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Cynical Hostility, Depressive Symptoms, and the Expression of Inflammatory Risk Markers for Coronary Heart Disease

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Although the prognostic significance of depression and hostility has been established, little is known about how they operate together to influence disease processes. This study explored the independent and interactive relationships between these constructs and the expression of inflammatory markers implicated in the pathogenesis of coronary heart disease. One hundred adults completed measures of cynical hostility and depressive symptoms, and had blood drawn to assess serum levels of interleukin-1β, interleukin-6, and tumor necrosis factor-α. Depression was directly related to inflammatory markers, but hostility was not. A significant interaction between hostility and depression emerged. Among participants scoring low in depressive symptoms, hostility was positively associated with interleukin-6 and tumor necrosis factor-α concentrations. Hostility's association with these inflammatory markers was much weaker among participants with moderate depressive symptoms, however, and virtually nil among participants with severe depressive symptoms. Neither depression nor hostility was associated with interleukin-1β concentrations. These findings highlight the importance of considering both the independent

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and interactive relationships among psychosocial characteristics involved in disease.

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Accumulating evidence indicates that psychosocial characteristics contribute to morbidity and mortality in the context of coronary heart disease (CHD) (for a review, see Rozanski *et al.*, 1999). The strongest evidence of this process derives from studies exploring the prognostic significance of depressive symptoms and cynical hostility. In this regard, prospective studies have documented an elevated incidence of CHD among initially healthy persons who endorse depressive symptoms (Anda *et al.*, 1993; Barefoot and Schroll, 1996; Everson *et al.*, 1996; Ford *et al.*, 1998; Pratt *et al.*, 1996; for a review, see Musselman *et al.*, 1998). Parallel findings have emerged in studies of established cardiac disease; the risk of mortality is elevated among CHD patients who are depressed (Carney *et al.*, 1988; Frasure-Smith *et al.*, 1993,1995; for a review, see Glassman and Shapiro, 1998). The prognostic significance of cynical hostility also has been established in prospective studies. Adults with a cynically hostile attitude show higher rates of incident CHD, a greater risk of premature mortality, and increased cause-specific mortality in the context of CHD (Barefoot *et al.*, 1983; Dembroski *et al.*, 1989; Matthews *et al.*, 1977; Miller *et al.*, 1996; Shekelle *et al.*, 1983; for reviews, see Matthews, 1988; Smith, 1992).

Although the prognostic significance of depression and hostility has been established, little is known about how these constructs function together to influence disease outcomes. This dearth of knowledge is surprising given that hostility and depression have a strong tendency to cluster within individuals (Raynor *et al.*, 2002). These constructs also share a number of affective (anger, disgust, anxiety) and cognitive features (overgeneralizing, dichotomous thinking, automatic negative cognitions), although in the case of hostility much of the thought and affect is directed towards others, and in the case of depression it is directed towards the self (Smith, 1992). These observations raise questions about the extent to which depression and hostility promote disease independently or do so via redundant mechanisms. Of course, it is also possible that these constructs promote disease in an interactive fashion. Indeed, a recent study of healthy young adults found that cynical hostility and depressive symptoms interacted to predict higher levels of interleukin-6, an inflammatory molecule involved in the pathogenesis of CHD (Suarez, in press). While these are provocative findings, this study did not provide information about these constructs' independent relationships with interleukin-6, or their relationships with other inflammatory molecules known to be involved in atherosclerosis.

This study investigates the relationships among cynical hostility, depressive symptoms, and the biological processes implicated in the pathogenesis of CHD. Given the emerging consensus that atherosclerosis is a chronic inflammatory disease (Ross, 1999), we focus on circulating concentrations of the proinflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These cytokines are soluble molecules, which are released by white blood cells and vascular endothelial cells, and which orchestrate the inflammatory response. They contribute to the progression of CHD by facilitating the growth of atherosclerotic plaques, precipitating the rupture of established plaques, and potentiation of the coagulation processes involved in thrombus formation (Libby, 2001; Ross, 1999). In prospective studies, elevated circulating concentrations of IL-1β, IL-6, and TNF-α have been linked with an increased risk of morbidity and mortality due to CHD (Biasucci *et al.*, 1999; Ridker *et al.*, 2000a,b,c).

METHOD

Participants

One hundred adults participated in the investigation. The sample consisted primarily of women (68% female and 32% male). The participants averaged 30.2 (SD = 10.0) years of age and 15.0 (SD = 2.3) years of education. Total family incomes averaged $15,000–20,000 annually. The sample was ethnically diverse, composed of African Americans (48%), Caucasians (44%), Asian Americans (6%), and Latinos/Chicanos (2%). The majority of participants had never been married (64%). The rest were either married (18%) or separated/divorced (18%).

Participants were recruited as part of a larger study examining the relationship between clinical depression and inflammatory markers (Miller *et al.*, 2002). To be eligible for the study, participants had to be in good physical health, defined as having (a) no history of chronic medical illness, (b) no indications of acute infectious disease in the past 2 weeks, and (c) no prescription medications in the past 6 months apart from oral contraceptives. Other exclusion criteria included malnutrition as assessed by serum albumin; pregnancy in the past year; being menopausal or postmenopausal; or irregular menstruation.

Participants were community-dwelling adults recruited through advertisements in local newspapers and public transportation systems. The sample consisted of equal numbers of depressed and nondepressed participants. To qualify for the study, depressed participants had to meet the *DSM-IV* criteria for major depressive disorder ($N = 32$) or minor depressive disorder ($N = 18$) (American Psychiatric Association, 1994). Diagnoses were

made by trained interviewers utilizing the Depression Interview and Structured Hamilton (DISH) (Freedland *et al.*, 2002). Participants with comorbid Axis I disorders (other than generalized anxiety disorder, specific phobias, and nicotine dependence) were excluded on the basis of structured interviews with modified versions of the Diagnostic Interview Schedule (Robins *et al.*, 1981) and the Primary Care Evaluation of Mental Disorders (Spitzer *et al.*, 1994). The control subjects were required to have a lifetime history free of Axis I psychiatric disorders other than specific phobias and nicotine dependence.

Procedures

All participants attended an initial laboratory session. After the study procedures had been outlined by a research assistant, each subject provided written informed consent. There were no dropouts during this phase of the study. Subjects then participated in medical and psychiatric screening interviews, completed questionnaires regarding their health practices, and underwent a series of anthropometric measurements. The latter data were used to compute indices of total adiposity (*body mass index*) and central adiposity (*waist–hip ratio*). Participants were then seated in a comfortable chair and had three blood pressure readings collected at 2 min. intervals (Dinamap Pro 100; Critikon Corporation; Tampa, FL). Thirty-five-milliliters of blood was then drawn by antecubital venipuncture. After the blood had been centrifuged for 15 min. at $1000 \times g$, the serum was aspirated, divided into aliquots, and frozen at -70°C until the end of the study. At that time, thawed serum was used to assess inflammatory risk markers (see below for methods) and total serum cholesterol (by standard enzymatic techniques). To minimize random measurement error, subjects returned for a follow-up session 1 week later, during which most study variables were reassessed in an identical fashion. All of the subjects returned for this second session; however, we experienced venipuncture difficulties with two subjects and were not able to obtain follow-up blood samples from them. All blood draws were performed during the early morning hours to control diurnal variation. Upon completion of the study, participants were given $150 as compensation. These procedures were approved by the Institutional Review Board of Washington University.

Psychosocial Measures

The severity of participants' depressive symptoms was assessed using the Beck Depression Inventory (BDI) (Steer and Beck, 1996). The BDI is

a 21-item self-report measure with excellent psychometric characteristics. It showed high levels of internal consistency ($\alpha = 0.96$) and temporal stability (across 1 week, $r_s = 0.94$) in our sample. The extent of participants' cynical hostility was assessed using the 27-item version of the Cook–Medley Hostility Scale (Barefoot *et al.*, 1989). This scale exhibited good internal consistency in our sample ($\alpha = 0.85$). Because hostility was assessed during the second laboratory session only, we could not estimate the temporal stability of this scale.

Inflammatory Risk Markers

We assessed circulating levels of three inflammatory risk markers (IL-1β, IL-6, TNF-α) that have been implicated in the pathogenesis of CHD. The markers were assessed using commercially available, high-sensitivity ELISAs (R&D Systems, Minneapolis, MN). The intra-assay coefficients of variation for these kits are 4.6% (IL-6), 5.9% (TNF-α), and 15% (IL-1β). To evaluate the markers' temporal stability, Spearman rank-order correlations were computed between values derived from the two blood draws. The r_s values were 0.69 (IL-6), 0.60 (TNF-α), and 0.23 (IL-1β). The poor stability for IL-1β may have been the result of the low levels found in our subjects, more than one quarter of whom had values below the assay's detection threshold. A value of 0.10 pg/mL of IL-1β was assigned to these participants, corresponding to the minimum detection threshold provided by the manufacturer. Because the inflammatory markers had positively skewed distributions, they were transformed to log 10 values prior to statistical analysis. (For IL-6 the skew values were 2.69 and 2.10 at the initial and follow-up blood draws, respectively. The corresponding skew values were 2.87 and 3.15 for TNF-α and 7.13 and 3.33 for IL-1β.) Aggregate indices were then created for each marker by averaging logged values across sessions.

RESULTS

Descriptive Statistics

Participants' average score on the BDI was 12.30, corresponding to a mild level of depressive symptoms. However, there was considerable variability around this average (SD = 13.16), and scores fell fairly evenly across the entire distribution (skew coefficient = 0.66), owing to the inclusion of healthy controls as well as participants with both minor and major depression. The average score on the Cook–Medley Scale was 9.84, which

corresponds to mean values found in other samples of community-dwelling adults (Barefoot *et al.*, 1993). There was considerable variability around this average as well (SD = 5.56), and scores fell fairly evenly across the entire distribution (skew coefficient = 0.49). As would be expected of constructs that cluster within individuals and share many features, depressive symptoms and cynical hostility were highly correlated in this sample, $r = 0.63$, $p < 0.001$. Note that the strong relation between these predictors should, if anything, diminish our chances of detecting independent and interactive relationships between these constructs and inflammatory markers (Aiken and West, 1991). The mean values for inflammatory markers were 0.26 pg/mL (SD = 0.49) for IL-1β, 2.44 pg/mL (SD = 1.81) for IL-6, and 5.63 pg/mL (SD = 7.07) for TNF-α, all of which are in the range one would expect from young, healthy adults. In terms of zero-order correlations between psychosocial constructs and inflammatory molecules, depressive symptoms were negatively related to levels of IL-1β ($r = -0.28$, $p < 0.01$), positively related to IL-6 ($r = 0.26$, $p < 0.01$), and unrelated to TNF-α ($r = 0.15$, ns). Cynical hostility was not significantly related to IL-1β ($r = -0.08$, ns) or TNF-α ($r = 0.05$, ns), but was positively associated with IL-6 ($r = 0.19$, $p < 0.05$).

Preliminary Analyses

The preliminary analyses sought to identify potential confounds that might provide alternative explanations for any relationships among cynical hostility, depressive symptoms, and inflammatory markers. The potential confounds considered were demographic characteristics (age, gender, ethnicity, education, income, marital status) and CHD risk factors (cigarette smoking, body mass index, waist–hip ratio, total serum cholesterol, mean arterial pressure, oral contraceptive use). As the correlations in Table I illustrate, seven of these variables (age, ethnicity, education, cigarette smoking, body mass index, waist–hip ratio, oral contraceptive use) showed consistent univariate relationships with hostility, depression, and inflammation, and were thus used as covariates in multivariate analyses testing the study's primary hypotheses.

Cynical Hostility, Depressive Symptoms, and Inflammatory Markers

The study's primary hypotheses were examined by computing a series of hierarchical multiple regression equations in which the expression of each inflammatory marker was predicted by three blocks of variables entered consecutively. The blocks consisted of (a) the seven potential confounds

Table I. Relations Between Depressive Symptoms, Cynical Hostility, Inflammatory Molecules, and Biobehavioral Characteristics

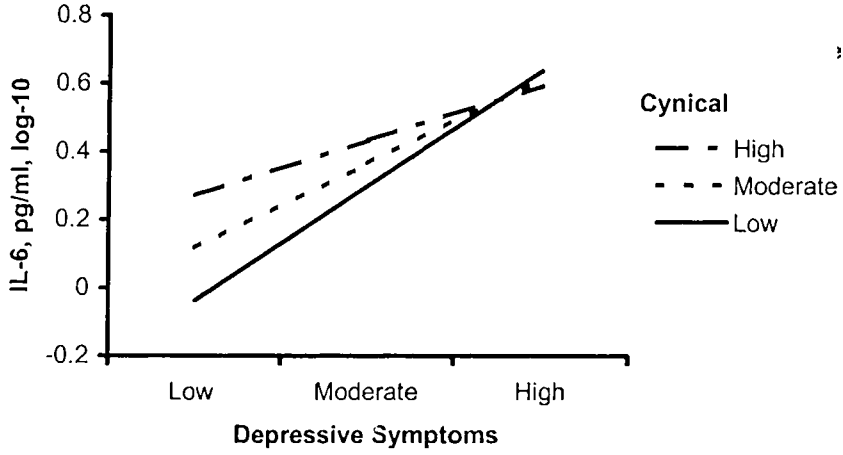
Biobehavioral characteristic	Dep. symp.	Cyn. host.	IL-1β	IL-6	TNF-α
Age	−0.04	−0.07	−0.19	0.25*	−0.02
Gender (male/female)	−0.04	−0.15	0.16	0.13	0.12
Ethnicity (White/Black/other)	0.10	0.20*	0.18	0.18	0.11
Education (years)	−0.30**	−0.16	0.05	−0.15	0.08
Income (annual)	−0.19	−0.02	−0.10	0.11	−0.04
Married (no/yes)	0.09	0.04	0.04	−0.12	−0.04
Regular smoker (no/yes)	0.57***	0.56***	−0.10	0.10	−0.10
Body mass index	0.31***	0.13	−0.15	0.63***	0.08
Waist–hip ratio	0.28**	0.24*	−0.25*	0.22*	−0.18
Serum cholesterol	0.00	−0.03	−0.07	0.12	−0.05
Mean arterial pressure	0.19	0.13	0.19	−0.05	−0.17
Oral contraceptives (no/yes)	0.20*	−0.26**	−0.01	−0.20*	−0.04

Note. Values in cells are Pearson's correlations (for continuous variables) or point–biserial correlations (for categorical variables). Dep. Symp. = Depressive symptoms; Cyn. Host. = Cynical hostility.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

identified in preliminary analyses, (b) the independent effects of depressive symptoms and cynical hostility, and (c) a product term representing the interactive relationship between these factors. When a statistically significant interaction emerged, it was interpreted according to the guidelines outlined by Aiken and West (1991). This procedure involved plotting simple regression lines in which inflammatory markers were regressed upon depressive symptoms as a function of three values of cynical hostility. Following Aiken and West's recommendations (Aiken and West, 1991), low values of each factor were defined as 1 standard deviation below the sample mean, moderate values as at the sample mean, and high values as 1 standard deviation above the sample mean.

A significant independent relationship emerged between depressive symptoms and IL-6. To the extent that they endorsed more severe depressive symptoms, participants exhibited higher circulating concentrations of IL-6 ($B = 0.02$, $SE = 0.006$, $\beta = 0.88$, $t = 3.04$, $p < 0.004$). Although cynical hostility was not independently associated with IL-6 ($B = 0.008$, $SE = 0.01$, $\beta = 0.17$, $t < 1.0$, ns), a significant depressive symptoms × cynical hostility interaction illustrated why this might be the case (for the interaction term, $\Delta R^2 = 0.03$, $F_\Delta = 4.95$, $p < 0.03$). As the data in Fig. 1(A) illustrate, among participants who scored low in depressive symptoms, cynical hostility was positively associated with IL-6 concentrations. However, the association between hostility and IL-6 was much weaker among participants with moderate depressive symptoms, and virtually nil among participants with the highest levels of depressive symptoms.

1A.



1B.

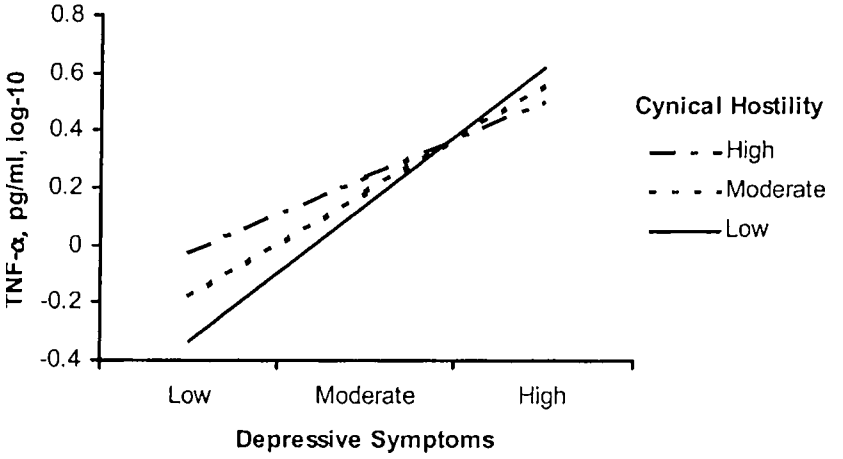


Fig. 1. Cynical hostility, depressive symptoms, and the expression of interleukin-6 (Panel A) and tumor necrosis factor-α (Panel B). Following the guidelines articulated by Aiken amd West (1991), low levels of each factor were defined as 1 standard deviation below the sample mean, moderate levels as at the sample mean, and high levels as 1 standard deviation above the sample mean.

A similar pattern of findings emerged for TNF-α. There was a significant positive relationship between depressive symptoms and TNF-α concentrations ($B = 0.03, SE = 0.01, \beta = 0.96, t = 2.57, p < 0.02$). Cynical hostility was not independently associated with TNF-α ($B = 0.004$, $SE = 0.02$, $\beta = 0.09$, $t < 1.0$, ns). However, as the data in Fig. 1(B) illustrate, there was a significant depressive symptoms $\times$ cynical hostility interaction for this marker (for the interaction term, $\Delta R^2 = 0.05$, $F_\Delta = 4.21$, $p < 0.04$). Whereas cynical hostility was positively associated with TNF-α concentrations among participants lower in depressive symptoms, this association was much weaker among participants with moderate depressive symptoms, and virtually nil among participants with the highest levels of depression.

For IL-1β, neither the independent effects of depressive symptoms and cynical hostility (depression: $B = 0.02$, $SE = 0.02$, $t = 1.15$, ns; hostility: $B = 0.04$, $SE = 0.02$, $t < 1.6$, ns), nor their interaction, achieved statistical significance (for the interaction term, $\Delta R^2 = 0.00$, $F_\Delta < 1.0$, ns).

Because this study was designed to enroll participants who either were clinically depressed or had a negative psychiatric history, some readers may wonder whether it was appropriate to treat depressive symptoms as a continuous variable in these analyses. We elected to do so because (a) we believe that depression is best viewed as a dimensional rather than a categorical entity and (b) our sample had a fairly continuous distribution of depressive symptoms as a result of including participants with both minor and major depression. Nevertheless, to allay concerns about this strategy, we computed a follow-up series of regression equations, in which participants were categorized as nondepressed (BDI scores of 0–9), mildly depressed (10–16), moderately depressed (17–29), or severely depressed (30$\geq$) according to guidelines provided by the scale's creators (Steer and Beck, 1996). A similar pattern of findings emerged in these analyses. For TNF-α, there was a significant positive relationship between depression category and cytokine concentration ($B = 0.163$, $SE = 0.054$, $\beta = 0.57$, $t = 3.01$, $p < 0.003$), as well as a significant interactive relationship between depression category and cynical hostility (for the interaction term, $\Delta R^2 = 0.038$, $F_\Delta = 4.12$, $p < 0.05$). For IL-6, the findings were in a similar direction, though weaker in nature. The independent relationship between depression category and IL-6 concentration was nonsignificant ($B = 0.027$, $SE = 0.03$, $\beta = 0.16$, $t = 0.91$, $p = 0.37$), and the interactive relationship between depression category and cynical hostility dropped to $p < 0.13$ (for the interaction term, $\Delta R^2 = 0.01$, $F_\Delta = 2.37$), although both of these effects were in the same direction as the findings presented earlier. Given the loss of statistical power associated with transforming a predictor from continuous into categorical, it is not surprising that slightly weaker results emerged in this follow-up analysis.

DISCUSSION

Mounting evidence indicates that depressive symptoms and cynical hostility increase the risk of morbidity and mortality due to CHD. Although these factors share many features, and cluster within individuals, it is not clear how they operate together to influence disease outcomes. This study began to address this problem by exploring the independent and interactive relationships between these constructs and biological processes involved in the pathogenesis of CHD. We found a significant independent relationship between depressive symptoms and inflammatory markers. To the extent that they endorsed more severe depressive symptoms, participants exhibited higher circulating concentrations of both IL-6 and TNF-α. These findings contribute to a growing body of evidence linking depressive symptoms with inflammatory processes (Appels *et al.*, 2000; Dentino *et al.*, 1999; Kop *et al.*, 2002; Lutgendorf *et al.*, 1999; Maes *et al.*, 1997; Miller *et al.*, 2002), and in doing so, highlight an important pathway through which depression might contribute to morbidity and mortality in CHD (Carney *et al.*, 2002; Kop and Cohen, 2001).

Although we did not find evidence of an independent relationship between cynical hostility and inflammatory markers, the significant interaction between depressive symptoms and cynical hostility offered a plausible explanation for this null finding. As Fig. 1 shows, among participants who scored low in depressive symptoms, cynical hostility was positively associated with IL-6 and TNF-α concentrations. Cynical hostility's association with inflammatory markers was much weaker among participants with moderate levels of depressive symptoms, however, and virtually nil among participants with the highest levels of depressive symptoms. In other words, a positive relation between cynical hostility and inflammatory markers dissipated as the severity of depressive symptoms increased. This is a classical additive interaction with a ceiling effect.

What might explain this pattern of findings? According to the transactional model, cynically hostility fosters a pattern of abrasive social interactions, which activate biological processes involved in disease progression (Smith, 1992). Whereas abrasive social interactions might promote such biological processes among euthymic individuals (Miller *et al.*, 1999), their capacity to do so could be blunted among depressed individuals, who are likely to be withdrawn from social activities. It is also possible to advance a physiological explanation for these findings. Low-density lipoproteins (especially oxidatively modified lipoproteins) can trigger inflammatory responses (Libby, 2001; Ross, 1999). Mounting evidence indicates that cynically hostile individuals have elevated levels of low-density lipoproteins compared with their nonhostile counterparts (Brindley *et al.*, 1993; Suarez *et al.*, 1998). While

this process could promote inflammation among normal individuals, its effects would be abrogated among depressed individuals, who have decreased levels of low-density lipoproteins (Morgan *et al.*, 1993; Suarez, 1999). Regardless of the mechanism(s) responsible, the pattern of findings obtained here suggests that cynical hostility and depressive symptoms activate the inflammatory response through different pathways. If these factors operated through a similar pathway, IL-6 and TNF-α levels should have been comparably elevated in participants endorsing high cynical hostility/low depressive symptoms and low cynical hostility/high depressive symptoms. This was not the case.

These findings are partially consistent with a recent study exploring cynical hostility, depressive symptoms, and IL-6 expression in healthy, young men (Suarez, in press). Although this study also found evidence of an interaction, the relationship between these factors took a slightly different form, with hostility and depression operating synergistically to increase the expression of IL-6. The reason(s) underlying these discrepant findings are unclear. The studies differed with respect to gender composition (68% vs. 0% female), severity of participants' depression (clinical vs. nonclinical samples), rates of cigarette smoking (19% vs. 0%), and use of oral contraceptives (16% vs. 0%). Differences in health practices seem unlikely to explain the discrepant findings, however, as the current study statistically controlled for this. Given that hostility's affective, behavioral, and physiological manifestations differ by gender (Miller *et al.*, 1999; Smith *et al.*, 1990; Smith and Brown, 1991), it is tempting to speculate that the interactive relationship between depressive symptoms and cynical hostility assumes a different form in men and women. In exploratory analyses, we did test for a three-way interaction between gender, depression, and hostility in predicting inflammatory markers. A reliable interaction between these variables did not emerge. However, with the small number of males in this study, power to detect this effect was quite limited, and we think it would be premature to rule out the gender-difference hypothesis. Thus, it will be critical for future research to explore this issue further, as well as elucidate gender's role in shaping affective experiences (e.g., anger, sadness) and endocrine processes (metabolic and reproductive hormones) that elicit inflammation.

The cross-sectional design of this study precludes us from making any causal inferences regarding the associations between depressive symptoms, cynical hostility, and inflammatory markers. Products of the inflammatory response can induce symptoms of dysphoria, irritability, and anhedonia (Maier and Watkins, 1998; Musselman *et al.*, 2001; Yirmira, 1996); hence, it is possible that inflammation, rather than depression and hostility, represents the starting point in this process. To clearly delineate the relations among these factors, prospective longitudinal studies with multiple assessments will be

necessary. The study also was not optimally designed to explore the relations between depressive symptoms and cynical hostility. In future research it will be important to address this issue in population-based samples that include a more complete distribution of scores on both measures, and/or a "four-corners" design that crosses high vs. low depressive symptoms with high vs. low cynical hostility. The findings also were not entirely consistent across inflammatory markers. The lack of an effect for IL-β may be attributable to its low stability across the follow-up period, or the fact that our assay was unable to reliably detect this marker in more than one quarter of the sample. Finally, because this study's outcome measures were limited to inflammatory markers, future research will need to examine whether its findings extend to clinical outcomes such as morbidity and mortality. Along these lines, it bears noting that a study of patients undergoing percutaneous transluminal coronary angioplasty found an interactive relationship between trait anger (a common affective manifestation of hostility) and vital exhaustion (a state of fatigue, irritability, and malaise, all of which can accompany depression), such that patients endorsing high levels of both traits had an elevated incidence of recurrent cardiac events (Mendes de Leon *et al.*, 1996). Despite these limitations, our findings provide a preliminary indication of the value of considering both the independent and interactive relationships between depressive symptoms and cynical hostility. They also suggest a biological pathway through which these factors might contribute to the pathogenesis of CHD, as well as other medical conditions that involve inflammatory cytokines (e.g., diabetes mellitus, rheumatoid arthritis, multiple sclerosis).

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