Negative and competitive social interactions are related to heightened proinflammatory cytokine activity

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Research has consistently documented that social relationships influence physical health, a link that may implicate systemic inflammation. We examined whether daily social interactions predict levels of proinflammatory cytokines IL-6 and the soluble receptor for tumor necrosis factor-α (sTNFαRII) and their reactivity to a social stressor. One-hundred twenty-two healthy young adults completed daily diaries for 8 d that assessed positive, negative, and competitive social interactions. Participants then engaged in laboratory stress challenges, and IL-6 and sTNFαRII were collected at baseline and at 25- and 80-min poststressor, from oral mucosal transudate. Negative social interactions predicted elevated sTNFαRII at baseline, and IL-6 and sTNFαRII 25-min poststressor, as well as total output of sTNFαRII. Competitive social interactions predicted elevated baseline levels of IL-6 and sTNFαRII and total output of both cytokines. These findings suggest that daily social interactions that are negative and competitive are associated prospectively with heightened proinflammatory cytokine activity.

competition | social stress | immunology

Research has consistently documented that social relationships influence physical health (1, 2). People who are more socially integrated live longer (3) and are less likely to experience specific disease outcomes, including heart attacks (4) and upper respiratory illness (5). One way social relationships may influence health is through inflammation, a natural, early response of the immune system that is essential to fighting infections and repairing injured tissue. Communication molecules known as proinflammatory cytokines coordinate and promote inflammatory processes. Although acute inflammation is adaptive, chronic inflammatory activity can contribute to adverse health outcomes. Specifically, increases in proinflammatory cytokines IL-6 and TNF-α have been linked to hypertension (6), atherosclerosis (7), coronary heart disease (8, 9), depression (10), diabetes (11), and some cancers (12, 13).

Social ties have also been linked to aspects of inflammation, and they may play a role in the relationship between inflammation and health. People who are socially integrated or have larger social networks have been found to have lower plasma levels of IL-6 and C-reactive protein (CRP), a byproduct of IL-6 activity (14). A cold and conflict-ridden early family environment has been tied to elevated levels of CRP in adulthood (15). Chronic relationship stress characterized by conflict, mistrust, and instability, although not consistently related to basal levels of proinflammatory cytokines, have been tied to greater lipopolysaccharide-stimulated IL-6 production 6 mo later (16). Similarly, hostile married couples engaging in a conflict interaction in the laboratory had higher levels of IL-6 24 h later compared with those engaging in a supportive interaction (17), and married women with rheumatoid arthritis who experienced more spousal criticism showed an increase in sIL-2R, a marker of disease activity, when experiencing interpersonal stress (18).

Several important issues need to be addressed, however. First, as yet, it is unknown whether studies relating chronic relationship stress and acute evaluative stress episodes translate to natural settings and to the experiences of everyday social interactions. Second, most studies investigating potential links between social relationships and inflammation have been cross-sectional, assessing social relationships or manipulating social interactions at one point in time; prospective evidence is needed. Third, it is unknown exactly what kinds of events may be related to inflammatory processes. We investigated the potential importance of negative, competitive, and positive daily interactions on inflammatory activity. Previous studies have focused largely on negative interactions. Few studies have examined the relationship between positive interactions and inflammatory processes, although decreased inflammatory activity has been tied to greater social support (19) and social integration (14), suggesting that such a relationship is tenable. Whether competitive interactions predict inflammatory activity is also unknown. There is evidence that competition influences physiological functioning, as competition has been linked to heightened cortisol (20–22) and cardiovascular reactivity to stress (23). These physiological changes may be because of the fact that competitive interactions are typically evaluative in nature, and social evaluation is known to engage both the hypothalamic pituitary adrenal system (24) and the cardiovascular system (25). Social evaluation is also known to up-regulate inflammatory processes (26), but no study has, as yet, related competitive social encounters to proinflammatory cytokine activity.

Finally, existing studies have related psychosocial factors only to basal levels of cytokines or to lipopolysaccharide-stimulated cytokine production. It is possible that social interactions affect not only basal levels but also stress sensitivity: that is, reactivity to stressors. Accordingly, the present investigation examined the relation of social interactions to both basal inflammatory activity and also to increases in cytokines in response to acute stress.

Participants completed nightly diaries for 8 d, reporting on positive, negative, and competitive social interactions. Within 4 d, participants engaged in the Trier Social Stress Test (TSST), a laboratory-based social-stress task. Oral fluids were collected before the stressor and at two time points poststressor to assess participants' proinflammatory levels and reactivity to stressful tasks. On the basis that negative and competitive daily events impose a stress burden, we hypothesized that negative and competitive daily interactions would be related to higher basal cytokine levels. We also examined whether positive interactions were related to lower basal levels of proinflammatory cytokines. We further hypothesized that exposure to negative and competitive social events would be related to increased sensitivity to social threats, reflected in elevated proinflammatory cytokine responses to laboratory stressors. We predicted that positive daily events may relate to reduced proinflammatory cytokine activity in response to social threat.

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Table 1. Descriptives for baseline and poststressor inflammatory levels and social interactions

Variable	Mean	SD	Range
Baseline IL-6 (pg/mL)	2.30055	3.487517	0.069–26.671
25 min poststressor IL-6 (pg/mL)	2.56081	3.484687	0.128–21.033
80 min poststressor IL-6 (pg/mL)	2.86058	4.655060	0.083–32.478
Baseline sTNFαRII (pg/mL)	17.8422	14.93169	1.04–86.34
25-min poststressor sTNFαRII (pg/mL)	20.3419	17.50325	1.60–85.81
80-min poststressor sTNFαRII (pg/mL)	21.7790	18.20864	1.69–96.20
Positive social interactions	32.1393	24.19457	0.00–159.00
Negative social interactions	7.6516	5.81139	0.00–38.00
Competitive social interactions	3.5410	2.52311	0.00–8.00

Daily positive and negative social interactions are directly comparable, but competitive interactions were described only on days when one occurred.

Results

Descriptive statistics are reported in Table 1. Overall, participants reported more positive social interactions than they did negative and competitive social interactions over the 8-d period.

Cytokine values exceeding three SDs from the mean were excluded from analyses [one outlier each for baseline IL-6 and the type II soluble receptor for TNF-α(sTNFαRII) at 25- and 80-min poststressor; two outliers for IL-6 at 25- and 80-min poststressor]. IL-6 and sTNFαRII values were skewed, and so were log-transformed to correct for nonnormality. Correlations among the three types of social interactions and inflammatory cytokine measures are reported in Table 2.

To examine the relationship between daily social interactions and inflammatory responses, we conducted a series of regression analyses. First, we identified potential covariates: sex, ethnicity, body mass index, experimental condition (see below), stressful life events [participants were asked to list stressful events they had encountered during the preceding 6 mo and to rate the experience of each event on a scale from −3 (very negative) to +3 (very positive); scores were created by summing totals across events], perceived stress as measured by the Perceived Stress Scale (27), depressive symptoms as measured by the Beck Depression Inventory (28), consumption of caffeine and alcohol, and cigarette smoking have previously been shown to influence levels of proinflammatory cytokines (29). Accordingly, we examined whether these variables should be treated as covariates in the analyses. Sex was significantly correlated with baseline sTNFαRII ($r = -0.195$, $P < 0.05$); and both sex ($r = -0.200$, $P < 0.05$) and ethnicity ($r = -0.187$, $P < 0.05$) were significantly correlated with sTNFαRII 80-min poststressor. Hence, sex and ethnicity were included as covariates in analyses of those outcomes. Baseline levels of proinflammatory cytokines were included as covariates in all analyses of poststressor cytokine levels. To test our hypotheses, IL-6 and sTNFαRII measures were separately regressed on the number of positive, negative, and competitive social events reported over the 8 d.

Inflammatory Levels at Baseline. As predicted, negative social events were related to higher sTNFαRII at baseline ($\beta = 0.219$, $P = 0.014$), and competitive social interactions were related to marginally higher baseline levels of IL-6 ($\beta = 0.175$, $P = 0.054$) and significantly higher baseline levels of sTNFαRII ($\beta = 0.178$, $P = 0.050$) (Tables S1 and S2).

Inflammatory Reactivity. Negative social interactions were related to higher IL-6 25-min poststressor ($\beta = 0.132$, $P = 0.032$) (Table S1) and to sTNFαRII 25-min poststressor ($\beta = 0.124$, $P = 0.043$) (Table S2). Competitive social interactions were not related to stress-induced reactivity. Although positive interactions were not correlated with any cytokine measures (Table 2), in analyses that controlled for baseline, positive social interactions were related to higher sTNFαRII 25-min poststressor ($\beta = 0.128$, $P = 0.034$) (Table S2).

To further examine these relations, we conducted area-under-the-curve (AUC) analyses, which consider the full pattern of data for total output of both IL-6 and sTNFαRII using a trapezoid equation. (30). Competitive interactions predicted total output of both IL-6 ($\beta = 0.193$, $P = 0.035$) and sTNFαRII ($\beta = 0.190$, $P = 0.037$). Negative social interactions predicted total output of sTNFαRII ($\beta = 0.210$, $P = 0.021$). Positive interactions were not associated with total output of either IL-6 or sTNFαRII.

Potential Alternative Explanations. The numbers of positive, negative, and competitive interactions were positively correlated (Table 2), which is not uncommon in the literature assessing daily experiences (31, 32). Nevertheless, this finding raises the possibility that higher proinflammatory cytokine levels are related to a greater number of daily social interactions, rather than to specific subtypes

Table 2. Correlations among positive, negative, and competitive social events and cytokine levels

	Positive social events	Negative social events	Competitive social events	Baseline IL-6	IL-6 25-min poststressor	IL-6 80-min poststressor	Baseline sTNFαRII	sTNFαRII 25-min poststressor	sTNFαRII 80-min poststressor
Positive social events		0.414**	0.181*	−0.001	0.071	0.073	0.019	0.081	0.007
Negative social events			0.473**	0.066	0.178	0.095	0.214*	0.250**	196*
Competitive social events				0.175	0.159	0.208*	0.204*	0.201*	0.200*
Baseline IL-6					0.743**	0.823**	0.507**	0.418**	0.488**
IL-6 25-min poststressor						0.803**	0.564**	0.633**	0.579**
IL-6 80-min poststressor							0.418**	0.404**	0.541**
Baseline sTNFαRII								0.757**	0.760**
sTNFαRII 25-min poststressor									0.813**
sTNFαRII 80-min poststressor									

*$P < 0.05$; **$P \leq 0.01$.

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of social interactions. Accordingly, we examined the relation of the total number of social interactions reported by participants across the 8 d to baseline, poststress 25-min, and poststress 80-min assessments for both cytokines. None of the analyses showed significant effects. Moreover, all correlations were negative, indicating that the propensity to be social does not explain the results.

A second possibility is that individual differences in the propensity to experience daily social experiences as valenced is related to production and stress reactivity of proinflammatory cytokines. To address this issue, we compared cytokine levels of people high on both positive and negative daily interactions to the rest of the sample. We used median splits to identify people high and low on negative and on positive daily interactions, and we compared those who were high on both types of daily interactions to the remainder of the sample. Using *t* tests, we then compared the two groups' IL-6 and sTNFαRII levels at each time point (baseline, 25- and 80-min poststressor). There were no significant differences or trends (all $P > 0.30$), suggesting that the tendency to construe daily interactions in valenced terms does not explain the results.

Competitive Events. The term "competitive events" is a broad concept that may be construed in a variety of ways. Accordingly, we conducted an internal analysis of the events that were described. Three categories of events that are conceptually distinct emerged: (*i*) competitive leisure time activities, such as sports (42.9%); (*ii*) academic- or work-related competitive events (38.67%); and (*iii*) competing for another person's attention, such as a romantic partner or friend (17.6%). We related each of these categories to baseline proinflammatory cytokine levels and reactivity during acute stress. Leisure time competitive activities did not predict any of the cytokine measures. Academic/work-related competitive events predicted baseline IL-6 ($\beta = 0.162$, $P < 0.075$) (marginally) and baseline sTNFαRII ($\beta = 0.199$, $P < 0.026$). Competing for another's attention significantly predicted baseline levels of IL-6 ($\beta = 0.223$, $P = 0.014$). Thus, whereas leisure competition does not appear to be associated with inflammatory activity (all $P > 0.90$), academic/work competition and competing for another's attention appear to be. It should be noted, however, that only 522 competitive events (or an average of 4.28 per person) were reported, and so further research addressing the effects of subtypes of competitive events on inflammatory activity is needed.

Ethnicity. Because the sample was multiethnic, we tested for possible ethnic differences in the relationship between the types of social interactions and proinflammatory cytokine levels. Ethnicity (Asian American, European American) and the product of ethnicity and social interaction were entered into the regression model. Ethnicity did not interact with social interactions in predicting proinflammatory cytokine levels (*SI Text*).

Discussion

Previous research has demonstrated the health-compromising effects of relationships rife with conflict and negativity and has suggested that alterations in inflammatory activity may be a potential link. Accordingly, we predicted that negative and competitive interactions would be associated with higher basal levels of proinflammatory cytokine activity and that positive interactions would be associated with lower levels. We also predicted that negative and competitive interactions would lead to stress sensitivity in the production of proinflammatory cytokines in response to threat, and that positive interactions would be associated with less stress sensitivity.

Tests of these hypotheses revealed that negative and competitive interactions were related to proinflammatory cytokine activity. Negative social interactions significantly predicted higher baseline levels of sTNFαRII, sTNFαRII and IL-6 responses following a social stressor, and total output of sTNFαRII. The experience of competitive interactions over the 8 d was associated with higher IL-6 (marginally significant) and sTNFαRII at baseline and with greater overall output of both IL-6 and sTNFαRII.

The present findings raise the questions of why daily social experiences are related to inflammation and by what routes. Negative and competitive social interactions represent daily interpersonal stressors, which are reported to be the most frequent type of stressor experienced in people's daily lives and are more predictive of negative physical and mental health than other types of stressors (33). Frequent repeated exposure to such stressors may create chronic stress, which leads to low-grade systemic inflammation (34, 35). Physiologically, stress hormones may mediate the link between daily social interactions and inflammation. Social stressors, including negative social interactions, lead to increases in cortisol (24, 36), and cortisol tends to have a suppressive effect on inflammatory processes, inhibiting production of proinflammatory cytokines and stimulating production of anti-inflammatory cytokines (37). However, repeated exposure to social stress and cortisol may lead to resistance to the anti-inflammatory effects of glucocorticoids (38, 39). Other stress hormones, including prolactin and corticotrophin-releasing hormone (CRH), have also been shown to have proinflammatory effects, depending on tissue and cell type (40–42). Thus, the link between inflammatory processes and negative and competitive social interactions may also be mediated by an increase in prolactin or CRH in response to stress. Negative social interactions also lead to increases in blood pressure and heart rate (43, 44), indices of activity of the autonomic nervous system, which is consistent with rodent models showing that social stress increases sympathetic activity (45). Given that sympathetic activity is positively related to inflammation, whereas parasympathetic activity is inversely related to inflammation (46, 47), it is plausible that negative and competitive daily social interactions up-regulate inflammatory activity via the autonomic nervous system.

Whereas negative interactions are predominantly hostile encounters, competitive events may be inherently more variable. However, the reliabilities of positive, negative, and competitive event measures were all high (0.952, 0.833, and 0.778, respectively). Nevertheless, despite the high reliability of the competitive events measure, the category included leisure activities, academic/work-related competition, and competing for a person's attention, which may relate to proinflammatory activity in different ways. An internal analysis revealed that this relationship was indeed the case. Leisure time competition was unrelated to proinflammatory cytokine activity, perhaps because such events are construed as challenging rather than threatening (48). Both academic/work competitive events and competing for another person's attention, however, did show relations to proinflammatory activity; these events may be more threatening because the stakes are higher. At present, these conclusions should be considered tentative, as the overall frequency of competitive events and these subtypes is modest.

We had predicted that positive daily social interactions would be tied to lower proinflammatory cytokine levels and reactivity to stress. These hypotheses were not supported, and the one significant finding was in the opposite direction. That is, unexpectedly, when baseline levels were controlled, positive interactions were related to higher sTNFαRII 25-min poststressor. Simple correlations did not show these relations, and positive interactions were not associated with total output of either cytokine in AUC analyses, and so it is possible that this finding is not reliable. Moreover, previous research has tied social integration to lower levels of CRP (49), and social support to lower—not higher—levels of IL-6 (50). If the effect proves to be a reliable one, it may be that positive social interactions do not mirror social support or social integration. An alternative explanation is that some positive social interactions occurred as efforts at social support when participants were experiencing stress, and thus, the increased inflammatory activity may have reflected stress responses, rather than positive experiences with others.

The long-term health consequences of the present findings are unknown. It is unlikely that the specific stressors over the short time span of the present study have any health effects, especially in a young healthy population. Moreover, some inflammation is desirable, as it promotes healing of physical injury. However, recurrent and repeated activation of the inflammatory response is deleterious to health (51). Thus, cumulatively, a greater number of daily negative and competitive social interactions may, over time, predict inflammation-related disorders and exacerbate existing illnesses that are sensitive to inflammation. This is an important direction for future research.

Some limitations warrant caution in interpreting the results. First, the correlational nature of the study precludes definitive conclusions regarding direction of causality. Although this concern is attenuated by the prospective nature of the study, it is not entirely eliminated. It may be that higher levels of inflammatory markers sTNFαRII and IL-6 lead to more negative and competitive social interactions. However, previous work has shown that experimentally induced IL-6 leads to social withdrawal (52), suggesting that higher levels of inflammatory cytokines would lead to fewer daily social interactions overall. Alternatively, a third variable may be implicated. For example, depressed people perceive their social interactions to be more negative and rejecting (53) and tend to have higher concentrations of proinflammatory cytokines (54). However, depressive symptoms and several other individual difference variables related to social interactions were not correlated with the cytokine assessments in the present study.

Third, although all participants came for the laboratory portion of the study within 4 d of completing the daily diaries, how intervening daily social interactions may have influenced inflammatory levels and reactivity is unknown. In addition, details regarding with whom and about what the social interactions centered were not controlled for, because only some participants provided enough detail to make such coding meaningful. Note, however, that these factors would add random error to the results, thus diminishing, rather than augmenting the likelihood of confirming the hypotheses.

Finally, proinflammatory cytokines were assessed via oral mucosal transudate (OMT), which poses a qualification. sTNFαRII collected via OMT has been validated only in HIV patients (55), who are a special population, and IL-6 measured via OMT is only modestly correlated with plasma levels (56). Nevertheless, similar to systemic inflammatory processes, oral inflammatory activity also increases in response to social stress (57, 58) and depression (59, 60), suggesting a relation between systemic and oral inflammatory activity. At the very least, inflammatory markers measured by OMT reflect peripheral, localized inflammation in the mouth, a critical site for immune response, as it is a primary avenue by which bacteria and viruses can enter and infect the body. Moreover, oral inflammatory activity is also implicated in the pathogenesis of periodontal disease (61), which is linked to other systemic disease including diabetes and cardiovascular diseases (62, 63).

In conclusion, the present results suggest that everyday social interactions marked by negativity or competition are predictive of inflammatory activity. Although the impact of any single such interaction may be minor, cumulatively, they may have a sustained effect on inflammatory processes and therefore may have implications for mental and physical health outcomes related to inflammation.

Methods

Participants. Prospective participants at a large university were recruited via ads offering $120 for participation in the study. Respondents were screened and excluded if they had any major mental or physical health condition or were on any mental health, cardiovascular, or neuroendocrine-related medications. Pregnant and lactating women were also excluded. The final sample included 122 students and employees (53 men and 69 women): 38.5% of the sample was European American and 61.5% of the sample was Asian American. All participants provided written consent.

Daily Diary. Participants described their daily social interactions over 8 d using a paper-diary format. Each evening, participants reported the number of positive and negative social interactions lasting at least 10 min that they had experienced during the day. The participants then described the most positive and the most negative event of the day (see description of types of events below). Participants also described the most competitive event they had experienced that day, although they did not report the number of competitive social interactions experienced during the day. Participants were provided examples of positive, negative, and competitive social events. The total number reported of each type of social event was summed across the 8 d to create the three composite scores of positive, negative, and competitive social events.

With respect to positive social interactions, most participants described spending time with friends or receiving support from a partner, friends, or family. With respect to negative social interactions, participants typically described interactions that involved conflict with family or friends. With respect to competitive social interactions, participants typically reported competing with others for the attentions of a potential or current partner, friend, or parent; feeling competitive during an academic or work-related activity; or competing during a leisure activity, such as a game.

Stress Challenge Procedure. Within 4 d of the end of the daily diary period, participants reported to the university's General Clinical Research Center for the laboratory portion of the study. Participants were scheduled in the afternoon to control for the diurnal rhythm of inflammatory activity (64) and asked to refrain from eating, exercising, and consuming caffeine 1 h before the laboratory session.

Upon arriving, participants completed a health questionnaire that inquired about their general health status and health behaviors, including smoking habits, alcohol and caffeine consumption, and exercise. Participants also completed questionnaires assessing mood, social functioning and coping, although these measures were not part of the present study.

All participants completed the TSST, a well-established laboratory stressor that reliably activates the biological stress response (65) and up-regulates inflammatory activity (66). Participants prepared for (5 min) and delivered a 5-min speech on their qualifications for being an administrative assistant and performed a mental arithmetic task in the presence of a panel. The participants were randomized to one of three conditions that manipulated whether the panel responses were positive or negative; in a third condition, there was no panel. Results concerning this manipulation have been reported elsewhere (25), and for purposes of the present study, data were collapsed across this variable. (As noted in *Results*, condition was evaluated as a potential covariate but was not related to proinflammatory cytokine levels). Immediately following the speech task, participants engaged in a 5-min mental arithmetic task in which they started at 2,935 and counted backward first by 7s and then by 13s aloud while the experimenter pushed them to go more quickly. Participants then completed a posttask questionnaire packet and were compensated and debriefed before dismissed.

Inflammatory Activity. Proinflammatory cytokine levels were assessed using OMT, a filtrate of blood plasma that has been used in previous research assessing stress-related inflammatory activity (67, 68). Participants provided the first OMT sample 10 min into the laboratory session (baseline) and 25- and 80-min after the onset of the TSST. OMT was collected using an Orasure Collective Device (Epitope): a pad is placed between the lower cheek and the gum for 2 min and then put in an accompanying vial for storage.

OMT samples were delivered to the Center for Interdisciplinary Research in Immunology and Disease at the University of California at Los Angeles, where they were assayed for IL-6 and sTNFαRII. Because TNF-α is difficult to detect as it is quickly cleared from circulation, we measured the type II soluble receptor for TNF-α, which is a more stable measure of and correlates well with TNF-α activity (69). The IMx automated microparticle enzyme immunoassay system was used for IL-6, whereas the Quantikine Human sTNFαRII enzyme immunoassay kit by R&D Systems was used for sTNFαRII. The inter- and intra-assay coefficients of variation for sTNFαRII were less than 4.1% and 7.5%, respectively, and less than 9% and 3.3%, respectively, for IL-6. The Bradford method using the Bio-Rad protein assay kit with bovine plasma albumin as the standard was used to quantify protein in the oral fluids collected. IL-6 and sTNFαRII results are reported using analyte-to-protein ratios, as they control for differences in salivary flow rate and are therefore more reliable than analyte values alone (67).

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