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Effects of perceived stress and uplifts on inflammation and coagulability

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Abstract

We investigated whether depressed mood and chronic hassles and uplifts predicted levels of hemostasis markers D-Dimer and type-1 plasminogen activator inhibitor (PAI-1), as well as the proinflammatory markers interleukin-6 (IL-6) and soluble intercellular adhesion molecule-1 (sICAM-1) in 108 healthy individuals. One hundred eight African-American and Euro-American men and women were studied (58 men, 50 women; mean age = 36.5 ± 8 years). D-Dimer, PAI-1, IL-6, and sICAM-1 plasma levels were analyzed from fasting venous blood samples. Data were analyzed via hierarchical linear regression and followed with partial correlation analysis. Regression analyses combined with partial correlation analyses suggested that increases in hassle frequency predicted elevated levels of sICAM-1 ($p = .034$), and increases in hassle severity predicted elevated levels of D-Dimer ($p = .017$). Increases in uplift intensity predicted lower levels of PAI-1 ($p = .004$) as well as showed a trend for decreased IL-6 ($p = .069$). Depressed mood did not significantly predict any dependent variable. These results were independent of sociodemographic, biological, and other related mood variables. The findings suggest that for even relatively healthy persons, increased perceptions of hassles are independently associated with greater inflammation and hypercoagulability, whereas increased perceptions of uplifts are independently associated with decreased hypercoagulability.

Descriptors: Inflammation, Hemostasis, Stress, Hassles, Uplifts, Depression

The deleterious effects of chronic stress and depression on cardiovascular health have been documented for decades (Centers for Disease Control, 2004; Levenstein, Smith, & Kaplan, 2001; Strine, Greenlund, Brown, Mokdad, & Balluz, 2004). The physiological pathways by which stress and depression might exert their negative effects on cardiovascular health are numerous but incompletely understood. For example, stress and depression are often linked with poorer health behaviors (such as smoking, poor diet, and sedentary lifestyle) and thus may impact disease progression via the mediation of health behaviors (Levenstein et al., 2001; Strine et al., 2004). In addition, distress and depression are often related to ethnic and socioeconomic status, which are, in turn, related to accessibility of health care services (Centers for Disease Control, 2004; Gee & Payne-Sturges, 2004). Finally, although there appear to be direct relationships between negative mood states and inflammatory immune processes (Panagiotakos et al., 2004; Rosenkranz et al., 2003; Wright, Strike, Brydon, & Steptoe, 2005), these relationships have not always been found in clinical and nonclinical populations (Annique et al., 2005; Steptoe, Kunz-Ebrecht, & Owen, 2003).

Alterations in proinflammatory and hemostasis processes play crucial roles in atherosclerosis initiation, progression, and ultimately acute coronary events (Folsom, 2001; Plutzky, 2001; Ross, 1999). Not surprisingly, markers for these processes are increasingly being examined in the context of the effects of mental disorders on cardiovascular risk progression. Several studies examining clinical depression in otherwise healthy persons have noted elevations in inflammatory cytokines interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and interleukin-1 beta (IL-β) in persons with major depressive disorder compared to those with subclinical or no depression (Maes et al., 1997; Miller, Stetler, Carney, Freedland, & Banks, 2002; Owen, Eccleston, Ferrier, & Young, 2001; Penninx et al., 2003; Thomas et al., 2005). In addition, several large-scale studies have reported elevations in acute phase proteins (such as C-reactive protein and fibrinogen) for persons with clinical levels of depressed mood or history of major depression (Douglas, Taylor, & O'Malley, 2004; Ford & Erlinger, 2004; Lederbogen et al., 2001; Panagiotakos et al., 2004; Penninx et al., 2003). Relations between subclinical depressive symptoms and inflammatory and procoagulant activities in otherwise healthy persons are mixed

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and therefore less clear (Douglas et al., 2004; Steptoe et al., 2003; Suarez, Lewis, Krishnan, & Young, 2004).

In terms of chronic stress in otherwise healthy populations, studies with stressed Alzheimer caregivers have reported increases in IL-6 compared to age-matched, non-caregiver controls (Kiecolt-Glaser et al., 2003; Lutgendorf et al., 1999), and our group has also reported an increase in plasma levels of procoagulant marker D-Dimer in caregivers versus non-caregiving controls (von Kanel et al., 2005). Vital exhaustion, another model for chronic stress, has been consistently shown to be associated with alterations in hemostasis, particularly with respect to impaired fibrinolysis (Kop, Hamulyak, Pernot, & Appels, 1998; Raikkonen, Lassila, Keltikangas-Jarvinen, & Hautanen, 1996; van der Ven et al., 2003; van Diest, Hamulyak, Kop, van Zandvoort, & Appels, 2002; von Kanel, Frey, & Fischer, 2004). However, apart from these relatively specific models of chronic stress, little is known about potential effects of chronic perceived stress on inflammation and hemostatic function in otherwise healthy persons.

D-dimer, a degradation product of fibrin, reflects both coagulant and fibrinolytic activity (Lip & Lowe, 1995). Plasminogen activator inhibitor-1 (PAI-1), well known for its crucial role in inhibiting fibrinolysis (Juhan-Vague, Morange, & Christine Alessi, 1999), is also an acute phase protein (Hoekstra, Geleijnse, Schouten, & Kluft, 2004). Circulating levels of soluble intercellular adhesion molecule-1 (sICAM-1) provide an indication of ICAM-1 (Gearing et al., 1992), an adhesion molecule expressed on the surface of endothelial cells that plays an important role in the early steps of atherosclerosis (Huo & Ley, 2001) via its mediation of adhesion of leukocytes to the endothelium and subsequent transmigration in the vessel wall (Ross, 1999).

Interleukin-6 (IL-6) is a pleiotropic cytokine that is well known for its role in numerous proinflammatory functions (Heinrich et al., 2003). For example, in addition to promoting the expression of ICAM-1 on endothelial cells (Caldenhoven et al., 1994), IL-6 is a major catalyst for the acute phase response promoting release of acute phase proteins such as C-reactive protein and fibrinogen, as well as PAI-1 (Streetz, Wustefeld, Klein, Manns, & Trautwein, 2001). Importantly, all of these molecules have been shown to be independent predictors of coronary artery disease (CAD) morbidity and mortality across different populations (Danesh et al., 2001; Haim et al., 2002; Kohler & Grant, 2000; Rattazzi et al., 2003; Ridker, Hennekens, Roitman-Johnson, Stampfer, & Allen, 1998).

Thus, although the effects of chronic stress and clinical depression on alterations in hemostasis and inflammation have been documented, it is not well understood whether gradations in depressed mood and perceptions of chronic stress impact these clinically relevant physiological processes in healthy, relatively young populations. In addition, the potential buffering effects of positive appraisals of life events are also poorly understood. We therefore investigated whether perceptions of chronic stress and uplifts as well as depressed mood in relatively young, healthy individuals predicted levels of plasma levels of hemostasis variables fibrin D-dimer (DD) and PAI-1, the cytokine IL-6, and sICAM-1.

Method

Participants

Participants were recruited by local advertisement or by word of mouth to participate in a larger study examining the links between stress and the sympathetic nervous system. The Institutional Review Board of the University of California San Diego approved the study protocol, and all participants provided written informed consent.

Approximately 350 potential subjects volunteered for the study. After screening for eligibility and availability of participants for the study, 132 completed the study and 108 participants had complete data available for this analysis. Persons who were not enrolled in the study were those who did not meet the eligibility criteria or could not be excused from work to participate in the study. Participants were excluded if they had a diagnosis of clinical illness other than hypertension (e.g., diabetes, severe asthma), sleep disorders warranting CPAP or other treatment, were taking prescription drugs other than for hypertension, had blood pressure (BP) $\geq$ 180/110 mm Hg, or had a history of psychosis. In addition, post-menopausal women, women who self-reported premenstrual syndrome, or women taking oral contraceptives or who were pregnant were excluded from the study. Participants whose systolic or diastolic BP was $\geq$ 140/90 mm Hg (based on an average of three assessments of seated BP after 5 min of rest) were categorized as being hypertensive. All participants had a normal electrocardiogram (e.g., no signs of left ventricular hypertrophy). Participants on an antihypertensive drug regimen underwent a 3-week tapering phase of their medication during which BP was closely monitored. No participants were regularly taking other prescription drugs.

Demographic and Health Characteristics

Participants' ethnic status was based on self-identification. Body mass index (BMI) was computed as the ratio of body weight in kilograms divided by the square of height in meters (kg/m^2). Smokers were defined as those who currently smoked more than one cigarette per day. Social class was determined using the clinician-rated Hollingshead 2-Factor Index of Social Position, which considers the subject's stated occupation and education (Hollingshead, 1957). The two factors are then weighted and combined into a global index of social class of five incremental levels with level 1 representing the highest social position.

Self-Report Questionnaires

Participants completed the following questionnaires relating to mood and stress.

Center for Epidemiological Studies Depression Scale (CESD). The CESD is a 20-item gold-standard depression scale that has been in use for several decades (Radloff, 1977). It is often used in outcomes research with clinical populations and has been shown to have excellent reliability and validity in several populations (Eaton, Muntaner, Smith, Tien, & Ybarra, 2003; Radloff, 1977).

Cook–Medley Stress. This four-item subscale of the well-known, reliable, and valid Cook–Medley Hostility Inventory (Cook & Medley, 1954; Smith & Frohm, 1985) is was used to assess feelings of chronic stress over the past month. We have previously used this subscale in examining racial differences in stress and blood pressure responses (Mills, Berry, & Dimsdale, 1997).

Combined Hassles and Uplifts Scale (CHUS). This 53-item questionnaire was used to measure both perceived hassles and perceived uplifts over the past month. This scale is divided into four subscales: Hassles Frequency, which is the number of events rated as a hassle; Hassles Severity, which is the average of Likert-

based ratings of the severity of each hassle; Uplifts Frequency, which is the number of events rated as an uplift; and Uplifts Intensity, which is the average of Likert-based ratings of the intensity of each uplift. Participants may rate events as hassles, uplifts, or both. This questionnaire has been shown to have good reliability and validity, predicting mood and somatic health outcomes (DeLongis et al., 1982; DeLongis, Folkman, & Lazarus, 1988; Zarski, 1984) as well as being somewhat related to positive and negative affect (Kanner, Coyne, Schaefer, & Lazarus, 1981).

Measures of Hemostasis and Inflammation

All participants had fasting venous blood samples drawn at 7:00 a.m. to avoid circadian influences on variables of interest. An indwelling 22-gauge forearm catheter was placed with minimal cuff stasis. Plasma for all assays (D-Dimer, PAI-1, IL-6, and sICAM-1) was obtained from whole blood drawn into 10-cc plastic tubes containing 3.8% of sodium citrate, after discarding the first 2 ccs of whole blood. Immediately following the draw, the blood was spun in a refrigerated centrifuge between 4°C and 8°C for 10 min at 3000 × *g*. The plasma was aliquoted into polypropylene tubes for different assays and stored in a −80°C freezer until assayed. IL-6 was assessed first, followed by sICAM-1 assays, to avoid possible degradation from freezing–thawing of plasma samples. Hemostasis molecules were assayed using the same aliquot of plasma (distinct from the one used for IL-6 and sICAM-1).

Plasma D-Dimer, PAI-1 antigen (both from Asserachrom, Diagnostica Stago, Asnières, France), sICAM-1, and IL-6 (both from R&D Systems, Minneapolis, MN) were determined by commercially available enzyme-linked immunosorbent assays (ELISAs). The intra-assay coefficients of variation for the D-dimer, PAI-1, sICAM-1, and IL-6 ELISAs were 2.5%, 3.1%, 3.4%, and 3.8%, respectively. The respective interassay coefficients of variation for these four assays were 9.5%, 5.6%, 3.4%, and 4.2%.

Statistical Analyses

Data were analyzed using hierarchical linear regression via the SPSS (version 11.5) statistical software package (Chicago, IL). Due to nonnormality of the distributions of the hemostasis and inflammation markers, all plasma data were log-transformed prior to analysis; however, for clarity, all measures are given in original units. Of these 108 participants, 10 did not have data for sICAM-1, and 1 had missing data for IL-6. One participant had sICAM-1 values 3 *SD* above the mean (996 ng/ml), and 2 participants had D-Dimer values 3 *SD* above the mean (2184 ng/ml, 4651 ng/ml). These 3 persons with extreme values were excluded from their respective analyses.

Separate linear regressions were conducted with each log-transformed inflammatory marker as the dependent variable, with two blocks within each regression analysis. The first block consisted of biological and sociodemographic variables that have been shown to influence hemostasis and inflammation processes to varying degrees (Hioki et al., 2001; von Kanel, Mills, Fainman, & Dimsdale, 2001; Wilkerson & Sane, 2002; Winkler, 1997). These covariates were BMI, age, gender, ethnicity, smoking status, hypertension status, and social class; all were correlated at $p < .10$ with at least one plasma marker in our data set. The second block consisted of the stress and depression predictor variables: the CESD, the Cook-Medley Stress, and the four subscales of the CHUS. Because we used 12 predictor variables for our data set of 108 participants, our alpha level was set to .10 for the purpose of identifying significant predictor variables within the multiple regression (alpha levels for the omnibus *F* test remained at .05).

Table 1. *Sociodemographic and Biological Characteristics of Sample (n = 108)*

Demographic characteristic	Number (*N*) or mean value with standard deviation (*M* ± *SD*)
African-American	*N* = 49
Euro-American	*N* = 59
Women	*N* = 50
Men	*N* = 58
Age (years)	*M* = 36.5 (± 8)
BMI	*M* = 26.3 (± 5)
Smokers	*N* = 19
Nonsmokers	*N* = 89
Hypertensives (BP ≥ 140/90 mm Hg)	*N* = 19
Nonhypertensives	*N* = 89
CESD Depression Score	*M* = 10.6 (± 9.5)
CHUS[a] Hassles Frequency Score	*M* = 29.9 (± 10.3)
CHUS Hassles Severity Score	*M* = 1.4 (± 0.33)
CHUS Uplifts Frequency Score	*M* = 34.0 (± 9.4)
CHUS Uplifts Intensity Score	*M* = 1.9 (± 0.37)
PAI-1 (ng/mL)	*M* = 34.1 (± 43.7)
D-Dimer (ng/mL)	*M* = 249 (± 137.6)
IL-6 (pg/mL)	*M* = 1.7 (± 1.3)
sICAM-1 (ng/mL)	*M* = 221.8 (± 111.7)

[a]CHUS: Combined Hassles and Uplifts Scale.

To better clarify the relationship between the significant predictor of a hemostasis/inflammatory factor in the multiple regression model while controlling for other variables, we conducted partial correlation analyses. The association of the psychological variable with each hemostasis/inflammatory marker of interest was examined, while controlling for relevant sociodemographic and/or biological variables as well as other psychological scales that were correlated at $p < .10$ with the psychological variable examined. These analyses were conducted to help resolve any ambiguities on whether certain psychological variables were indeed significant predictors of changes in the hemostasis or inflammatory marker of interest, or possibly appeared significant due to colinearity with any other psychological variables. Alpha levels for significance for partial correlations were set to .05. Because IL-6 and sICAM-1 had only one psychological predictor to examine via partial correlation, alpha levels for these analyses remained at .05. For PAI-1 and D-Dimer, Bonferroni corrections were used to adjust for multiple comparisons (i.e., $\alpha/2$ for D-Dimer, and $\alpha/3$ for PAI-1).

Results

Characteristics of participants are depicted in Table 1. Hierarchical linear regressions revealed that increasing Hassles Frequency as well as decreasing social class, being a smoker, and being African-American predicted elevated plasma sICAM-1, $F(13,95) = 3.2$, $p = .001$. This model accounted for 33.7% of the variance in sICAM-1, with hassles frequency predicting 2.8% of the variance. Decreasing Uplifts Intensity as well as increasing age and being African-American and a smoker predicted higher plasma IL-6, $F(13,106) = 2.5$, $p = .006$. This model accounted for 25.7% of the variance in IL-6, with uplifts intensity predicting 2.8% of the variance.

Increasing Cook–Medley Stress, decreasing Uplifts Intensity, and increasing Uplifts Frequency predicted elevations in PAI-1,

Table 2. *Partial R^2 Values (p Value) for Predictors of Markers in Multiple Regression Analyses*

	sICAM-1	IL-6	PAI-1	D-Dimer
Ethnicity	.044 (.022)	.063 (.006)		
Gender				.112 (<.0001)
Age		.029 (.060)		.010 (.0004)
Hypertension status			.024 (.040)	
BMI			.231 (<.0001)	.036 (.027)
Social class	.043 (.024)			
Smoking status	.033 (.047)	.022 (.072)		
CES-Depression				
CHUS Hassles Frequency	.028 (.065)			
CHUS Hassles Severity				.030 (.043)
CHUS Uplifts Frequency			.023 (.048)	
CHUS Uplifts Intensity		.028 (.063)	.012 (.072)	.027 (.053)
Cook–Medley Stress			.016 (.099)	

as did hypertension diagnosis and increasing BMI, $F(13,105) = 6.6$, $p = .0000$. This model explained 48.2% of the variance in PAI-1, with 1.6% of the variance explained by Cook–Medley Stress, 2.3% of the variance explained by uplifts frequency, and 1.2% of the variance explained by uplifts intensity. Finally, increasing CHUS Hassles Severity, decreasing CHUS Uplifts Intensity, increasing age and BMI, and female gender all predicted increases in D-Dimer, $F(13,105) = 3.8$, $p = .0000$. This model accounted for 34.9% of the variance in D-Dimer, with hassles severity predicting 3% of the variance and uplifts intensity predicting 2.7% of the variance. Results for these hierarchical regressions (including partial r^2 values and p values for each significant predictor) are depicted in Table 2.

Next, we examined bivariate correlations between the Cook–Medley Stress, CESD, and the CHUS scales. These correlations are presented in Table 3. The Cook–Medley Stress questionnaire, the CESD, and the CHUS hassles scales were significantly correlated with each other. The CHUS uplifts scales were correlated with each other, but not with the CESD or Cook–Medley Stress scales. Interestingly, the hassles severity and uplifts intensity subscales, as well as the hassles frequency and uplifts frequency subscales, were highly and significantly *positively* correlated, perhaps due to shared method variance (as the methods for identifying and rating each hassle/uplift are identical).

Given that some regression models had several psychological scales that appeared as significant predictors of hemostasis/inflammatory variables, and given that some of these psychological scales were related to each other, we conducted partial correlation analyses with the variables of interest. In these analyses, each significant psychological predictor variable was examined for its relation with the dependent marker, while controlling for significantly related psychological scales as well as significantly related sociodemographic and biological variables.

Results indicated that the partial correlation of hassles frequency with sICAM-1 (controlling for ethnicity, smoking, social class, CESD, hassles severity, uplifts frequency, and Cook–Medley Stress) was significant, partial $r = .23$, $p = .034$. The partial correlation of uplifts intensity with IL-6 (controlling for smoking, age, ethnicity, hassles severity, and uplifts frequency) was marginal, partial $r = -.17$, $p = .069$. For PAI-1, the partial correlation of uplifts intensity with PAI-1 (controlling for BMI, hypertension diagnosis, hassles severity, and uplifts intensity) was significant, partial $r = -.26$, $p = .004$. The partial correlation of Cook–Medley Stress with PAI-1 (controlling for BMI, hypertension diagnosis, CESD, hassles frequency, and hassles severity) was not significant, partial $r = .15$, $p = .112$, nor was the partial correlation of uplifts frequency with PAI-1 (controlling for BMI, hypertension, hassles frequency, hassles severity, and uplifts intensity), partial $r = .15$, $p = .10$. For D-Dimer, the partial correlation of hassles severity (controlling for BMI, gender, age, and all other psychological variables) was significant, partial $r = .23$, $p = .017$, whereas the partial correlation for uplifts intensity with D-Dimer (controlling for BMI, gender, age, hassles severity, and uplifts intensity) was not significant, partial $r = -.14$, $p = .138$.

Thus, results of our partial correlation analyses confirmed that increased hassles severity uniquely predicted increased D-Dimer, increased hassles frequency uniquely predicted increased sICAM-1, and increased uplifts intensity uniquely predicted decreased PAI-1, with a trend for decreased IL-6.

Discussion

Although the literature suggests that depression and chronic stress are associated with alterations in hemostasis and inflammatory activity, it is unclear whether these effects can also be

Table 3. *Bivariate Correlations of Psychological Variables*

	CESD	CHUS Hassles Frequency	CHUS Hassles Severity	CHUS Uplifts Frequency	CHUS Uplifts Intensity	Cook–Medley Stress
CESD		.432**	.405**	.059	−.111	.623**
CHUS Hassles Frequency			.164*	.461**	−.129	.232*
CHUS Hassles Severity				−.171*	.185*	.376**
CHUS Uplifts Frequency					.168*	−.057
CHUS Uplifts Intensity						−.064

**Correlation is significant at the <.05 level (two-tailed).
*Correlation is significant at the <.10 level (two-tailed).

detected among relatively healthy populations independent of sociodemographic and health status variables. In addition, little is known about potential buffering effects of positive appraisals of life events on hemostatic and inflammatory processes. Our results indicate that for a relatively healthy (with the exception of mild hypertension) sample of Euro-American and African-American men and women, hassles and uplifts significantly and independently predict changes in hemostasis and inflammation markers, independent of sociodemographic, biological, and related psychological measures, including depressed mood. Specifically, we have found that increasing uplifts intensity independently predicts decreases in PAI-1, and shows a trend to decrease IL-6. Increasing hassles severity independently predicts increases in D-Dimer, and increasing hassles frequency independently predicts increases in sICAM-1. Notably, decreasing social class was also associated with increased sICAM-1, a finding that has been previously reported and discussed by our group (Hong, Nelesen, Krohn, Mills, & Dimsdale, 2006).

Taken together, these results suggest that perceived chronic stress and uplifts may have a unique and significant effect on inflammatory processes as well as hemostasis. As mentioned earlier, IL-6, in addition to promoting inflammatory processes related to increased ICAM-1 expression (Caldenhoven et al., 1994), is a potent instigator of the acute phase response (Streetz et al., 2001). Thus IL-6 promotes the release of PAI-1 as well as fibrinogen (which eventually leads to formation into fibrin and, subsequently after degradation, to D-Dimer). In examining the net interactions of these inflammatory and haemostatic markers, our data suggest that the net effect of increased hassles may serve to promote hypercoagulabilty, whereas the effect of increased uplifts may serve to decrease hypercoagulability. In addition, increased perceptions of hassles may serve to increase other inflammatory processes as reflected by increases in IL-6 and sICAM-1. Future research with a wider array of key hemostatic and inflammatory markers and a path modeling approach would be necessary to further confirm these contentions.

Interestingly, depression ratings did not predict any variables for our sample. The mean value of CESD scores for our 108 participants was 11, with a median of 9; clinical cutoff scores for depression with the CESD are generally greater than 16 (Zich & Attkisson, 1990). Thus, our sample reported low levels of depressive mood, and lack of significant associations may have been due to a floor effect.

This study's cross-sectional nature limits inferences on the directionality of variations in inflammatory and hemostasis markers and perceived stress and uplifts. It cannot be established whether increases in inflammatory markers in our participants may be driving higher appraisals of stress or vice versa. To further elucidate such an unidirectional relationship, path modeling would be warranted. Secondly, because we do not have measures on general personality traits, we cannot confirm or contest whether the connections of hassles and uplifts (positive and negative appraisals of life events) with these markers are more due to dispositional factors such as optimism and/or pessimism rather than the absence or presence of perceived minor negative and positive life events per se. Although this study did not specifically measure positive and negative affect, it should be noted that the associations of hassles and uplifts with inflammatory factors were independent of depressive symptoms and perceived stress. The independent association of uplifts with decreased levels of inflammatory markers suggests that positive appraisal of minor life events may serve to buffer one against negative immune insults. A recent review suggests that positive affect may be associated with reduction in disease progression potentially via direct but also via indirect mechanisms, including through stress appraisal and subsequent physiological responses to stress (Pressman & Cohen, 2005). Given that the uplifts scale has been noted to be mildly to moderately correlated with positive affect (Kanner et al., 1981), future studies could determine whether this seemingly protective effect is, in fact, due more to positive affectivity or, in fact, due to a difference in perception of events independent of mood. It is interesting to note that the combined hassles and uplifts scale used here allows the rater to determine whether a particular event is a hassle, an uplift, or both. In general, it remains to be seen whether the association of decreased inflammation with *positive perception* of ordinary life events is, in fact, due more to positive affective tendencies and dispositional factors (i.e., optimism) or more to, for example, coping strategies. Again, path modeling would help to better elucidate the exact mechanisms by which positive appraisals of life events confer decreased inflammation and its presumed protective effects on immunity.

In summary, our data suggest that even in relatively healthy individuals, chronic negative appraisals of minor life events are associated with increased circulating levels of inflammatory factors, whereas persistent positive appraisals of minor life events are associated with decreased levels of these factors. These effects are independent of sociodemographic, cultural, and biological influences. Future research examining the potential independent contributions of positive and negative perceptions of events on these pivotal physiological processes is warranted.

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