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Brief report

Association between C-reactive protein and depressive symptoms in women with rheumatoid arthritis

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ABSTRACT

Converging lines of evidence support an association between systemic inflammation and depressive symptoms. Neuroimmune pathways may account for the high prevalence of depression in individuals with inflammatory conditions such as rheumatoid arthritis (RA). However, this relationship is complicated by factors linked to both inflammatory disease activity and mood, such as pain and physical disability. The goal of this cross-sectional study was to examine the relationship between C-reactive protein (CRP) and depressive symptoms among 173 women with RA. Somatic symptoms of depression and circulating CRP were significantly associated in regression analyses adjusted for body mass index ($\beta = .19$, $p < .05$), but this relationship was attenuated when pain and disability were included as covariates ($\beta = .09$, $p = .24$). CRP was not significantly associated with negative mood symptoms of depression. Findings suggest that depression in the context of RA may result from the overlap of somatic depressive and RA symptoms rather than neuroimmune pathways.

In response to infection, cytokines coordinate biological changes to clear the pathogen and promote tissue repair. Peripheral proinflammatory cytokines also act on neural substrates to produce psychiatric symptoms including fatigue, anorexia, impaired learning and memory, and reductions in exploratory, social, and sexual behavior (Dantzer et al., 2008; Maier and Watkins, 1998). These "sickness behaviors" are hypothesized to serve evolutionary functions by prioritizing recuperation and allocating metabolic resources to fighting infection.

Striking overlap between sickness behaviors and symptoms of clinical depression has stimulated scientific interest in the role of inflammation in the pathophysiology of mood disorders (Maes, 1995; Raison et al., 2006). In healthy adults, experimental administration of inflammatory stimuli transiently increases both sickness behaviors and negative mood (Reichenberg et al., 2001; Wright et al., 2005). Community-based studies report a positive correlation between depressed mood and circulating markers of inflammation such as C-reactive protein (CRP; Bremmer et al., 2008; Ford and Erlinger, 2004; Suarez, 2004). These converging lines of evidence support a positive association between systemic inflammation and both somatic and affective depressive symptoms.

Neuroimmune pathways are postulated to explain the high prevalence of depression in inflammatory conditions such as rheumatoid arthritis (RA; Dantzer et al., 2008; Lorton et al., 2008). RA is a female-predominant autoimmune disease characterized by chronic inflammation of multiple joints and elevated levels of circulating inflammatory markers. Depression is a common comorbidity in RA patients, with a prevalence rate of 20% (Dickens et al., 2002; Katz and Yelin, 1993). Preliminary evidence supports an association between biomarkers of systemic inflammation (e.g., CRP and erythrocyte sedimentation rate) and depressive symptoms in RA patients (Dessein et al., 2004; Odegard et al., 2007). However, these biomarkers also reflect RA activity (Wolfe, 1997), and the association between inflammation and depression may be confounded by factors linked to both disease activity and mood such as pain, physical disability, and medications. Because symptoms of RA overlap considerably with somatic symptoms of depression (e.g., fatigue and sleep difficulties), the extent to which inflammatory processes are related to these sickness behavior-like symptoms versus negative mood in RA also warrants examination.

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Table 1
Descriptive statistics and bivariate correlations ($n = 173$).

Demographic/general health	M (S.D.) or %	Correlation coefficients			
		CRP	CES-D total	CES-D negative mood	CES-D somatic
Age (years)	58.9 (10.4)	.08	−.13	−.06	−.05
Body mass index (kg/m^2)	28.0 (6.1)	.13	.12	.06	.18*
Ethnicity (Caucasian)[a]	95%	.04	.03	.07	.08
College/graduate degree[a]	56%	.15*	−.03	−.04	.04
Married[a]	66%	.14	−.10	−.18*	−.07
Postmenopausal[a]	80%	.11	−.08	−.05	.02
Current smoker[a]	8%	−.05	.00	.10	.10
Rheumatoid arthritis variables					
RA duration (years)	16.3 (10.8)	.03	−.02	−.04	−.05
Current corticosteroid use[a]	44%	.16*	.12	.06	.13
Current use of TNF inhibitors[a]	31%	−.19*	.03	.01	.07
Pain in past week (15 cm VAS)	4.7 (3.4)	.29***	.17*	.16*	.30***
mHAQ disability index (0–3)	.7 (.6)	.29***	.10	.12	.20**
Physician-rated RA activity (VAS)	2.5 (2.5)	.33***	.00	−.02	.07
Physician-rated RA severity (VAS)	4.9 (3.3)	.21**	−.03	−.05	.08
Inflammatory markers					
C-reactive protein (mg/L)[b]	12.5 (18.1)	–	.13	.06	.20**

[a] Point-biserial.
[b] Correlation computed using log-transformed values.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

The goal of this study was to examine the relationship between CRP[1] and depressive symptoms among women with RA. We hypothesized that CRP would be positively associated with depressive symptoms, especially somatic symptoms, but that this relationship would be attenuated when pain and disability were statistically controlled.

1. Methods

1.1. Participants

Data for the present analyses were collected in a study of risk factors for cardiovascular disease in women with RA (Kao et al., 2008). Participants were recruited from the University of Pittsburgh Medical Center Arthritis Network outpatient practices between 2000 and 2004. Eligibility requirements included RA diagnosis at age ≥16 years and RA duration ≥2 years. The sample includes 173 women for whom self-report measures of depressive symptoms were collected.

1.2. Procedure

Participants visited the General Clinical Research Center after overnight fasting and provided blood samples before 11 a.m. for assessment of CRP. At this time, they also completed self-report measures, and a physician completed a physical examination and rating of disease activity and severity using 10 cm visual analog scale (VAS). Participants also completed electron beam computed tomography to assess coronary artery calcification; these data are reported elsewhere (Kao et al., 2008) and are not included in the current analyses.

1.3. Measures

1.3.1. Depressive symptoms

The Center for Epidemiological Studies—Depression Scale (CES-D; Radloff, 1977) is a 20-item scale assessing the frequency of depressive symptoms in the past week. Total scores range from 0 to 60 with higher scores indicating more depressive symptomatology. The CES-D contains four subscales (negative affect, lack of positive affect, somatic complaints, and interpersonal symptoms), and the five-item negative affect and somatic symptom subscales were examined in addition to the total score. The CES-D has been used in a variety of clinical populations, including individuals with RA, and has demonstrated excellent psychometric properties (Blalock et al., 1989).

1.3.2. CRP

CRP was measured using latex immunonephelometry at the Laboratory of Clinical Biochemistry Research (University of Vermont, Burlington, VT, USA). Samples were assayed in a single batch and blinded to clinical data. This assay has inter-assay coefficient of variation <5%. Because of skewed distribution, CRP values were log-transformed prior to analyses.

1.3.3. RA-related disability and pain

Participants completed the modified Health Assessment Questionnaire (mHAQ), a well-validated instrument used to calculate arthritis-related disability (Pincus et al., 1983). The 15 cm VAS component of the mHAQ was used to determine pain. Participants also reported on current medications, including use of corticosteroids and anti-cytokine agents.

1.3.4. Covariates

General health and demographic covariates examined for inclusion in the multivariate models included participant age, ethnicity, education, marital status, body mass index (BMI; calculated from measurements of weight and height), menopausal status, and current smoking. Pearson correlations were examined to identify which demographic and general health covariates should be included in models.

1.4. Statistical analyses

Statistical analyses were conducted using SPSS for Windows (version 15.0). Primary analyses were hierarchical linear regression analyses to determine the variance in depressive symptomatology (total, depressed mood, and somatic) accounted for by CRP and RA-related factors. First, general health and demographic covariates that were significantly correlated with depressive symptoms ($p < .05$, two-tailed) were entered in the first step of the model, followed by log-transformed CRP. The second set of models included RA-related variables associated with CES-D scores ($p < .05$, two-tailed). In these fully adjusted models, demographic and general health covariates were entered in the first step, RA-related variables in the second step, and CRP in the third step.

2. Results

Characteristics of the sample are presented in Table 1, along with bivariate correlations between demographic and general health factors, CRP, and depressive symptoms. Mean CES-D scores were 15.1, comparable to previous RA samples (Covic et al., 2006), and 40% of respondents had scores that exceeded the cutoff of 16 suggestive of clinical depression (Radloff, 1977). Higher education was associated with higher CRP, married women reported less

[1] Relationships between erythrocyte sedimentation rate and depressive symptoms were also examined. No significant associations were observed in unadjusted or adjusted models, and these data are not shown.