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Depressive Symptoms, Race, and Circulating C-Reactive Protein: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

Denise Janicki Deverts, Ph.D.
Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213. Phone: 412-268-3295; Fax: (412) 268-3294

Sheldon Cohen, Ph.D.
Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213

Vicki G. DiLillo, Ph.D.
Department of Psychology, Ohio Wesleyan University, Delaware, OH 43015

Cora E. Lewis, MD., M.S.P.H., F.A.C.P., F.A.H.A.
Division of Preventive Medicine, University of Alabama School of Medicine, Birmingham AL, 35205

Catarina Kiefe, M.D., Ph.D.
Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA 01655

Mary Whooley, M.D.
Department of General Internal Medicine, University of California, San Francisco, CA 94143

Karen A. Matthews, Ph.D.
Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213

Abstract

Objective—To examine the prospective association of depressive symptoms with circulating C-reactive protein (CRP) and determine the direction of that association.

Methods—Using data from 2544 healthy participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study (ages 33–45, 55% female, 42% black), we examined the prospective association of depressive symptoms, as measured by the Centers for Epidemiologic Studies Depression Scale (CES-D), with circulating CRP five years later.

Results—Depressive symptoms at CARDIA Year 15 predicted CRP at Year 20, independent of demographic characteristics, biological and medical risk factors, health behaviors, and Year 15 CRP. This association, however, was conditional upon race such that the increase in CRP with increasing depressive symptoms was present in blacks but not whites. In neither blacks nor whites did Year 15 CRP predict Year 20 depressive symptoms. Among black participants, when examined in separate analyses, higher scores on the depressed affect and somatic symptoms subscales of the CES-D, and lower scores on the positive affect subscale were associated with greater Year 20 CRP. The interpersonal problems subscale was unrelated to CRP. When all four subscale scores were entered simultaneously in the same model, black participants' scores on the

Correspondence to: Denise Janicki Deverts.

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positive affect and somatic symptoms subscales emerged as independent predictors of Year 20 CRP whereas the depressed affect and interpersonal problems subscales did not.

Conclusions—Depressive symptoms may be more closely linked to inflammation in blacks than in whites.

Keywords

C-reactive protein; Center for Epidemiologic Studies Depression Scale; CES-D; positive affect; blacks; prospective study

Introduction

The comorbidity of mental depression with chronic physical disease has been well-established (1–3). Moreover, converging evidence from psychosocial, medical, and epidemiologic research suggests that greater severity of depressive symptoms is associated with greater risk for incident disease among healthy individuals (4,5), as well as accelerated disease progression and more functional limitations among persons with pre-existing medical conditions (6,7).

The association of poorer physical health with depressive symptomatology may be greater for blacks than whites (8–11). For example, diagnosed depression has been associated with increased odds of comorbid hypertension and diabetes in both black and white adults, but the effect is substantially larger in blacks (11). Also, in a case-control study of persons with type 2 diabetes, greater symptoms of depression were associated with a greater odds of having poor control of at least two of three intermediate outcomes (systolic blood pressure, blood glucose, low-density lipoprotein cholesterol) in blacks but not whites (10).

One mechanism through which depression might influence physical health is via modulation of inflammatory processes. Cross-sectional findings have offered preliminary support for this proposed mechanism, with concentrations of pro-inflammatory cytokines and acute phase proteins being higher in persons with major depression relative to their non-depressed counterparts (12,13), and greater among those with worse symptoms of depression in non-clinical populations (14). Though informative in terms of supporting the hypothesized link between depression and inflammation, cross-sectional studies fall short of determining the causal direction of the association.

Several longitudinal studies conducted in the general population have expanded upon the cross-sectional research by examining the direction of the depression-inflammation association (15–22). Of particular interest are three studies that were both truly prospective in design (i.e., controlled for baseline levels of the dependent variable) and examined the depression-inflammation association in both directions (18,19,22). Two of these studies found elevated C-reactive protein (CRP) concentrations to predict subsequent depressive symptoms—but not the reverse, between 5 and 12 years of follow-up (19,22). The third, which examined CRP and interleukin (IL)-6, found depressive symptoms to predict increased IL-6 six years later, but found no support for the reverse association. CRP, however, was unrelated to depressive symptoms in either direction (18).

With one exception (22), the existing longitudinal research on depression and inflammation has been based on data collected from predominantly white (85–100%), middle-aged and older samples. Although Matthews and colleagues (22) employed a racially heterogeneous sample, they did not test the interaction of depressive symptoms with race. However, an earlier report from the same sample found a race-by-depressive symptoms interaction when predicting another disease risk outcome, coronary artery calcification, wherein depressive

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symptoms were associated with more detectable plaque in African-Americans but was not associated with plaque in whites (9). Given that blacks are at disproportionately greater risk for morbidity and mortality from all causes relative to their white counterparts (23), and that there is evidence to suggest that depression may have a stronger association with health-related outcomes among blacks relative to whites (8–11), the relative scarcity of data on the depression-inflammation association among non-whites is a significant limitation of this body of research.

The objective of the present study was to provide further prospective examination of the link between depressive symptoms and inflammation in a large multi-site sample of young (age 33–45 years) black and white United States adults. The Center for Epidemiologic Studies Depression Scale (CES-D) (24) was used to measure depressive symptoms and circulating CRP concentrations to approximate inflammation. The relatively young age and racial diversity of the present sample enabled us to expand upon previous research both by presenting findings that are more generalizable to the larger U.S. population and by examining whether the depression-inflammation association differs between blacks and whites.

In exploratory analyses we examined whether four subsets of depressive symptoms—depressed affect; positive affect; somatic symptoms; and interpersonal problems (24), were differentially related to circulating CRP. We were especially interested in whether reduced positive affect has implications for health apart from those conveyed by elevated negative affect (25,26). For example, among persons experimentally infected with a cold virus, lower trait positive affect—independent of trait negative affect, was associated with greater illness symptoms, with that association being partially mediated by pro-inflammatory cytokines (27). Thus, it is possible that associations between depressive symptoms and inflammation, regardless of direction, may be driven by lower scores on the positive affect subscale, rather than higher scores on the other three negatively-worded subscales.

Methods

Subjects

In 1985–1986, 5115 adults aged 18–30 years were recruited into CARDIA at four sites: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. The sampling strategy resulted in a population-based cohort that was balanced by race (52% black), sex (55% female), and education (40% with < 12 years of education) both overall and within each clincial center. (for additional detail see (28)). Follow-up examinations were conducted in 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), 2000–2001 (Year 15), and 2005–2006 (Year 20), with retention rates of 90%, 86%, 81%, 79%, 74%, and 72% of the surviving cohort, respectively. Institutional review committee approval was obtained at each site and written informed consent was obtained from participants at each examination.

Exclusions—Of the 5115 participants who were enrolled in CARDIA at Year 0, 3548 (56.7% female; 46.5% black) attended the Year 20 exam. Data from Year 20 participants were excluded from the present analyses if missing information on any of the following variables: Year 15 or 20 CRP (*n*=516); Year 15 or 20 depressive symptoms (*n*=109); any of the Year 20 demographic, physiological, or health behavior variables that were included as covariates in all analyses (see below; *n*=110).[1] Data from an additional 279 participants

[1]Exclusionary criteria are listed in the order that they were applied to the sample. *N*s reflect the number of participants excluded from the resulting dataset after previous exclusions already had been made. Thus, excluded participants may have been missing data on more than one of the criterion variables, even though they are counted as missing data on only one variable.

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were excluded because CRP values at Year 15 or Year 20 exceeded 10 mg/L, the standard criterion for determining the presence of active infection (29). The present report is based on data from the remaining 2544 participants. Relative to CARDIA participants who attended the Year 20 exam but were not included here, the present sample was approximately equal in age (mean age at Year 20: 45.20±3.55 *vs*. 45.07±3.67, $t[3546] = .98$, $p = .33$) and education (mean years: 15.68±2.54 *vs*. 15.85±2.43, $t[3546] = 1.76$, $p<.08$), but was less likely to be female (55.0% *vs*. 61.0%, $chi^2 = 10.43$, $p<.002$), and less likely to be black (41.8% *vs*. 52.3%, $chi^2 = 32.14$, $p<.001$).

Measures

C-reactive protein—At the Year 15 and 20 examinations, bloods for measurement of CRP were collected in 2-mL blue top (citrated) vacutainer tubes and centrifuged at 4°C for approximately 20 minutes. Citrated plasma was promptly separated from cells, transferred to a cryovial, and frozen at −70°C. Frozen samples were shipped to the University of Vermont where CRP was measured using high-sensitivity nephelometry-based methods (BNII nephelometer, Dade Behring). The assay range was 0.175–1100 mg/L, (intrassay CVs, 2.3–4.4%; inter-assay CVs, 2.1–5.7%). Resulting CRP values were log_{10}-transformed to normalize the distribution. Measurement of CRP was blind to depressive symptom scores.

Depressive symptoms—Symptoms of depression were assessed at Years 15 and 20 using the 20-item CES-D (24). Using a four-point scale (0 = rarely or none of the time to 3 = most or all of the time) participants indicated how often they had experienced given symptoms during the preceding week. Four positively worded items were reverse-scored (e.g., *I felt happy*) and then a depressed mood score was created by summing responses across the twenty items (possible range 0–60). Scores ≥16 are thought to indicate depressed mood of clinical significance (24). The CES-D has been found to have good internal consistency and adequate test-retest reliability; construct validity of the scale is supported by correlations with other self-report measures, clinical ratings of depression, and clinical interviews (24). Depressive symptom scores were skewed toward lower values and thus were square-root transformed to approximate a normal distribution.

CES-D subscale scores were computed by summing scores on the specific items determined to comprise each subscale. Compositions of the four subscales were as follows: depressed affect, seven items (e.g., *I felt depressed*); positive affect, four items (e.g., *I felt happy*); somatic symptoms, seven items, (e.g., *my appetite was poor*); and interpersonal problems, two items (e.g., *I felt lonely*). Scores on each subscale were square-root transformed to approximate a normal distribution. This four-factor structure has been replicated in both white (30) and black (31,32) populations, and confirmed in a recent meta-analysis of 28 studies (33).

Covariates

Standard covariates are described below. These include the following factors known to be related to circulating CRP and/or inflammation more generally, as well as to depressive symptoms: demographic variables (age, sex, race, education); physiological variables (BMI, SBP, glucose, insulin, HDL, LDL, triglycerides); health behaviors (smoking, alcohol consumption, physical activity); oral contraceptive (OC) or hormone therapy (HT) use (women); total number of diagnosed medical conditions; and total number of inflammation-related medications. Year 15 and Year 20 measures of covariates (except age, sex, and race) were examined for associations with Year 20 CRP. As associations of CRP with Year 20 variables were equivalent or larger than those with Year 15 variables, Year 20 measurements were included as covariates. Results were similar when Year 15 covariates were substituted (data not shown).

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Demographic variables—Participant age, sex, and race were assessed by self-report during the initial telephone interview prior to enrollment. Education was assessed at all CARDIA exams by asking participants to report the highest grade (year) of school they had completed (range: 0–20). Year 20 education was included in the present analyses.

Physiological measures—Standard procedures were used for the collection and measurement of physiological covariates (BMI (kg/m^2), lipids (HDL, LDL, cholesterol), glucose, insulin, and SBP) at all CARDIA exams, and have been described in detail previously (28).

Major/chronic health conditions and medications—At Year 20, participants reported whether they *ever* had been diagnosed with any of twenty-seven major or chronic health conditions (e.g., hypertension, diabetes, cancer). Participants also reported on current over-the-counter and prescription medications, including OC/HT (women). Additional details are available on the CARDIA website (http://www.cardia.dopm.uab.edu/). From these data, a *medical conditions* variable was created by summing the total number of medical diagnoses reported at Year 20. A *medications* variable was created by summing the total number of reported medications with the potential to influence inflammatory processes (e.g., immunosuppressants, anti-inflammatory agents (including aspirin and other NSAIDS), corticosteroids, statins, antihypertensives, and antidepressants).

Health behaviors—Self-reported health behaviors were obtained by interview at each CARDIA exam. Measures included smoking status (current/former *vs*. never), alcohol consumption (total drinks per week), and physical activity (expressed in exercise units (EU); details on scoring procedures are available elsewhere (34)). All scales used to assess health behaviors are documented on the CARDIA website (http://www.cardia.dopm.uab.edu/).

Statistical analyses

Statistical analyses were performed using SAS v9.1 (SAS Institute Inc, Cary, NC). T-tests were used to compare means of continuous variables, with Satterthwaite correction in the event of unequal variances. All regression analyses examining the association of Year 15 depressive symptoms with Year 20 CRP and those examining the association of Year 15 CRP with Year 20 depressive symptoms included the standard covariates described above: demographics; physiological variables; health behaviors; OC/HT; medical conditions; and inflammation-related medications. As indicated above, antidepressants were included in the total medications variable. Results of analyses with separate control for antidepressant use did not differ from those reported here. Prospective analyses also controlled for Year 15 levels of the Year 20 outcome. For analytic purposes, OC/HT use was represented by two dummy variables comparing women taking OC/HT and women with missing OC/HT data, respectively to OC/HT nonusers (men were included in this group). Similarly, smoking status was represented by two dummy variables comparing current/former smokers and persons with missing smoking status data to never smokers.

Moderation analyses were used to determine whether associations between depressive symptoms and CRP differed by race. These models were identical to the main effect models described above, save for the addition of the relevant race-by-predictor cross-product term. When examining whether the association of Year 15 depressive symptoms with Year 20 CRP differed between blacks and whites, a race-by-depressive symptoms interaction term was included. Analogously, when examining whether the association of Year 15 CRP with Year 20 depressive symptoms differed by race, a race-by-CRP interaction term was included.

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Results

Sample characteristics and correlations with Year 15 depressive symptoms and Year 20 CRP

Table 1 presents descriptive data for the entire sample and separately by race. As shown in the table, blacks scored higher than whites both on Year 15 depressive symptoms (t[2174] = 8.40, $p < .001$) and Year 20 CRP (t[2542] = 10.82, $p < .001$). Although average depressive symptom scores for both races were well below the criterion for probable clinical depression (CES-D score ≥16), roughly 10% of whites and 22% of blacks met or exceeded this criterion. With regard to study covariates, blacks and whites differed significantly ($p < .02$) on all variables except HDL, LDL, and percentage of current/former smokers (data not shown).

Table 2 displays correlations of continuous covariates with Year 15 depressive symptoms and Year 20 CRP, and Tables 3 and 4 display mean differences in these two variables across levels of dichotomous covariates. All three tables display data for the entire sample and separately by race. As shown in Table 2, Year 15 depressive symptoms were positively correlated with Year 20 CRP in the entire sample and among blacks; among whites, the association was in the same direction, but weaker. Cross-sectional correlations between depressive symptoms and CRP at Years 15 and 20, respectively, were small and failed to achieve statistical significance when examined separately for whites and blacks. As indicated in all three tables, most covariates correlated in expected directions with Year 15 depressive symptoms and Year 20 CRP, with associations being consistent across races.

Prospective association of depressive symptoms with future CRP

The first column of Table 5 displays the results of multivariate linear regression analyses examining the association of Year 15 depressive symptoms with Year 20 CRP in the entire sample. All analyses controlled for the standard covariates described above and Year 15 CRP. As indicated by the table, greater depressive symptoms at Year 15 were independently related to greater CRP concentrations at Year 20 (Model 1). Because Year 20 CRP was positively correlated with Year 20 depressive symptoms (see Table 2), the preceding prospective analysis was re-run with control for Year 20 depressive symptoms to ensure that earlier depressive symptoms were not simply acting as a proxy indicator of depression measured concurrently with the outcome (Model 2). Even when examined using this extremely conservative approach, Year 15 depressive symptoms remained an independent predictor of Year 20 CRP. By comparison, Year 20 depressive symptoms was not independently related to Year 20 CRP (B(SE) = .001(.006), $b = .004$, $p = .81$).

Moderation by race

Race moderated the association of Year 15 depressive symptoms with Year 20 CRP (B(SE) = .020(.010), $b = .070$, $p < .05$ for interaction). When analyses were conducted separately by race (see Table 5), the prospective association of greater depressive symptoms with greater CRP was apparent among blacks, but not whites.

Prospective association of CRP with future depressive symptoms

To rule out the possibility that CRP concentrations influenced the development of future depressive symptoms, we examined whether CRP at Year 15 predicted depressive symptoms at Year 20. Results of a multivariate linear regression analysis that included the standard covariates and Year 15 depressive symptoms revealed no association between Year 15 CRP and Year 20 depressive symptoms (B(SE) = −.043(.060), $b = -.016$, $p = .47$). This lack of association was consistent across blacks and whites (B(SE) = .057(.091), $b = .014$, $p = .53$ for interaction).

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Exploratory analyses: Differential associations of CES-D subscales with CRP

To determine whether the association of depressive symptoms with CRP is accounted for primarily by higher scores on one or more of the four depressive symptom subscales, the above analyses were repeated for the entire sample and separately by race substituting scores on each of the four subscales as the independent variable. Results of these analyses are presented in the bottom panel of Table 5. In the total sample, lower scores on the Year 15 positive affect subscale and higher scores on the somatic symptoms subscale each predicted greater Year 20 CRP concentrations, though these associations lost statistical significance in the more conservative analysis where controls were added for Year 20 positive affect and somatic symptoms, respectively. When analyses were conducted separately by race, scores on the depressed affect, positive affect, and somatic symptoms subscales each were independent predictors of Year 20 CRP for blacks, both before and after including control for the relevant Year 20 subscale. None of the subscales were associated with CRP in whites.

Using data from black participants only, a final exploratory analysis was conducted wherein scores on all four subscales were entered simultaneously into a single model to predict Year 20 CRP. Results showed independent associations of greater somatic symptoms (B(SE) = .088(.033), b = .085, p< .008) and less positive affect (B(SE) = .048(.022), b = .054, p< .03) with greater Year 20 CRP, thus suggesting that these two subscales may be the most important indicators of future elevations in CRP among the black participants in this sample.

Discussion

In a sample of healthy black and white adults, we observed a unidirectional, prospective association between self-reported depressive symptoms and circulating CRP such that greater symptomatology at the Year 15 CARDIA exam was related to greater CRP at Year 20. This association was independent of demographic characteristics, physiological and medical risk factors, health behaviors, and Year 15 CRP. In contrast, Year 15 CRP did not predict depressive symptoms at Year 20.

Moderation analyses revealed that the association of Year 15 depressive symptoms with Year 20 CRP was conditional upon race, such that the effect was present in blacks but not whites. Racial specificity in regard to the importance of depressive symptoms in predicting physiological CHD risk factors previously has been reported in the CARDIA sample (35,36). Specifically, the association between depression history (i.e., number of times participants scored ≥16 on the CES-D across Years 5, 10, and 15) and Year 15 diabetes was stronger in blacks than whites (36). Also, greater depressive symptoms at Year 5 were found to predict greater risk of hypertension at Year 10 in black CARDIA participants only (35). One explanation for this race-related disparity in the association of depressive symptoms with poor health outcomes is that it occurs because the CES-D scores were higher and more variable in black compared to white CARDIA participants (36).

The moderating effect of race on the association of depression with CHD risk factors, however, is not specific to CARDIA. In a study of male Vietnam veterans, depressive symptoms were found to be positively associated with serum fasting glucose in both black and white participants, but the magnitude of the association was larger in blacks relative to whites (8). Similarly, in healthy, middle-aged women, CES-D scores ≥16 independently predicted diabetes risk three years later, but only among black participants (37). A later report based on data from this sample of middle-aged women found that race interacted with depressive symptoms in the prediction of aortic calcification, such that greater symptomatology was associated with greater calcification in black but not white women (9).

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Taken together, these findings suggest that depression may be more closely linked to physiologic outcomes in blacks relative to whites. The increased importance of depressive symptoms for blacks may be due to race differences in any of several physiologic mechanisms that have been proposed to explain how depression might influence pro-inflammatory processes. One suggested pathway involves chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis. Dysregulated HPA activity may promote glucocortiocoid receptor resistance and subsequent diminished responsiveness of immune cells to regulation by cortisol (38). There is evidence to suggest that blacks are at higher risk for dysregulated HPA activity than whites. Black female caregivers, for example, have been found to display flatter daily cortisol slopes compared to their white counterparts (39). Also, in the study of Vietnam veterans, cortisol, like glucose, increased with increasing depression and the effect was stronger in black relative to white men (8).

Although it is possible that the depression-inflammation association may be stronger in blacks than whites, our failure to observe any association among white participants was unexpected. The present study differed from much of the earlier longitudinal research on depression and inflammation in that our sample was comprised of relatively young rather than middle-aged and older adults. However, Elovainio and colleagues (15) reported a longitudinal association of depressive symptoms with future CRP in their exclusively white young adult sample (mean age 31.5±5.0 years). A fundamental difference between the present investigation and this earlier study is that we controlled for baseline CRP (hence examining CRP *change*) whereas Elovainio and colleagues did not. However, we did observe a marginal zero-order correlation of greater Year 15 depressive symptoms with higher Year 20 CRP among the whites in our sample ($p = .08$; see Table 2), thus suggesting some similarity between the present findings and those reported previously.

Another inconsistency with previous research (14) is our finding comparatively small cross-sectional correlations of depressive symptoms with CRP. This difference may be due to our excluding participants with CRP values >10mg/L, the cut point for current infection (29). Cross-sectional studies examining depressive symptoms and CRP have not been consistent with regard to excluding participants meeting this criterion. For example, some studies (e.g., (15,40)), made no exclusions based on CRP but included a control for current or recent infection. Other studies (e.g., (41)) did not report whether and/or how this issue was addressed. When we re-examined cross-sectional associations without excluding participants with CRP >10mg/mL (97 additional whites; 172 additional blacks) depressive symptoms were correlated with CRP at .09 (sample), .05 (whites), and .07 (blacks) (ps<.05) at Year 20. At Year 15, analogous correlations were .09 and .06 (ps< .02) for the total sample and whites, respectively. For blacks, the cross-sectional correlation at Year 15 was marginal ($r = .04$, $p = .12$). We consider these relationships spurious, since these elevations in CRP are generally attributed to acute infections.

Though the direction of our findings among blacks—depressive symptoms predicting future CRP, is consistent with that reported for Elovanio's young adult sample, it conflicts with that reported by the only existing longitudinal study that included a substantial proportion of non-whites, wherein CRP predicted future depressive symptoms (22). This discrepancy might be attributed to Matthews and colleagues' (22) sample being comprised entirely of peri-menopausal women, and including Asians and Hispanics in addition to blacks and whites.

Exploratory examination of the four CES-D subscales revealed unique associations of the positive affect and somatic symptoms subscales with CRP, with effects being driven largely by data from the black participants. CRP also increased with increasing depressed affect when examined in black participants only; however, when all subscales were examined

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simultaneously, only positive affect and somatic symptoms remained independent predictors. The reliability of positive affect as a predictor of future CRP is consistent with our expectation that lower scores on the positive affect subscale may be more influential on pro-inflammatory activity than higher scores on the other three subscales (26). Though not expressly predicted, the importance of somatic symptoms is not surprising, as Stewart and colleagues found that their results were driven primarily by scores on the somatic-vegetative cluster of the BDI (18).

We acknowledge a few limitations of the present study. First, CRP was measured only once at Year 15 and Year 20, respectively. Optimally, CRP should be measured at least twice, with an approximate two-week interval (29). Had we followed these guidelines, and thus obtained more reliable measures of CRP, our effect sizes likely would have been larger. Also, although the CES-D is a valid instrument for measuring depressive symptoms, and the CES-D has been shown to be related to health-related outcomes (42,43), associations between depressive symptoms and CRP assessed by this and other self-report measures tend to be smaller than those that arise when interview-assessed clinical depression is examined (14). Because only a small proportion of the present sample met the CES-D criterion for probable clinical depression at Year 15 we were unable to investigate a threshold effect. Finally, CRP is a non-specific index of inflammation, with circulating concentrations being determined by several contributing factors including, at minimum, chronic disease processes (e.g., atherosclerosis), obesity, and infection. Accordingly, even after controlling for several factors that might have influenced CRP concentrations, we cannot determine with certainty what physiological process or condition is being reflected in persons with relatively elevated CRP. Nevertheless, CRP remains a robust predictor of future coronary events (44), and the clinical utility of CRP as a tool for identifying populations who would benefit from preventive therapy has been established (45).

In sum, the present findings suggest a prospective association between non-clinical depressive symptomatology and future circulating CRP concentrations that is stronger in blacks than in whites. Because minimal research to date has been conducted on the inflammatory concomitants of depressive symptoms in blacks, the present data provide new insight into one possible explanation for the recognized racial discrepancies in risk for some diseases. Additional research is necessary to establish the reliability of this finding, and to uncover the psychobiological mechanisms that underlie the association.

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Acronyms

B	unstandardized beta
b	standardized beta
BDI	Beck Depression Inventory
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults Study
CES-D	Centers for Epidemiologic Studies Depression Scale (CES-D)
CRP	C-reactive protein
CV	coefficient of variation
HDL	high density lipoprotein cholesterol
HT	hormone therapy
LDL	low density lipoprotein cholesterol
NSAIDS	nonsteroidal anti-inflammatory drugs
OC	oral contraceptive
OC/HT	oral contraceptive/hormone therapy
SD	standard deviation
SE	standard error
t	Student's *t*

References

1. Lesperance F, Frasure-Smith N. Depression in patients with cardiac disease: A practical review. J Psychosom Res 2000;48:379–391. [PubMed: 10880660]
2. Morrison MF, Petitto JM, Ten Have T, Gettes DR, Chiappini MS, Weber AL, Brinker-Spence P, Bauer RM, Douglas SD, Evans DL. Depressive and anxiety disorders in women with HIV infection. Am J Psychiatry 2002;159:789–796. [PubMed: 11986133]
3. Newport DJ, Nemeroff CB. Assessment and treatment of depression in the cancer patient. J Psychosom Res 1998;45:215–237. [PubMed: 9776368]
4. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: A meta-analysis. Diabetes Care 2008;31:2383–2390. [PubMed: 19033418]
5. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: The problems and implications of overlappng affective dispostions. Psychol Bull 2005;131:260–300. [PubMed: 15740422]
6. de Jonge P, Spijkerman TA, van den Brink RH, Ormel J. Depression after myocardial infarction is a risk factor for declining health related quality of life and increased disability and cardiac complaints at 12 months. Heart 2006;92:32–39. [PubMed: 15890765]
7. Spiegel D, Giese-Davis J. Depression and cancer: Mechanisms and disease progression. Biol Psychiatry 2003;54:269–282. [PubMed: 12893103]
8. Boyle SH, Surwit RS, Georgiades A, Brummett BH, Helms MJ, Williams RB, Barefoot JC. Depressive symptoms, race, and glucose concentrations: The role of cortisol as mediator. Diabetes Care 2007;30:2484–2488. [PubMed: 17630268]
9. Lewis TT, Everson-Rose SA, Colvin A, Matthews KA, Bromberger JT, Sutton-Tyrrel K. Interactive effects of race and depressive symptoms on calcification in African American and white women. Psychosom Med 2009;71:163–170. [PubMed: 19188530]

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10. Duru OK, Gerzoff RB, Selby JV, Brown AF, Ackermann RT, Karter AJ, Ross S, Steers WN, Herman WH, Waitzfelder B, Mangione CM. Identifying risk factors for racial disparities in diabetes outcomes: The Translating Research into Action for Diabetes Study. Medical Care 2009;47:700–706. [PubMed: 19480090]
11. Stecker T, Fortney JC, Steffick DE, Prajapati S. The triple threat for chronic disease: Obesity, race, and depression. Psychosomatics 2006;47:513–518. [PubMed: 17116953]
12. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9:853–858. [PubMed: 9367546]
13. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2002;90:1279–1283. [PubMed: 12480034]
14. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. Psychosom Med 2009;71
15. Elovainio M, Keltikangas-Jarvinen L, Pulkki-Raback L, Kivimaki M, Puttonen S, Viikari L, Rasanen L, Mansikkaniemi K, Viikari J, Raitakari OT. Depressive symptoms and C-reactive protein: The Cardiovascular Risk in Young Finns Study. Psychol Med 2006;36:797–805. [PubMed: 16623962]
16. Matthews KA, Schott LL, Bromberger J, Cyranowski J, Everson-Rose SA, Sowers MF. Associations between depressive symptoms and inflammatory/hemostatic markers in women during the menopausal transition. Psychosom Med 2007;69:124–130. [PubMed: 17289830]
17. Hamer M, Molloy GJ, de Oliveira C, Demakakos P. Persistent depressive symtomatology and inflammation: To what extent do health behaviors and weight control mediate this relationship? Brain Behav Immun. 2009 doi:10.1016/j.bbi.2009.01.005.
18. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun. 2009 doi:10.1016/j.bbi.2009.04.011.
19. Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GDO, Rumley A, Marmot M, Ferrie JE. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med 2009;39:413–423. [PubMed: 18533059]
20. Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: The InCHIANTI Study. Biol Psychiatry 2009;65
21. van den Biggelaar AHJ, Gussekloo J, de Craen AJM, Frolich M, Stek ML, van der Mast RC, Westendorp RGJ. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. Exp Gerontol 2007;42:693–701. [PubMed: 17350781]
22. Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers MF. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain Behav Immun 2010;24:96–101. [PubMed: 19683568]
23. Sorlie PD, Backlund E, Keller JB. US mortality by economic, demographic, and social characteristics: The National Longitudinal Mortality Study. Am J Public Health 1995;85:949–956. [PubMed: 7604919]
24. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401.
25. Denollet J, Pedersen SS, Daemen J, de Jaegere P, Serruys PW, van Domburg RT. Reduced positive affect (anhedonia) predicts major clinical events following implantation of coronary-artery stents. J Intern Med 2008;263:203–211. [PubMed: 18069998]
26. Pressman SD, Cohen S. Does positive affect influence health? Psychol Bull 2005;131:925–971. [PubMed: 16351329]
27. Doyle WJ, Gentile DA, Cohen S. Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure. Brain Behav Immun 2006;20:175–181. [PubMed: 16023829]

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28. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DRJ, Liu K, Savage PJ. CARDIA: Study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41
29. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: Application to clinical and public practice. Circulation 2003;107:499–511. [PubMed: 12551878]
30. Hertzog C, Van Alstine J, Usala P, Hultsch DF, Dixon R. Measurement properties of the Center for Epidemiological Studies Depression Scale (CES-D) in older populations. Psychol Assess 1990;2:64–72.
31. Nguyen HT, Kitner-Triolo M, Evans MK, Zonderman AB. Factorial invariance of the CES-D in low socioeconomic status African Americans compared with a nationally representative sample. Psychiatry Res 2004;126:177–187. [PubMed: 15123397]
32. Williams CD, Taylor TR, Makambi K, Harrell J, Palmer JR, Rosenberg L, Adams-Campbell LL. CES-D four-factor structure is confirmed, but not invariant, in a large cohort of African American women. Psychiatry Res 2007;150:173–180. [PubMed: 17291596]
33. Shafer A. Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. J Clin Psychol 2006;62:123–146. [PubMed: 16287149]
34. Jacobs DR, Hahn L, Haskell WL, Pirie P, Sidney S. Validity and reliability of a short physical activity history: CARDIA and the Minnesota Heart Health Program. J Cardiopulm Rehabil 1989;9:448–459.
35. Davidson KW, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA Study. Arch Intern Med 2000;160:1495–1500. [PubMed: 10826464]
36. Knox S, Barnes A, Kiefe C, Lewis C, Iribarren C, Matthews KA, Wong N, Whooley M. History of depression, race, and cardiovascular risk in CARDIA. Int J Behav Med 2006;13:44–50. [PubMed: 16503840]
37. Everson-Rose SA, Torrens JI, Meyer PM, Kravitz HM, Powell LH, Bromberger JT, Pandy D, Matthews KA. Depressive symptoms, insulin resistance and risk of diabetes in women at midlife. Diabetes Care 2004;27:2856–2862. [PubMed: 15562197]
38. Miller GE, Cohen S, Ritchey KA. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid resistance model. Health Psychol 2002;21:531–541. [PubMed: 12433005]
39. McCallum TJ, Sorocco KH, Fritsch T. Mental health and diurnal salivary cortisol patterns among African American and European American female dementia family caregivers. Am J Geriatr Psychiatry 2006;14:684–693. [PubMed: 16861373]
40. Penninx BW, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, Ferrucci L, Harris T, Pahor M. Inflammatory markers and depressed mood in older persons: results from the Health, Aging, and Body Composition study. Biol Psychiatry 2003;54:566–572. [PubMed: 12946885]
41. Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The associaiton between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. J Occup Health Psychol 2005;10:344–362. [PubMed: 16248685]
42. Rowan PJ, Haas D, Campbell JA, Maclean DR, Davidson KW. Depressive symptoms have an independent, gradient risk for coronary heart disease incidence in a random, population-based sample. Ann Epidemiol 2005;15:316–320. [PubMed: 15780780]
43. Wulsin LR, Evans JC, Vasan RS, Murabito JM, Kelly-Hayes M, EJ B. Depressive symptoms, coronary heart disease, and overall mortality in the Framingham Heart Study. Psychosom Med 2005;67:697–702. [PubMed: 16204426]
44. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation 2003;107:363–369. [PubMed: 12551853]
45. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. NEJM 2008;359:2195–2207. [PubMed: 18997196]

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Table 1

Sample characteristics for the entire sample and separately by race[1, 2, 3]

	Sample (*n* = 2544)	Whites (*n* = 1481)	Blacks (*n* = 1063)
Age at Year 15	40.20 (3.55)	40.65 (3.32)	39.58 (3.76)
Women	55.0% (1399)	52.7% (780)	58.2% (619)
Year 20 education (years)	16 (9–20)	16 (9–20)	14 (9–20)
Year 15 CRP (mg/L)	2.01 (2.16)	1.71 (1.93)	2.43 (2.38)
Year 20 CRP (mg/L)	1.78 (1.93)	1.45 (1.77)	2.23 (2.28)
Year 15 depressive symptoms	8.66 (7.57)	7.55 (6.75)	10.21 (8.35)
Year 20 depressive symptoms	9.01 (7.66)	8.10 (6.96)	10.29 (8.37)
BMI (kg/m^2)	28.65 (6.62)	27.42 (6.24)	30.38 (6.76)
SBP (mmHg)	116.13 (15.04)	112.71 (12.82)	120.88 (16.54)
HDL (mg/dL)	54.91 (16.62)	54.84 (16.78)	55.01 (16.40)
LDL (mg/dL)	110.07 (31.66)	110.31 (31.14)	109.73 (32.39)
Triglycerides (mg/dL)	103.83 (60.81)	110.17 (65.35)	95.01 (52.64)
Glucose (mg/dL)	96.92 (23.40)	95.53 (18.84)	98.86 (28.45)
Insulin (mg/dL)	15.67 (10.47)	14.42 (9.79)	17.41 (11.13)
Medical conditions	1 (0–16)	1 (0–16)	1 (0–12)
Medications	0 (0–6)	0 (0–6)	0 (0–4)
Taking OC/HT (women)	13.9% (195)	18.2% (142)	8.6% (53)
Taking antidepressants	10.3% (261)	13.0% (193)	6.4% (68)
Current/former smoker	36.9% (938)	37.5% (555)	36.0% (383)
Alcohol consumption (drinks/week)	4.66 (9.39)	5.24 (8.66)	3.84 (10.28)
Physical activity (EU)	351.20 (279.12)	379.80 (263.79)	311.35 (294.71)

[1] BMI = body mass index; SBP = systolic blood pressure; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; OC/HT = oral contraceptives/hormone therapy; EU = exercise units

[2] Values presented as mean (standard deviation; SD), median (range), or % (*n*)

[3] Data for all values collected at Year 20 unless otherwise specified

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Table 2

Pearson correlations of continuous sample characteristics with Year 15 depressive symptoms and Year 20 CRP (log_{10}) for the entire sample and separately by race.[2]

	Year 15 depressive symptoms			Year 20 CRP		
	Sample	**Whites**	**Blacks**	**Sample**	**Whites**	**Blacks**
Age at Year 15	−.03	−.03	.02	−.02	−.00	.04
Year 20 education	−.16***	−.07**	−.17***	−.13***	−.11***	−.01
Year 15 CRP	.06**	.04	.04	.66***	.62***	.68***
Year 20 CRP	.10***	.05†	.09***	-	-	-
Year 15 depressive symptoms	-	-	-	.10***	.05†	.09***
Year 20 depressive symptoms	.55***	.50***	.59***	.07***	.04	.04
BMI	.07	.06*	.01	.48***	.43***	.48***
SBP	.07***	−.01	.06*	.17***	.15***	.08*
HDL	−.02	−.03	−.01	−.19***	−.19***	−.19***
LDL	−.03	−.01	−.05	.09**	.10***	.09**
Triglycerides	.05*	.07*	.07*	.20***	.28***	.17***
Glucose	.09***	.08**	.08**	.17***	.16***	.16***
Insulin	.06*	.06*	.02	.32***	.32***	.28***
Medical conditions	.21***	.22***	.21***	.14***	.14***	.16***
Medications	.11***	.12***	.11***	.07***	.05†	.13***
Alcohol consumption	.02	.01	.06*	−.03	−.01	−.01
Physical activity	−.14***	−.11***	−.13***	−.16***	−.13***	−.16***

† $p<.10$.

* $p< .05$.

** $p< .01$.

*** $p< .001$

[1] CRP = C-reactive protein; BMI = body mass index; SBP = systolic blood pressure; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol

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Table 3

Mean differences in Year 15 depressive symptoms by level of model covariate[1]

	Sample (*n*=2544)		Whites (*n*=1481)		Blacks (*n*=1063)	
	Mean (SD)	**t_{diff}**	**Mean (SD)**	**t_{diff}**	**Mean (SD)**	**t_{diff}**
Sex		2.22*		.74		1.82†
Men	8.22 (6.99)		7.36 (6.33)		9.57 (7.74)	
Women	9.03 (8.00)		7.73 (7.11)		10.66 (8.73)	
Smoker status		5.90***		3.09**		5.74***
Never	7.98 (7.17)		7.13 (6.56)		9.12 (7.79)	
Current/former	9.79 (8.10)		8.25 (7.05)		12.02 (8.97)	
OC/HT (women)		2.91**		1.05		1.95†
No	9.14 (8.17)		7.88 (7.25)		10.61 (8.92)	
Yes	7.28 (6.22)		6.94 (5.50)		8.19 (6.41)	
Antidepressant use						
No	8.29 (7.16)	6.28***	7.09 (6.14)	5.50***	9.83 (8.05)	5.25***
Yes	11.94 (9.93)		10.62 (9.38)		15.68 (10.53)	

*$p < .05$.

**$p < .01$.

***$p < .001$.

[1] SD = standard deviation; t_{diff} = Student's *t*; OC/HT = oral contraceptive/hormone therapy

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Table 4

Mean differences in Year 20 CRP by level of model covariate[1]

	Sample (*n*=2544)		Whites (*n*=1481)		Blacks (*n*=1063)	
	Mean (SD)	**t_{diff}**	**Mean (SD)**	**t_{diff}**	**Mean (SD)**	**t_{diff}**
Sex		5.04***		3.02**		3.46***
Men	1.45 (1.63)		1.20 (1.39)		1.84 (1.90)	
Women	2.04 (2.28)		1.68 (2.04)		2.51 (2.49)	
Smoker status		1.98*		3.18**		.32
Never	1.75 (2.06)		1.35 (1.71)		2.29 (2.36)	
Current/former	1.82 (2.00)		1.61 (1.89)		2.11 (2.12)	
OC/HT (women)		7.83***		7.76***		3.90***
No	1.89 (2.19)		1.43 (1.86)		2.42 (2.42)	
Yes	2.99 (2.57)		2.71 (2.42)		3.75 (2.83)	
Antidepressant use		.44		.43		2.38*
No	1.76 (2.02)		1.44 (1.76)		2.33 (2.25)	
Yes	1.88 (2.17)		1.53 (1.89)		3.47 (2.61)	

*$p < .05$.

**$p < .01$.

***$p < .001$.

[1] SD = standard deviation; t_{diff} = Student's *t*; OC/HT = oral contraceptive/hormone therapy

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Table 5

Multivariate associations of Year 15 depressive symptoms and symptom subscores with Year 20 CRP.[1]

	Entire sample (*n* = 2544)		Whites (*n* = 1481)		Blacks (*n* = 1063)	
	B(SE)	**b**	**B(SE)**	**b**	**B(SE)**	**b**
CES-D depressive symptoms						
Model 1	.013 (.005)	.034*	.002 (.007)	.006	.028 (.008)	.079***
Model 2	.012 (.006)	.032†	−.001 (.008)	−.002	.031 (.009)	.089***
Depressed affect						
Model 1	.024 (.016)	.021	.006 (.024)	.005	.044 (.022)	.044*
Model 2	.028 (.018)	.025	.002 (.026)	.002	.055 (.024)	.055*
Positive affect						
Model 1	.030 (.014)	.031*	.012 (.019)	.013	.057 (.019)	.063**
Model 2	.028 (.015)	.029†	.007 (.021)	.007	.059 (.021)	.066**
Somatic symptoms						
Model 1	.033 (.017)	.029*	−.009 (.024)	−.007	.077 (.023)	.074***
Model 2	.026 (.019)	.023	−.019 (.026)	−.016	.075 (.026)	.072**
Interpersonal problems						
Model 1	.031 (.029)	.015	.037 (.044)	.016	.033 (.038)	.019
Model 2	.023 (.031)	.011	.016 (.047)	.007	.035 (.040)	.020

Model 1 covariates: age, sex, race (total sample), education, diagnoses, medications, OC/HT, BMI, LDL, HDL, triglycerides, glucose, insulin, smoking status, alcohol consumption, physical activity, Year 15 CRP

Model 2 covariates: Model 1 + Year 20 depressive symptoms

† $p<.07$.

* $p< .05$.

** $p< .01$.

*** $p< .001$.

[1] B = unstandardized beta; SE = standard error; *b* = standardized beta; CES-D = Center for Epidemiologic Studies Depression Scale