sizes observed across studies (Howren et al., 2009) may partially stem from the varying percentages of racial/ethnic minorities and that (b) the somatic symptoms may be more atherogenic than the nonsomatic symptoms (particularly among non-Hispanic Whites) because of their stronger association with inflammatory markers predictive of CVD. Regarding point (b), it is also worth noting that subclinical atherosclerosis and the accompanying inflammation could contribute to the development of somatic depressive symptoms (see below).

On one level, the present findings are in line with past results suggesting that the somatic symptoms are more strongly related to inflammatory markers than the other depressive symptom clusters (Deverts et al., 2010; Duivis et al., 2013; Michal et al., 2013; Stewart et al., 2009). On another level, our findings conflict with those of Deverts and colleagues (2010). Those researchers reported that the somatic and positive affect clusters independently predicted 5-year changes in CRP among non-Hispanic Blacks, but no depressive symptom-CRP relationships were observed among non-Hispanic Whites.

We considered several possible explanations for this discrepancy. First, the associations observed in the prospective study by Deverts and colleagues reflect the depression-to-future-inflammation relationship only, whereas our cross-sectional associations likely reflect the bidirectional influences of depressive symptoms on systemic inflammation and vice versa (see below). This could have produced larger, statistically significant effect sizes among non-Hispanic Whites in our study, although it does not explain the absence of associations in the non-Hispanic Black group. Second, both studies utilized depressive symptom scales that have been shown to be reliable and valid in various racial/ethnic groups (Callahan and Wolinsky, 1994; Huang et al., 2006) and assessed the same inflammatory marker using similar methods. However, as was noted Deverts and colleagues (2010), the depressive symptom scores of non-Hispanic Whites in their sample were lower and exhibited less variability than those of non-Hispanic Blacks. Thus, restricted range may have also contributed to the lack of a depressive symptoms-CRP association among non-Hispanic Whites in that study. In contrast, the means and standard deviations for the PHQ-9 variables were comparable across racial/ethnic groups in our study. Third, it is possible that we detected associations in the non-Hispanic White group only because the effect size is small and this group is approximately 2–4 times larger than the Other Race/ethnicity groups. However, low statistical power is likely not a major concern, given that all groups consisted of 1000+ adults and the regression coefficients in the non-Hispanic Black, Mexican American, and Other Hispanic groups were numerically close to zero. Furthermore, our non-Hispanic Black group was larger than that of Deverts et al. (2010), and we did have the power to detect significant differences in the regression coefficients between the racial/ethnic groups. Given the small number of investigations, the conflicting pattern of results, and the speculative nature of these explanations, there is a need to examine race/ethnicity as a moderator in future studies of the depression–inflammation relationship.

There are a number of potential explanations for why the somatic symptoms of depression, but not the nonsomatic

symptoms, were associated with serum CRP in our study. First, the somatic cluster may have stronger links with the putative mechanisms underlying the depression–inflammation relationship, such as autonomic dysfunction, hypothalamic–pituitary–adrenal axis (HPA) hyperactivity, and obesity (Kop and Gottdiener, 2005; Miller et al., 2003). Consistent with this notion, the somatic symptoms have been found to have stronger associations with indices of autonomic dysfunction (lower heart rate variability; de Jonge et al., 2007) and abdominal obesity (higher waist-to-hip ratio; Wiltink et al., 2013) than the cognitive symptoms.

Second, the somatic symptoms may be more likely to be a consequence of systemic inflammation than the nonsomatic symptoms. Increasing evidence supports the role of inflammation in the etiology of at least some cases of depression (Dantzer, 2004; Raison et al., 2006). For instance, administration of lipopolysaccharide or proinflammatory cytokines in rodents induces sickness behavior, which is a syndrome characterized by affective, cognitive, and behavioral changes strikingly similar to depressive symptoms (Dantzer et al., 2008). Research on humans complements these animal findings, as most hepatitis C and cancer patients undergoing interferon-α treatment (which produces elevations in proinflammatory cytokines) experience physical symptoms similar to the somatic depressive symptoms, including sleep disturbance, fatigue, and appetite changes (Dantzer et al., 2008). In contrast, only about half of these patients experience the affective and cognitive symptoms (Dantzer et al., 2008). Peripherally released proinflammatory cytokines can access the brain via several routes, including leaky regions in the blood–brain barrier, active cytokine transport molecules, and afferent fibers of the vagus nerve (Raison et al., 2006). Once these cytokine signals reach the brain, they can cause hyperactivity in the hypothalamic–pituitary–adrenal axis and alterations in serotonergic, norepinephrinergic, and dopaminergic function (Raison et al., 2006), which are the major neurobiological systems involved in depression (Hasler et al., 2004). Therefore, it is plausible that elevations in inflammatory markers preceded and contributed to increases in the somatic depressive symptoms in our study.

Third, confounders that predict both subsequent depression and inflammatory marker levels may have stronger relationships with the somatic symptoms. Candidate third factors include obesity, smoking, and genetic variants related to serotonergic function and systemic inflammation (Korhonen et al., 2007; Luppino et al., 2010; McCaffery et al., 2006). Our results provide indirect support for BMI, but not for smoking or alcohol use, as a partial mediator or confounder. BMI accounted for 45% (full sample) and 37% (non-Hispanic Whites) of the somatic symptoms-CRP relationship; however, smoking and alcohol group explained less than 3% each. Due to the cross-sectional nature of this study, however, we cannot determine whether BMI is operating as a mediator or confounder. Fourth, it is possible that an elevated somatic symptom score is a marker of greater depression severity or a positive history of a depressive disorder (Carney and Freedland, 2012), given that residual symptoms that persist following depression treatment are often somatic in nature (Conradi et al., 2011; Hybels et al., 2005). Meta-analytic evidence suggests that the association of depressive disorders with CRP is stronger than the association of subsyndromal depressive symptoms with CRP (Howren et al., 2009).

Among our study's strengths are a representative sample with large numbers of non-Hispanic Black and Mexican American adults, the use of a multidimensional depressive symptoms measure, and the assessment of a stable inflammatory marker (Pearson et al., 2003). Our investigation, however, also has limitations. As is mentioned above, the cross-sectional nature of the NHANES data precluded us from establishing the directionality of the observed somatic symptoms-CRP relationship and determining whether BMI was operating as a mediator or a confounder. In addition, data for only one nonspecific marker of systemic inflammation was available; however, CRP is moderately correlated with levels of the proinflammatory cytokine IL-6 and is considered to be an emerging risk factor for CVD (Hackam and Anand, 2003; Stewart et al., 2009).

5. Conclusions

In summary, we found that the relationship between depressive symptom severity and serum CRP was largely due to the somatic symptoms (sleep disturbance, fatigue, appetite changes, and psychomotor retardation/agitation) and was moderated by race-ethnicity (associations were observed only among non-Hispanic Whites). Our findings raise three intriguing, albeit speculative, possibilities worthy of evaluation in future studies. One, the somatic depressive symptoms may be more predictive of future cardiovascular outcomes, in part, due to their stronger link with CVD-relevant inflammatory markers. Two, systemic inflammation may explain a greater portion of the excess CVD risk of depressed patients of European origin than those of African American and Latino descent. Three, inflammatory-based depression – i.e., depression stemming from peripheral immune activation (Dantzer et al., 2008; Raison et al., 2006) – may be particularly prevalent among non-Hispanic Whites.

References

Abraham, G., Sundaram, V., Mathew, M., Leslie, N., Sathiah, V., 2009. C-reactive protein, a valuable predictive marker in chronic kidney disease. Saudi J Kidney Dis. Transplant. 20, 811.

Boyle, S.H., Jackson, W.G., Suarez, E.C., 2007. Hostility, anger, and depression predict increases in C3 over a 10-year period. Brain Behav. Immun. 21, 816–823.

Callahan, C.M., Wolinsky, F.D., 1994. The effect of gender and race on the measurement properties of the CES-D in older adults. Med. Care 32, 341–356.

Cameron, I.M., Cardy, A., Crawford, J.R., du Toit, S.W., Hay, S., Lawton, K., Mitchell, K., Sharma, S., Shivaprasad, S., Winning, S., 2011. Measuring depression severity in general practice. Discriminatory performance of the PHQ-9, HADS-D, and BDI-II. Br. J. Gen. Practice 61, e419.

Carney, R.M., Freedland, K.E., 2012. Are somatic symptoms of depression better predictors of cardiac events than cognitive symptoms in coronary heart disease? Psychosom. Med. 74, 33–38.

Casas, J.P., Shah, T., Hingorani, A.D., Danesh, J., Pepys, M.B., 2008. C-reactive protein and coronary heart disease: a critical review. J. Intern. Med. 264, 295–314.

Chilcot, J., Rayner, L., Lee, W., Price, A., Goodwin, L., Monroe, B., Sykes, N., Hansford, P., Hotopf, M., 2013. The factor structure of the PHQ-9 in palliative care. J. Psychosom. Res. 75, 60–64.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawarence Earlbaum Associates, Hillsdale, NJ.

Conradi, H.J., Ormel, J., de Jonge, P., 2011. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. Psychol. Med. 41, 1165–1174.

Dantzer, R., 2004. Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. Eur. J. Pharmacol. 500, 399–411.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.

Davidson, K.W., Rieckmann, N., Rapp, M.A., 2005. Definitions and distinctions among depressive syndromes and symptoms: implications for a better understanding of the depression–cardiovascular disease association. Psychosom. Med. 67 (Suppl.1), S6–S9.

de Jonge, P., Mangano, D., Whooley, M.A., 2007. Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. Psychosom. Med. 69, 735–739.

Deverts, D.J., Cohen, S., DiLillo, V.G., Lewis, C.E., Kiefe, C., Whooley, M., Matthews, K.A., 2010. Depressive symptoms, race, and circulating c-reactive protein: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Psychosom. Med. 72, 734–741.

Duivis, H.E., Vogelzangs, N., Kupper, N., de Jonge, P., Penninx, B.W.J.H., 2013. Differential associations of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). Psychoneuroendocrinology 38, 1573–1585.

Epstein, F.H., Ross, R., 1999. Atherosclerosis—an inflammatory disease. N. Engl. J. Med. 340, 115–126.

Everson, S.A., Goldberg, D.E., Kaplan, G.A., Cohen, R.D., Pukkala, E., Tuomilehto, J., Salonen, J.T., 1996. Hopelessness and risk of mortality and incidence of myocardial infarction and cancer. Psychosom. Med. 58, 113–121.

Gan, W.Q., Man, S.F.P., Senthilselvan, A., Sin, D.D., 2004. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 59, 574–580.
Gimeno, D., Kivimäki, M., Brunner, E.J., Elovainio, M., De Vogli, R., Steptoe, A., Kumari, M., Lowe, G.D.O., Rumley, A., Marmot, M.G., Ferrie, J.E., 2009. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol. Med. 39, 413–423.
Hackam, D.G., Anand, S.S., 2003. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. JAMA 290, 932–940.
Hamer, M., Molloy, G.J., de Oliveira, C., Demakakos, P., 2009. Persistent depressive symptomatology and inflammation: to what extent do health behaviours and weight control mediate this relationship? Brain. Behav. Immun. 23, 413–418.
Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacology 29, 1765–1781.
Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71, 171–186.
Huang, F.Y., Chung, H., Kroenke, K., Delucchi, K.L., Spitzer, R.L., 2006. Using the Patient Health Questionnaire-9 to measure depression among racially and ethnically diverse primary care patients. J. Gen. Intern. Med. 21, 547–552.
Hybels, C.F., Steffens, D.C., McQuoid, D.R., Krishnan, K.R.R., 2005. Residual symptoms in older patients treated for major depression. Int. J. Geriatr. Psychiatry 20, 1196–1202.
Kaptoge, S., Di Angelantonio, E., Pennells, L., Wood, A.M., White, I.R., Gao, P., Walker, M., Thompson, A., Sarwar, N., Caslake, M., Butterworth, A.S., Amouyel, P., Assmann, G., Bakker, S.J.L., Barr, E.L.M., Barrett-Connor, E., Benjamin, E.J., Björkelund, C., Brenner, H., Brunner, E., Clarke, R., Cooper, J.A., Cremer, P., Cushman, M., Dagenais, G.R., D'Agostino Sr., R.B., Dankner, R., Davey-Smith, G., Deeg, D., Dekker, J.M., Engström, G., Folsom, A.R., Fowkes, F.G.R., Gallacher, J., Gaziano, J.M., Giampaoli, S., Gillum, R.F., Hofman, A., Howard, B.V., Ingelsson, E., Iso, H., Jørgensen, T., Kiechl, S., Kitamura, A., Kiyohara, Y., Koenig, W., Kromhout, D., Kuller, L.H., Lawlor, D.A., Meade, T.W., Nissinen, A., Nordestgaard, B.G., Onat, A., Panagiotakos, D.B., Psaty, B.M., Rodriguez, B., Rosengren, A., Salomaa, V., Kauhanen, J., Salonen, J.T., Shaffer, J.A., Shea, S., Ford, I., Stehouwer, C.D.A., Strandberg, T.E., Tipping, R.W., Tosetto, A., Wassertheil-Smoller, S., Wennberg, P., Westendorp, R.G., Whincup, P.H., Wilhelmsen, L., Woodward, M., Lowe, G.D.O., Wareham, N.J., Khaw, K.-T., Sattar, N., Packard, C.J., Gudnason, V., Ridker, P.M., Pepys, M.B., Thompson, S.G., Danesh, J., 2012. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N. Engl. J. Med. 367, 1310–1320.
Kessel, A., Elias, G., Pavlotzky, E., Zuckerman, E., Rosner, I., Toubi, E., 2007. Anti-C-reactive protein antibodies in chronic hepatitis C infection: correlation with severity and autoimmunity. Hum. Immunol. 68, 844–848.
Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc. Natl. Acad. Sci. U. S. A. 100, 9090–9095.
Kline, R.B., 2010. Principles and Practice of Structural Equation Modeling, third ed. Guilford Press, New York.
Kop, W.J., Gottdiener, J.S., 2005. The role of immune system parameters in the relationship between depression and coronary artery disease. Psychosom. Med. 67, S37–S41.
Korhonen, T., Broms, U., Varjonen, J., Romanov, K., Koskenvuo, M., Kinnunen, T., Kaprio, J., 2007. Smoking behaviour as a predictor of depression among Finnish men and women: a prospective cohort study of adult twins. Psychol. Med. 37, 705–715.
Krause, J.S., Bombardier, C., Carter, R.E., 2008. Assessment of depressive symptoms during inpatient rehabilitation for spinal cord injury: is there an underlying somatic factor when using the PHQ? Rehabil. Psychol. 53, 513–520.
Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr. Ann. 32, 509–515.
Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606–613.
Kubzansky, L.D., Sparrow, D., Vokonas, P., Kawachi, I., 2001. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom. Med. 63, 910–916.
Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W., Zitman, F.G., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatry 67, 220.
Manea, L., Gilbody, S., McMillan, D., 2012. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. Can. Med. Assoc. J. 184, E191–E196.
Matthews, K.A., Räikkönen, K., Sutton-Tyrrell, K., Kuller, L.H., 2004. Optimistic attitudes protect against progression of carotid atherosclerosis in healthy middle-aged women. Psychosom. Med. 66, 640–644.
McCaffery, J.M., Frasure-Smith, N., Dubé, M.-P., Théroux, P., Rouleau, G.A., Duan, Q., Lespérance, F., 2006. Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. Psychosom. Med. 68, 187–200.
Michal, M., Wiltink, J., Kirschner, Y., Wild, P.S., Münzel, T., Ojeda, F.M., Zeller, T., Schnabel, R.B., Lackner, K., Blettner, M., Zwiener, I., Beutel, M.E., 2013. Differential associations of depressive symptom dimensions with cardiovascular disease in the community: results from the Gutenberg Health Study. PLoS ONE 8, e72014.
Miller, G.E., Blackwell, E., 2006. Turning up the heat: inflammation as a mechanism linking chronic stress, depression, and heart disease. Curr. Dir. Psychol. Sci. (Wiley-Blackwell) 15, 269–272.
Miller, G.E., Freedland, K.E., Carney, R.M., Stetler, C.A., Banks, W.A., 2003. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. Brain Behav. Immun. 17, 276–285.
Omori, H., Tsuji, M., Sata, K., Iyonaga, C., Narimatsu, A., Mihara, S., Marubayashi, T., Tomiguchi, S., Nomori, H., Kohrogi, H., 2009. Correlation of C-reactive protein with disease severity in CT diagnosed emphysema. Respirology 14, 551–558.
Patten, S.B., Schopflocher, D., 2009. Longitudinal epidemiology of major depression as assessed by the Brief Patient Health Questionnaire (PHQ-9). Compr. Psychiatry 50, 26–33.
Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., Rifai, N., Smith, S.C., Taubert, K., Tracy, R.P., Vinicor, F., 2003. Markers of inflammation and cardiovascular disease. Circulation 107, 499–511.
Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol., England, 24–31.
Rosengren, A., Hawken, S., Ounpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W.A., Blackett, K.N., Sitthi-amorn, C., Sato, H., Yusuf, S., 2004. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet 364, 953–962.
Sokka, T., Pincus, T., 2009. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%–45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J. Rheumatol. 36, 1387–1390.
Stewart, J.C., Janicki, D.L., Muldoon, M.F., Sutton-Tyrrell, K., Kamarck, T.W., 2007. Negative emotions and 3-year progression of subclinical atherosclerosis. Arch. Gen. Psychiatry 64, 225–233.
Stewart, J.C., Rand, K.L., Muldoon, M.F., Kamarck, T.W., 2009. A prospective evaluation of the directionality of the depression–inflammation relationship. Brain Behav. Immun. 23, 936–944.
Stewart, J.C., Zielke, D.J., Hawkins, M.A.W., Williams, D.R., Carnethon, M.R., Knox, S.S., Matthews, K.A., 2012. Depressive symptom clusters and 5-year incidence of coronary artery calcification: the coronary artery risk development in young adults study. Circulation 126, 410–417.
Tien, P.C., Choi, A.I., Zolopa, A.R., Benson, C., Tracy, R., Scherzer, R., Bacchetti, P., Shlipak, M., Grunfeld, C., 2010. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. J. Acquir. Immune Defic. Syndr. 55 (316–322), 3. http://dx.doi.org/10.1097/QAI.1090b1013e3181e66216.
Tilg, H., Wilmer, A., Vogel, W., Herold, M., Nolchen, B., Judmaier, G., Huber, C., 1992. Serum levels of cytokines in chronic liver diseases. Gastroenterology 103, 264–274.
Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A., 2007. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. Int. J. Geriatr. Psychiatry 22, 613–626.
Wiltink, J., Michal, M., Wild, P., Zwiener, I., Blettner, M., Munzel, T., Schulz, A., Kirschner, Y., Beutel, M., 2013. Associations between depression and different measures of obesity (BMI, WC, WHtR, WHR). BMC Psychiatry 13, 223.
Wittkampf, K.A., Naeije, L., Schene, A.H., Huyser, J., van Weert, H.C., 2007. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. Gen. Hosp. Psychiatry 29, 388–395.