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Directionality of the relationship between depressive symptom dimensions and C-reactive protein in patients with acute coronary syndromes

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Abstract

Objective—Previous theoretical models predict that elevated inflammation may predict later depressive symptoms, but bidirectional associations are possible. We examined whether depressive symptoms or inflammation predict change in the other over a 3-month period in a sample of post-acute coronary syndrome (ACS) adults.

Methods—During hospitalization for their index ACS event (baseline), and then again 1 and 3 months later, 163 post-ACS patients completed the Beck Depression Inventory, a measure of depressive symptom severity with cognitive-affective and somatic-affective subscales. C-reactive protein (CRP) was also assessed at each visit; known correlates of depression and CRP were assessed at baseline. Path analyses were conducted to evaluate prospective associations among depressive symptoms and log-transformed CRP values and whether strength and/or directionality varied by specific depressive symptom dimensions.

Results—Baseline total depressive symptom severity predicted *a smaller decrease* in CRP from baseline to 1 month (unstandardized parameter estimates (B) = .04; $p < .001$) controlling for all covariates, as did baseline cognitive-affective depressive symptom severity (B = .10; $p = .02$). Baseline somatic-affective depressive symptom severity did not predict change in CRP (B = −.002; $p = .94$). CRP did not predict 1- or 3-month change in total, cognitive-affective, or somatic-affective depressive symptom severity. Results did not differ for men and women.

Conclusion—Greater cognitive-affective and total depressive symptom severity at the time of a cardiac event predicts a smaller decrease in CRP 1 month later, but there was no evidence in this study that CRP predicts change in depressive symptoms.

Keywords

depression; inflammation; acute coronary syndrome; depressive symptoms; risk factors; cardiovascular disease

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Introduction

Clinical depression diagnosis and depressive symptom severity are associated with elevated inflammation (1), and both depression and inflammation are independent risk factors for incident and recurrent cardiovascular events and mortality (2–6). Whereas several studies suggest that inflammation predicts subsequent change in depression (7–10), at least two recent studies have found that depression predicts subsequent change in inflammation (11, 12). Yet a third body of research points to complex, bidirectional relationships between inflammation and depression (13–15). The inconsistency among these studies has not been resolved, and it remains unclear whether depression or inflammation predicts subsequent change in the other.

Growing evidence suggests that somatic-affective depressive symptoms are particularly cardiotoxic (16–18), and thus consideration of depressive symptom dimensions may help clarify the relationship between depression and inflammation. In support of this argument, some studies have reported that cognitive-affective depressive symptoms do not predict inflammation (11, 19, 20), but that somatic-affective symptoms do (11). Yet another study found that both somatic symptoms and positive affect, but not depressed affect, independently predicted inflammation (12). These previous studies, however, have been limited to non-clinical samples and/or have used depression measures that primarily assess cognitive-affective symptoms. Moreover, other studies have demonstrated that administration of inflammatory agents elicits *both* somatic and cognitive depressive symptoms (21–23), with somatic symptoms often having an earlier onset, and cognitive symptoms having later onset (7). To clarify the association between depression and inflammation, studies based on clinical samples that use a broader assessment of depressive symptoms are therefore needed.

The first objective of the present study was to examine prospective associations of total depressive symptoms to low-grade systemic inflammation as measured by serum C-reactive protein (CRP) over a 3-month period in a sample of post-acute coronary syndrome (ACS) adults. We also examined and compared the independent prospective associations of both cognitive-affective and somatic-affective depressive symptoms to CRP.

Methods

Participants

Participants were 163 post-ACS patients in the Coronary Psychosocial Evaluation Study (COPES), a multicenter set of observational studies of patients hospitalized for ACS with data collection from May 2003 to April 2005. The Institutional Review Boards of the three university hospitals at which this study was conducted (Mount Sinai Hospital, New York, New York; Yale-New Haven Hospital; and Hospital of St. Raphael, New Haven, Connecticut) approved the protocol, and all participants provided written informed consent. Demographic characteristics of participants are shown in Table 1.

Procedures

Recruitment of patients occurred during hospitalization (baseline), as soon as patients were medically stable, and within 1 week of admission. All patients had a diagnosis of ACS (either acute myocardial infarction (MI) with or without ST-segment elevation or unstable angina) verified by study cardiologists using standard ACS criteria (24). In addition, participants had eligible scores on the Beck Depression Inventory (BDI) at baseline (0–4, indicating minimal depressive symptoms, or ≥ 10, indicating at least mild depressive symptoms). Completion of the BDI was repeated at 1- and 3-month follow-up; a fasting blood sample was obtained at each of the three time points. Certified staff used standard

protocols to measure height and weight and to obtain all risk factor data. All patients received evidence-based cardiac care during their ACS hospitalization.

Measures

CRP—Blood samples were maintained at 4°C until processing. After centrifugation, serum was drawn off and stored in aliquot portions at −70°C until the samples were shipped to a core laboratory (Specialty Laboratories, Valencia, CA) for high-sensitivity analysis of CRP. Concentrations of CRP were determined by turbidimetry (Bayer Diagnostics, Leverkusen, Germany). Only patients whose CRP level was measured during at least one visit were included in the analyses.

Depressive Symptom Severity—Depressive symptom severity was assessed with the BDI, (25) a 21-item self-report instrument with questions concerning the frequency and/or severity of depressive symptoms during the previous week (17). Patients rate the extent to which each symptom has been present or absent during the last week using a 4-point scale ranging from 0 to 3 for a total score of 0 – 63. BDI items also provide for the ascertainment of cognitive-affective (items 2–3, 5–9, 12, 14) and somatic-affective (items 1, 4, 10–11, 13, 15–17, 20–21) depressive symptom severity (17). The BDI has excellent psychometric properties, as shown with multiple community and medical samples (26). In the current study, Cronbach α at the baseline, 1-month, and 3-month assessments was above 0.90 for total BDI score, between 0.82 and 0.85 for the somatic-affective item score, and between 0.87 and 0.90 for the cognitive-affective item score.

Demographic and Biobehavioral Covariates—Information about age, gender, race/ethnicity (dichotomized as white or not), education (dichotomized as high school graduate or not), history of diabetes mellitus, history of any rheumatic condition, left ventricular ejection fraction (LVEF) (dichotomized as <40% or ≥ 40%), and antidepressant use at hospital admission or discharge was obtained at the baseline examination (see Table 1 for descriptive statistics).

Other primary risk factors for ACS, including mean arterial blood pressure, smoking status (current nonsmoker or current smoker), and height and weight (to compute body mass index [BMI]; calculated as weight in kilograms divided by height in meters squared), were assessed at baseline by physical examination, medical records, or self-report.

Data Analyses

Data analyses were modeled after those of Stewart and colleagues (11) and conducted using structured equation modeling software (Amos 17.0; SPSS Inc, Chicago, IL) (27). Level of CRP at each assessment was not normally distributed, and was thus log-transformed. The distributions of BDI scores at each assessment were also positively skewed. Although log transformation reduced the skew of BDI scores, we used untransformed BDI scores in all analyses to enhance interpretability of parameter estimates.1

Bivariate (i.e., Pearson) correlations were used to characterize the stability of BDI scores and CRP at baseline and at the 1- and 3-month follow-up visits. Bivariate correlations were also used to characterize the cross-sectional relationships between BDI scores and CRP at each visit. Cross-lagged path analyses were used to evaluate (1) baseline BDI as a predictor of CRP at 1 month, controlling for baseline CRP; (2) baseline CRP as a predictor of BDI at 1 month, controlling for baseline BDI; (3) 1-month BDI as a predictor of CRP at 3 months,

[1]We repeated all analyses with transformed BDI scores. Overall model fit and parameter estimates did not differ substantially in models with untransformed versus transformed BDI scores.

controlling for 1-month CRP; and (4) 1-month CRP as a predictor of 3-month BDI, controlling for 1-month BDI. The conceptual model guiding these analyses is presented in Figure 1.

Model fit was assessed by χ^2 tests, the comparative fit index (CFI), and the root mean square error of approximation (RMSEA) goodness-of-fit statistic. The χ^2 statistic measures the extent to which the model is consistent with observed data. A nonsignificant χ^2 statistic demonstrates that the difference between the hypothesized and observed patterns of relationships is not greater than that expected by chance, thus indicating that the hypothesized model is acceptable (28). The CFI is derived from a comparison of a hypothesized model with the independence model. Values of .95 or greater represent acceptable model fit. The RMSEA statistic adjusts the estimate of the absolute fit for the complexity of the hypothesized model. Smaller values of RMSEA indicate better model fit, with values less than .05 representing good model fit.

The PClose statistic was also used; a PClose value greater than .05 suggests that RMSEA is not significantly greater than its suggested cutoff of .05 (i.e., test of close fit). Parameters were estimated by full information maximum likelihood (FIML), which uses all of the observed data and is superior to traditional methods of handling missing data (such as pairwise or listwise deletion) (29).

As in Stewart and colleagues' work, (11) 4 variants of the path model shown in Figure 1 were estimated. The initial model (Model 1) included demographic variables (age, sex, race/ethnicity, and education) along with baseline, 1-, and 3-month total BDI score and CRP (Figure 2). Though not shown in the diagram, the model allowed for all correlations among the baseline variables. The equations for 1- and 3-month BDI and CRP included as predictors the corresponding measures at the previous visit (i.e., first-order autoregression). Thus, the estimates for the other predictors in each equation can be interpreted as the effect of that predictor on subsequent change in the outcome (e.g., 1- and 3-month change in CRP). Demographic variables were also allowed to affect change in BDI and CRP from baseline to 1- and 3-months, given that these covariates are plausible predictors of change in BDI and CRP, but the magnitude of the effect of each covariate on 1- and 3-month change was assumed not to vary.2 Finally, the following paths of primary interest (see Figure 1) were modeled: (1) from baseline BDI score to CRP at 1-month; (2) from baseline CRP to BDI score at 1-month; (3) from BDI score at 1-month to CRP at 3-months; and (4) from CRP at 1-month to BDI score at 3-months.

A fully controlled covariate model (Model 2) was then tested to examine whether the direction of the relationship between depressive symptoms and CRP was independent of variables known to influence these factors (30–34). This model added the effect of 5 risk factors on both CRP and BDI (i.e., BMI, history of diabetes mellitus, history of any rheumatic condition, antidepressant use at hospital admission or discharge, and smoking status) and 2 additional risk factors on CRP alone (mean arterial pressure and LVEF), because these covariates have been shown to be associated with CRP (31) and depression (31–34) .

To examine the differential predictive validity of specific symptom dimensions of depression in the depression-CRP relationship, we repeated the full model (Model 3), substituting both BDI cognitive-affective and somatic-affective subscale scores for BDI total scores (Model 3). As both BDI subscale scales were included in a single model, the results

[2]Adding these constraints did not result in a worse fit compared to a model without these constraints χ^2 (8, N =163) = 11.61, p = .17.

of this model demonstrate the effect of each depressive symptom dimension on CRP controlling for the other.

Finally, to examine whether the association between depressive symptom severity and CRP differs between men and women, a finding of previous studies, (35) multi-group path analyses were performed. In Models 1–3, we conducted χ^2 difference tests to examine possible gender differences in the coefficients of paths 1–4.

Given that our path models included the natural log transformation of CRP, the regression coefficients (B) for models predicting CRP are most interpretable if one calculates "$e^B - 1$" (36) . The result of this calculation equals the percent change in log-transformed CRP associated with each 1-point increase in BDI score. In this paper, we report "$e^{(5*B)} - 1$," where B is the regression coefficient for BDI predicting log-transformed CRP. The result equals the percent change in log-transformed CRP associated with each 5-point increase in BDI score.

Results

Bivariate Analyses: Associations Among Depressive Symptom Severity and Log-Transformed CRP

Baseline CRP was significantly correlated with 1-month CRP ($r = .29$, $p = .001$), and 1-month CRP was significantly correlated with 3-month CRP ($r = .40$, $p < .001$). CRP decreased by an average of 83% from baseline to the two follow-up assessments (Table 1). This finding is consistent with the course of recovery reported among other post-ACS patients. Among post-ACS patients in Phase Z of the A to Z Trial (37) as well as those in the MIRACL Study (38), for instance, median CRP decreased by approximately 74 to 88% over 4 months. In another study of 53 patients with unstable angina, 60% returned to a normal level of CRP (< 3 mg/L) during a 3-month follow-up period (39).

Baseline BDI score was significantly correlated with 1-month BDI score ($r = .78$, $p < .001$), and 1-month BDI score was significantly correlated with 3-month BDI score ($r = .74$, $p < .001$). Furthermore, BDI subscale scores were also significantly correlated with each other (all *r's* > .50) and with total BDI scores (all *r's* > .50) at each visit. Although baseline CRP was not correlated with baseline BDI total or subscale scores, 1- and 3-month CRP was significantly correlated with 1- and 3-month BDI scores, respectively (Table 2).

Multivariate Analyses: Prospective Associations Among Depressive Symptom Severity and Log-Transformed CRP

The unstandardized parameter estimates for Model 1, which controls for demographic factors, appear in Figure 2. Total BDI scores were strongly and positively related across visits, as were CRP values (all *Ps* < .001). Examination of the longitudinal, cross-lagged, depression-CRP paths revealed that each 5-point increase in baseline BDI score predicted a 28% smaller decrease in CRP from baseline to 1-month (B = .05, $e^{5*.05} = 1.28$, $p < .001$) (see statistical methods above), accounting for 10.9% of the variance in 1-month CRP that remained after removing the variance accounted for by baseline CRP and other covariates. Baseline CRP, however, did not predict change in BDI score from baseline to 1-month (B = −.05, $p = .88$). Similarly, BDI score at 1-month (B = .003, $p = .79$) did not predict change in CRP from 1- to 3-months, nor did CRP at 1-month (B = −.10, $p = .76$) predict change in BDI score from 1- to 3-months. Model 1 fit the data well, χ^2 (12, $N = 163$) = 17.85, $p = .12$, CFI = .99, RMSEA =.06 (90% confidence interval [CI] = .00–.11); PClose= .39. These results remained largely unchanged in Model 2, which controlled for additional covariates, χ^2 (27, $N = 163$) = 40.98, $p = .04$, CFI = .98, RMSEA =.06 (90% confidence interval [CI] = .01–.09); PClose= .35. Specifically, baseline BDI score continued to predict change in CRP

from baseline to 1-month (B = .04, $p < .001$). Baseline CRP did not predict change in BDI score from baseline to 1-month (B = −.02, $p = .96$). Similarly, BDI score at 1-month (B = .01, $p = .61$) did not predict change in CRP from 1- to 3-months, nor did CRP at 1-month (B = −.06, $p = .86$) predict change in BDI score from 1- to 3-months.

Model 3, in which both of the BDI subscale scores were substituted for the total BDI scores, did not fit the data as well but was still acceptable, χ^2 (44, $N = 163$) = 84.76, $p < .001$, CFI = .97, RMSEA =.08 (90% confidence interval [CI] = .05–.10); PClose= .04. Higher baseline cognitive-affective BDI score (B = .10, $e^{5*.10} = 1.65$, $p = .02$) significantly predicted change in CRP from baseline to 1-month, controlling for somatic-affective BDI score. Specifically, each 5-point increase in cognitive-affective BDI score predicted a 65% smaller decrease in CRP from baseline to 1-month, accounting for 8.4% of the variance in CRP remaining after removing the variance accounted for by baseline CRP and other covariates (including somatic-affective BDI score). The same was not true for baseline somatic-affective BDI score, which did not significantly predict change in CRP (B = −.002, $p = .94$). CRP did not predict change in either somatic-affective or cognitive-affective BDI score either from baseline to 1-month or from 1-month to 3-months. Neither somatic-affective nor cognitive-affective BDI score predicted change in CRP from 1- to 3-months (all *Ps* > .50). When somatic-affective symptoms were deleted from the model, the trimmed model was a better fit to the data, χ^2 (27, $N = 163$) = 47.45, $p = .01$, CFI = .97, RMSEA =.07 (90% confidence interval [CI] = .03–.10); PClose= .17.

Multiple-groups analyses indicated that gender did not moderate the association of depressive symptoms to CRP. Model 1 coefficients for baseline BDI score predicting 1-month CRP were similar for men (B = .03, $p < .02$) and women (B = .06, $p = .001$), and the test for any gender difference in paths 1 through 4 was nonsignificant, χ^2 (4, $N = 163$) = 6.19, $p = .19$. Tests for moderation by gender in Models 2 and 3 yielded similar results. As in the study conducted by Stewart and colleagues (11), the present study may have been underpowered to detect small moderating effects of gender.

When examining Models 1 through 3 without 1-month data, results were consistent with those reported above. Specifically, BDI score at baseline predicted change in CRP from baseline to 3-months (B = .04, $p = .003$). In contrast, CRP at baseline did not significantly predict change in BDI score from baseline to 3-months (B = .17, $p = .71$). Moreover, cognitive-affective (B = .16, $p < .001$), but not somatic-affective (B = −.03, $p = .37$), depressive symptoms significantly predicted change in CRP from baseline to 3-months. We further examined these longer lags with the 1-month data in the model. Baseline BDI score did not predict change in CRP from baseline to 3-months in this more comprehensive model (B = −.01, $p = .46$). This null finding is likely due to the strong association between 1- and 3-month CRP values ($r = .72$, $p < .001$).

Discussion

This study had two principle objectives. The first was to examine whether depressive symptoms or inflammation predict subsequent change in the other over a 3-month period in a sample of post-ACS adults. Overall, CRP decreased over 80% from hospitalization to 1-month—a finding is consistent with the course of recovery observed among other post-ACS patients (37–39). In cross-lagged path analytic models controlling for demographic and biobehavioral covariates of depressive symptoms and inflammation, we found that elevated baseline depressive symptoms severity predicted the degree of decrease in CRP from hospitalization to 1-month for both men and women. As baseline depressive symptom severity increased, there was a significantly lesser decrease in 1-month CRP. In contrast, CRP did not predict change in depressive symptom severity over 3 months of observation.

Of note, the magnitude of the unstandardized regression coefficients (B) cannot be compared across variables (i.e., BDI and CRP), as these coefficients are scale dependent.

The second objective of this study was to examine the prospective associations among depressive symptom dimensions and CRP. Using additional cross-lagged path analytic models, we found that cognitive-affective depressive symptom severity predicted the degree of decrease in CRP from hospitalization to 1-month, with greater symptom severity predicting a smaller CRP decrease; somatic-affective symptom severity was unrelated to CRP. Together, these findings suggest that total and cognitive-affective depressive symptom severity may predict poorer remission of underlying inflammation, which is implicated in the pathogenesis of recurrent CHD events in patients with ACS. To our knowledge, this is the first study to document a prospective association between depressive symptoms and inflammation in an adult population immediately following an ACS.

The present findings are in part consistent with two recent prospective longitudinal studies of depression and inflammation. The first of these studies found that greater baseline depressive symptom severity was associated with a 6-year increase in serum IL-6 among 263 healthy, older adults, independent of demographic and biobehavioral factors (11). The second showed a prospective association between greater baseline depressive symptom severity and a 20-year increase in CRP (12).Whereas both of these studies demonstrated that somatic-affective symptom severity, but not depressed affect, independently predicted subsequent changes in inflammation, the present findings in contrast suggest that this is not the case for CRP in post-ACS patients. Rather, change in CRP in the present study was best predicted by the cognitive-affective symptom dimension, and somatic-affective symptom severity was not independently related to subsequent change in CRP. The current finding also contrasts with a prospective occupational cohort study of British white-collar civil servants (19), which found that baseline CRP and IL-6 predicted cognitive symptoms of depression approximately 10 years later, and with a longitudinal study of inflammation and chronic stress among older community-based adults (20), which found that cognitive depressive symptoms did not predict 6-year change in IL-6. The most likely explanation for these discrepancies may lie in the nature of the samples. The current study involved a clinical sample with acutely elevated in-hospital inflammation, whereas the earlier studies each involved apparently healthy, community-based samples. Clinical conditions with such acute inflammation may therefore feature a qualitatively different relationship between depression and inflammation. In support of this argument, one cross-sectional study showed that elevated total and cognitive-affective depressive symptoms among 32 heart failure patients were significantly, positively correlated with tumor necrosis factor-alpha (TNF-α) (40). The current study extends this finding to patients with ACS using a longitudinal design.

Although the present findings are inconsistent with an inflammation-induced model of depression, in which markers of increased inflammation lead to onset or worsening of depressive symptoms, the possibility that such a model has relevance in the context of a hospitalization for ACS cannot yet be discarded. Studies that have provided support for inflammation-induced depression have predominantly involved either animal models (41) or samples of humans who have been administered exogenous, proinflammatory treatments (42). In contrast, the current study examined endogenous, naturally occurring concentrations of CRP.

What mechanisms might explain the prospective association of depression to inflammation? There are at least two plausible pathways: one via the intermediate effects of health behaviors and a second involving a more direct physiological pathway. Individuals with depression evidence poorer compliance with medical treatment, and this poorer compliance

may also help to explain the observed temporal relationship between depression and inflammation. A recent meta-analysis showed that depressed patients are 3 times more likely than nondepressed patients to be noncompliant with dietary recommendations, prescribed medication, health behavior recommendations, and diagnostic/screening follow-up (43). Post-ACS patients with depression are also less likely than those without depression to follow recommended behavior and lifestyle changes intended to reduce the risk of subsequent cardiac events, including recommendations for a low-fat diet, regular exercise, stress reduction, and socialization (44). Compared to post-ACS patients without depression, they are also less likely to take their prescribed cardiac medications, quit smoking, and attend cardiac rehabilitation (45, 46). Of note, this lack of adherence may be a manifestation of hopelessness, a cognitive-affective symptom of depression, as depressed patients who are hopeless may believe that no action will prove helpful in ameliorating their condition. Similarly, depression might be associated with deficits in cognitive functioning that are essential to remembering and following through with treatment recommendations, such as taking medication. These conjectures regarding the association between depression and noncompliance may thus help explain why only cognitive-affective and not somatic-affective depressive symptom severity predicted the degree of decrease in CRP in the present study.

Many behavioral factors mentioned above, including sedentary lifestyle, poor diet, alcohol intake, disturbed sleep, and weight change are cross-sectionally associated with both depression and inflammation (47), and each is a plausible mediator of the depression-to-inflammation relationship (48–50). Although BMI was unrelated to depressive symptom severity in the current study, higher adiposity, perhaps secondary to sedentary lifestyle, may represent a particularly important mechanism by which depression affects level of inflammation, contributing as it does to production of proinflammatory cytokines and acute-phase reactants (51). Similarly, physical inactivity and tobacco use, which are common among patients with depression, have direct effects on inflammation (52, 53). These putative mechanisms linking depression and inflammation will need to be assessed repeatedly and explored in subsequent samples of post-ACS patients.

It has also been suggested that the association between depression and inflammation may be related to neuroendocrine and autonomic dysregulation (9). Activation of the sympathetic nervous system and hypothalamus-pituitary-adrenal axis has been causally implicated in proinflammatory and acute-phase reactant expression in animal models (54, 55), and depression is associated with increased circulating cortisol, which is known to exert long-term effects on lipid metabolism and inflammation by promoting the accumulation of triglycerides in adipocytes (56). Furthermore, patients with depression display exaggerated inflammatory and sympathetic nervous system responses to acute psychosocial stress tasks (57). As Pace and colleagues suggest, these increased responses to acute stressors, if representative of everyday life, might result in a chronic state of low-grade inflammation.

The clinical significance of the present findings must also be considered. To do so, one might apply the regression equation from Model 2 of the current study to two hypothetical people—one without depressive symptoms (BDI score = 0) and another with elevated depressive symptoms (BDI score = 16). If those two hypothetical people had the predominant characteristics of our sample (i.e., were white males with more than a high school education who smoked but had no history of diabetes or rheumatoid conditions), then the person without baseline depressive symptoms would have a predicted 1-month CRP of 2.66 mg/L, whereas the person with elevated baseline depressive symptoms would have a predicted 1-month CRP of 3.30 mg/L, a difference with potentially important prognostic implications. Although the cardiotoxic level of CRP among post-ACS patients 1-month after

hospitalization has not been clearly established, it is thought that in-hospital CRP greater than 3 mg/L is associated with worse cardiac prognosis (39).

This study has the following strengths: 1) it features a sample of post-ACS patients; 2) it includes measures of both cognitive-affective and somatic-affective depressive symptoms; and 3) it uses a longitudinal design with repeated assessments of depression and CRP. Notwithstanding these strengths, the study also has limitations. First, only one marker of inflammation was assessed, and it is possible that the relationship between other inflammatory markers and depression differs. Second, because the sample included only 24 (15%) non-White adults, these findings may not generalize to other racial or ethnic groups. Third, only a single assessment of depressive symptom severity and CRP was obtained at each time point. As Stewart and colleagues (11) noted, within-person variation of inflammatory markers (58) may have compromised the reliability of the estimates, and reliability would have been increased had 2 separate measurements been gathered and averaged for each time point. Although within-person variation of depressive symptoms has also been documented (26), the large correlations between baseline, 1-, and 3-month BDI scores suggest that unreliability in depression assessment was not a limitation of the present study. However, the short follow-up and timing of our initial assessment of depression may have contributed to several of the null findings reported in our models, as assessments of depression that occur 2 or more weeks after an index MI have stronger associations with cardiac outcomes than assessments that occur sooner after the index event (59). Future longitudinal studies should vary the timing of assessment of both depression and inflammation to explore these differential relations further. Finally, the analyses in this study did not include a clinical diagnosis of depression, and it remains possible that the relationship between depression and inflammation differs when considering depressive symptoms versus depression diagnosis. However, the inclusion of antidepressant medication use as a covariate did not affect any of the findings.

In summary, this study suggests that both greater total and cognitive-affective depressive symptom severity at the time of an ACS predicts a smaller decrease in CRP from the time of event to 1-month follow-up among men and women. These findings imply that depression may prolong the pro-inflammatory state seen in ACS and thereby contribute to increased risk for early death and recurrent ACS associated with depression.

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Abbreviations

IL-6	interleukin-6
CRP	C-reactive protein
TNF-α	tumor necrosis factor-alpha
ACS	acute coronary syndrome
MI	myocardial infarction
CHD	coronary heart disease
COPES	Coronary Psychosocial Evaluation Study

BDI	Beck Depression Inventory
CFI	comparative fit index
RMSEA	root mean square error of approximation
AIC	Akaike Information Criterion
FIML	full information maximum likelihood
BMI	body mass index
LVEF	left ventricular ejection fraction

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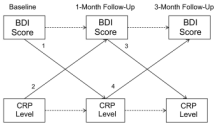

Figure 1.
Conceptual path analytic model. Abbreviations: BDI, Beck Depression Inventory; CRP, C-reactive protein. Note. The variables represented in this figure are observed values and not change scores.

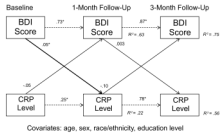

Figure 2.

Base path analytic model with unstandardized path estimates. Abbreviations: BDI, Beck Depression Inventory; CRP, C-reactive protein. *p < .05. Note. The variables represented in this figure are observed values and not change scores.

Table 1

Characteristics of 163 patients with acute coronary syndromes

Characteristic	Value
Demographic Factors	
Age, years [a]	59.61 (12.68)
Women, % (*n*)	43.6 (71)
Non-white, % (*n*)	14.7 (24)
High school graduates, % (*n*)	87.7 (143)
Clinical Factors	
Mean arterial pressure, mmHg[a]	84.78 (12.78)
BMI, kg/m^2[a]	30.65 (7.52)
History of diabetes mellitus, % (*n*)	27.6 (45)
History of rheumatic conditions, % (*n*)	25.8 (42)
LVEF < 40%, % (*n*)	14.1 (23)
ACS Type	
Unstable angina, % (*n*)	42.9 (70)
Non-ST segment elevation MI, % (*n*)	30.7 (50)
ST segment elevation MI, % (*n*)	26.4 (43)
Behavioral Factor	
Current smokers, % (*n*)	58.9 (96)
Depression Measures	
BDI Total Score (range, 0–63)[a]	
Baseline (n = 163)	8.68 (8.81)
1-month follow-up (n = 153)	7.63 (8.51)
3-month follow-up (n = 151)	7.19 (8.82)
BDI Somatic-Affective Score (range, 0–30)[a]	
Baseline (n = 163)	5.60 (5.21)
1-month follow-up (n = 153)	5.60 (5.21)
3-month follow-up (n = 151)	4.46 (4.97)
BDI Cognitive-Affective Score (range, 0–27)[a]	
Baseline (n =163)	2.67 (3.75)
1-month follow-up (n = 153)	2.31 (3.59)
3-month follow-up (n = 151)	2.38 (4.06)
Inflammation Measure	
CRP concentration, mg/L[b]	
Baseline (n = 158)	13.08 (32.58)
1-month follow-up (n = 121)	2.30 (4.59)
3-month follow-up (n = 125)	2.18 (4.51)

[a] Values are mean (SD);

[b] Values are median (interquartile range).

Note. BMI, body mass index; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; MI, myocardial infarction; BDI, Beck Depression Inventory; CRP, C-reactive protein.

Table 2

Unadjusted bivariate associations between log-transformed CRP and BDI scores

	Baseline Visit			1-month Follow-up			3-month Follow-up		
	Total BDI	**Somatic-Affective BDI**	**Cognitive-Affective BDI**	**Total BDI**	**Somatic-Affective BDI**	**Cognitive-Affective BDI**	**Total BDI**	**Somatic-Affective BDI**	**Cognitive-Affective BDI**
Baseline CRP	.05	.02	.08	.02	.04	−.07	−.03	−.05	−.07
1-month CRP	.38**	.35**	.38**	.38**	.40**	.26*	.33*	.33	.30
3-month CRP	.31**	.29*	.28*	.31*	.33**	.16	.22*	.21*	.15

* $p < .05$,

** $p < .001$.

Notes. BDI = Beck Depression Inventory; CRP = C-reactive protein

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