

## Special Article

# SYNERGISTIC RELATIONSHIPS AMONG STRESS, DEPRESSION, AND TROUBLED RELATIONSHIPS: INSIGHTS FROM PSYCHONEUROIMMUNOLOGY

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*Stress and depression consistently elevate inflammation and are often experienced simultaneously, which is exemplified by people in troubled relationships. Troubled relationships also elevate inflammation, which may be partially explained by their ability to engender high levels of stress and depression. People who are stressed, depressed, or in troubled relationships are also at greater risk for health problems than their less distressed counterparts. Inflammation, a risk factor for a variety of age-related diseases including cardiovascular disease, Type II diabetes, metabolic syndrome, and frailty, may be one key mechanistic pathway linking distress to poor health. Obesity may further broaden the health implications of stress and depression; people who are stressed or depressed are often overweight, and adipose tissue is a major source of proinflammatory cytokines. Stress, depression, and troubled relationships may have synergistic inflammatory effects: loneliness, subclinical depression, and major depression enhance inflammatory responses to an acute stressful event. The relationship between distress and inflammation is bidirectional; depression enhances inflammation and inflammation promotes depression. Interesting questions emerge from this literature. For instance, some stressors may be more potent than others and thus may be more strongly linked to inflammation. In addition, it is possible that psychological and interpersonal resources may buffer the negative inflammatory effects of stress. Understanding the links among stress, depression, troubled relationships, and inflammation is an exciting area of research that may provide mechanistic insight into the links between distress and poor health. Depression and Anxiety 30:288–296, 2013.*

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**Key words:** *biological markers; depression; cognition; life events/stress; interpersonal relationships; psychoneuroimmunology; antidepressants*

People who are stressed, depressed, or in troubled relationships are at greater risk for health problems than their less distressed counterparts.<sup>[1]</sup> For example, ma-

ajor depression enhances risk for osteoporosis, metabolic syndrome, coronary heart disease, myocardial infarction, and premature all-cause mortality.<sup>[2–6]</sup> Similarly,

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Contract grant sponsor: American Cancer Society Postdoctoral Fellowship; Contract grant number: 121911-PF-12–040-01-CPPB; Contract grant sponsor: Ohio State University Comprehensive Cancer Center Pelotonia Postdoctoral Fellowship; Contract grant sponsor: National Cancer Institute Research Supplement to Promote Diversity in Health-Related Research; Contract grant

number: CA126857; Contract grant sponsor: NIH; Contract grant numbers: CA131029, CA126857, CA154054, and AG029562.

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Received for publication 10 September 2012; Revised 7 January 2013; Accepted 21 January 2013

DOI 10.1002/da.22078

Published online 14 February 2013 in Wiley Online Library (wileyonlinelibrary.com).

compared to their less stressed counterparts, chronically stressed people were more vulnerable to the common cold and had higher cardiovascular disease and myocardial infarction incidence rates.<sup>[7-9]</sup> Troubled interpersonal relationships are also linked to multiple health problems including coronary heart disease, delayed wound healing, metabolic syndrome, and premature all-cause mortality.<sup>[10-13]</sup> Importantly, the links among stress, depression, troubled relationships, and health remain after controlling for important sociodemographic and health-relevant risk factors.

Growing evidence suggests that inflammation, a key component of the immune system's response to injury or infection, may be one potential pathway linking stress, depression, and troubled relationships to poor health. Chronic inflammation increases risk for premature all-cause mortality and age-related diseases such as cardiovascular disease, Type II diabetes, metabolic syndrome, neurodegenerative disorders, and frailty.<sup>[14-17]</sup>

In this review, we first discuss evidence that stress, depression, and troubled relationships elevate inflammation and briefly describe potential mechanistic pathways. Next, we examine the synergistic relationships among stress, depression, and troubled relationships and evaluate the clinical implications of distress-related inflammation. We also discuss evidence supporting the bidirectional relationship between distress and inflammation. We conclude by suggesting areas for future research. Throughout this review, we focus on the empirical adult human literature and common inflammatory mediators such as C-reactive protein (CRP), interleukin-1 beta (IL-1 $\beta$ ), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ).

## INFLAMMATION: A BIOLOGICAL CORRELATE OF STRESS, DEPRESSION, AND TROUBLED RELATIONSHIPS

Both major depression and depressive symptoms elevate inflammation.<sup>[18]</sup> For example, data from a meta-analysis demonstrated that people with major depression had higher IL-6 and TNF- $\alpha$  than those who were not depressed.<sup>[19]</sup> In addition, a series of epidemiological studies demonstrated that older adults with more depressive symptoms had higher IL-6 than those with fewer symptoms.<sup>[20-23]</sup> Similarly, older adults with higher levels of depressive symptoms had larger IL-6 responses to an influenza vaccine immune challenge than less depressed older adults.<sup>[24]</sup> The links among inflammation and clinical and subclinical depression have been replicated in chronically ill populations including cancer survivors and acute coronary syndrome (ACS) patients.<sup>[25-28]</sup>

Stress reliably enhances inflammation in naturalistic and laboratory contexts.<sup>[29-32]</sup> For example, students had higher inflammation levels, including stimulated IL-6 and IL-1 $\beta$  production, immediately after a stressful exam

compared with a lower stress baseline period.<sup>[33-36]</sup> In addition, IL-6, interferon (IFN) gamma, and other inflammatory markers were higher after a laboratory stressor (delivering an evaluated and timed speech) than before the stressor.<sup>[37-39]</sup>

Lower socioeconomic status (SES), a chronic stressor, is also associated with elevated inflammation. Lower SES people are more stressed than their higher SES counterparts.<sup>[40]</sup> In addition, chronic stresses such as restricted access to medical care, poor environmental conditions, and limited income are more commonly experienced by people with lower rather than higher SES.<sup>[41]</sup> Lower SES, whether measured by personal or household income, social class, work position, financial assets, or education level, is linked to elevated inflammation.<sup>[42-52]</sup>

Stress and depression are often experienced simultaneously,<sup>[53]</sup> which is exemplified by people in troubled relationships. For example, troubled relationships are a reliable risk factor for both clinical and subclinical depression,<sup>[54-56]</sup> and people in unsupportive relationships are less resilient to stress than those with more supportive relationships.<sup>[57-59]</sup> Indeed, troubled relationships are often conceptualized as one form of chronic stress that also engenders major depression or depressive symptomology.<sup>[56]</sup> Troubled relationships elevate inflammation, which may be partially explained by their ability to engender high levels of stress and depression.<sup>[54,55]</sup>

Observational studies of marital conflict discussions provide a unique window into the effects of troubled relationships on inflammation; behavioral coding systems assess actual relationship behaviors and thus do not rely on self-reported relationship quality. A provocative study using this paradigm demonstrated that wound healing, an inflammation-mediated event, was slower after a marital disagreement than a socially supportive discussion.<sup>[11]</sup> In addition, production of inflammatory cytokines at the wound site was lower following the conflict than the support discussion. In contrast to systemic inflammation, which is linked to a variety of age-related diseases,<sup>[14-17]</sup> local inflammation at the wound site is adaptive and critical to effective wound healing. These results show that marital conflict produces maladaptive immunological responses, as evidenced by differences in wound repair and cytokine production at the wound site.

Negative and hostile behaviors during a conflict discussion, such as blaming or interrupting the partner, appear to be particularly detrimental. A conflict discussion led to slower wound healing among couples displaying more hostile behaviors compared to those with fewer hostile behaviors.<sup>[11]</sup> Furthermore, while hostile couples had higher systemic inflammation following a conflict discussion compared to a social support discussion, low-hostile couples had similar levels of inflammation across both discussions.<sup>[11]</sup>

Loneliness, a state of perceived social isolation and interpersonal distress, also elevates inflammation. For instance, compared with people who felt more socially connected counterparts, those who felt lonelier had higher

inflammation, upregulated proinflammatory genes, and downregulated anti-inflammatory genes.<sup>[60–62]</sup> A preliminary mindfulness-based stress intervention concurrently reduced loneliness and downregulated proinflammatory gene transcription.<sup>[61]</sup> Taken together, these studies provide further support that troubled and distressed relationships, in this case as experienced by lonely people, have negative inflammatory effects.

Family members providing care for a loved one with Alzheimer's disease or a related dementia are, on average, more stressed, depressed, and lonely than noncaregivers.<sup>[63,64]</sup> Thus, it is not surprising that multiple studies show elevated inflammation among caregivers. For example, dementia family caregivers had higher IL-6 and TNF- $\alpha$  than noncaregivers.<sup>[65–67]</sup>

Stress, depression, and troubled relationships may also fuel longitudinal changes in inflammation over time, particularly among older adults. Indeed, more depressed older adults had larger IL-6 increases over 6 years than their less depressed counterparts.<sup>[68]</sup> Similarly, IL-6 increases over a 6-year period were about four times as large among spousal dementia caregivers than noncaregivers.<sup>[64]</sup> Furthermore, the IL-6 increases did not differ between current caregivers and former caregivers even several years after the death of the dementia patient. However, perceived stress and loneliness also did not differ between current and former caregivers, suggesting that psychological recovery from a stressor may be critical to reducing inflammation over time. Consistent with this possibility, people who recovered from an episode of major depression within the prior year continued to show higher levels of CRP compared with nondepressed controls.<sup>[69,70]</sup> Major depression is often followed by subclinical depressive symptoms, which may partially account for elevated inflammation after a depressive episode ends.

Stress, depression, and troubled relationships can influence inflammation through a variety of pathways. One common mechanism linking stress and depression to inflammation is health behaviors; people who are stressed or depressed often have poor health behaviors such as inactivity or smoking,<sup>[71,72]</sup> and these health choices can elevate inflammation.<sup>[48]</sup> Stress, depression, and troubled relationships also influence inflammation via the sympathetic and parasympathetic nervous systems. For example, stress activates the sympathetic nervous system, which causes the release of epinephrine and norepinephrine. In turn, these stress hormones stimulate the release of proinflammatory cytokines. A full review of mechanistic pathways is outside of the scope of this chapter; more detailed explanations are available elsewhere for the interested reader.<sup>[73–75]</sup>

In sum, there is a large body of evidence demonstrating that stress, depression, and troubled relationships elevate inflammation. In addition, initial evidence suggests that stress and depression may fuel longitudinal increases in inflammation over time, especially among older adults. Inflammation is a risk factor for age-related diseases,<sup>[14–17]</sup> suggesting one mechanistic pathway link-

ing stress, depression, and troubled relationships to poor health.

## SYNERGISTIC RELATIONSHIPS AMONG STRESS, DEPRESSION, AND TROUBLED RELATIONSHIPS

Stress, depression, and troubled relationships often occur simultaneously and may have synergistic effects on inflammatory responses.<sup>[53,76]</sup> Initial evidence suggests that people who are highly distressed about a task may have an exaggerated inflammatory reaction to that task.<sup>[35,77]</sup> For instance, people who were more anxious about an upcoming speech had higher postspeech IL-6 than those who were less anxious.<sup>[78]</sup> In addition, students who perceived an exam as very stressful had higher levels of the soluble interleukin-6 receptor (sIL-6r) than those who perceived it as less stressful.<sup>[79]</sup> Because sIL-6r potentiates the effects of IL-6 by increasing its inflammatory capabilities,<sup>[80]</sup> the sIL-6r data suggest that stress may exacerbate inflammatory activity.

Depression and loneliness may also prime the immune system's response to stressful events. For example, the stress of giving birth led to greater IL-6 increases among women with a history of major depression than those without a history of major depression.<sup>[81]</sup> In addition, healthy adults with higher levels of depressive symptoms produced more IL-6 in response to an acute laboratory stressor than those with lower levels of depressive symptoms.<sup>[82]</sup> Among healthy adults and posttreatment breast cancer survivors, inflammation was elevated after an acute laboratory stressor for those experiencing greater loneliness compared with those who were less lonely.<sup>[62,83]</sup>

In sum, stress, depression, and troubled relationships often occur simultaneously and mutually influence each other. The studies described above suggest that the combination of stressful events, depression, and troubled relationships may fuel immune dysregulation, and thus may further elevate risk for health problems.<sup>[84]</sup>

## CLINICAL IMPLICATIONS OF DISTRESS-RELATED INFLAMMATION

Inflammation is related to both the incidence and prognosis for a number of chronic medical conditions, including cancer, metabolic syndrome, rheumatoid arthritis, neurodegenerative disorders, asthma, gingivitis, and cardiovascular disease.<sup>[85–89]</sup> In addition, stress and depression are highly prevalent among people with chronic medical conditions.<sup>[90]</sup> Accordingly, stress- and depression-related inflammation have clear clinical implications for the management of these chronic conditions. The broad literature addressing stress and depression among medical populations is beyond the scope of

this review; we provide brief exemplars using two very different inflammatory conditions, gingivitis, and cardiovascular disease. We also discuss how obesity may exacerbate the links among stress, depression, inflammation, and inflammatory diseases.

Stress and depression enhance risk for gingivitis, a mild periodontal disease characterized by inflamed gums.<sup>[91-94]</sup> For example, spousal dementia caregivers had more gingival symptoms than noncaregivers, which was explained, in part, by caregivers' elevated stress and depressive symptoms.<sup>[95]</sup> A series of studies further demonstrated that stress elevated specific inflammatory markers that promoted gingival symptoms, suggesting one pathway through which stress affected gingivitis. Interleukin-8 (IL-8), which initiates degradation of connective tissue at inflamed gingival sites, was higher in students' gingival crevicular fluid (GCF) after delivering a videotaped and timed speech than after a control task.<sup>[96]</sup> Similarly, adults who reported more socially oriented stressful life events had higher IL-8 in their GCF than those who reported fewer events.<sup>[97]</sup> IL-1 $\beta$ , a cytokine that hampers bone formation and fosters periodontal tissue destruction, was elevated in the GCF of students who took a stressful exam compared with those who did not take an exam.<sup>[98]</sup> Furthermore, GCF IL-1 $\beta$  concentrations remained elevated 2 weeks after the exam ended,<sup>[99]</sup> suggesting that stressful events may have longer lasting prognostic potential for gingival symptoms.

There is a vast literature demonstrating that people who are highly stressed or depressed are more likely to develop cardiovascular disease and have worse disease-related outcomes than their less stressed or depressed counterparts.<sup>[2,100,101]</sup> Furthermore, numerous studies have demonstrated that stress and depression elevate CRP and IL-6, two inflammatory markers that promote cardiovascular disease, suggesting one mechanism linking cardiovascular disease, stress, and depression.<sup>[15,102]</sup> For instance, among women with suspected coronary ischemia, those with current depressive symptoms and a history of major depression had higher CRP and IL-6 and were more likely to develop cardiovascular disease than those who had neither.<sup>[103]</sup> In addition, men with ACS who had more depressive symptoms and higher levels of CRP experienced more adverse cardiac events than men with ACS who were less depressed and had lower levels of CRP.<sup>[101]</sup>

Obesity, a worldwide epidemic,<sup>[104]</sup> may further broaden the clinical implications of stress and depression. People who are highly stressed or depressed are more likely to be overweight than their less stressed or depressed counterparts.<sup>[105,106]</sup> Highly depressed people also experience greater increases in abdominal fat over time than those who are less depressed.<sup>[107]</sup> In addition, abdominal adiposity (i.e., belly fat) is a major source of proinflammatory cytokines including IL-6, TNF- $\alpha$ , and IL-1 $\beta$ ,<sup>[108,109]</sup> and is an important risk factor for a variety of diseases such as metabolic syndrome, Type II diabetes, and cardiovascular disease.<sup>[110,111]</sup> Importantly, stress, depression, and obesity independently el-

evate inflammation.<sup>[18,42]</sup> Thus, among people who are stressed or depressed, those who are also overweight are particularly at risk for elevated inflammation and inflammatory diseases.

Taken together, the gingivitis and cardiovascular disease findings suggest that stress and depression may exacerbate inflammatory diseases by elevating inflammatory markers that are implicated in risk of those diseases. Furthermore, the inflammatory effects of stress and depression are both local (as in the gingivitis studies) and systemic (as evidenced by the cardiovascular studies). Obesity may further exacerbate the relationships among stress, depression, and inflammation. Accordingly, distress-related inflammation has clinical implications for the management of inflammatory diseases.

## THE BIDIRECTIONAL RELATIONSHIP BETWEEN DISTRESS AND INFLAMMATION

The relationship between depression and inflammation is bidirectional; depression enhances inflammation and inflammation promotes depression.<sup>[112]</sup> Proinflammatory cytokine administration induces "sickness behaviors," behavioral changes that resemble the somatic symptoms evident in depression, such as anhedonia and lethargy.<sup>[113]</sup> For example, both IL-6 and negative affect increased following a typhoid vaccine.<sup>[114,115]</sup> In addition, depressed mood increased following an injection of endotoxin, bacterial toxins that provoke an inflammatory response.<sup>[116,117]</sup> IFN- $\alpha$  (IFN- $\alpha$ ) treatment results in symptoms consistent with major depression for a subset of people.<sup>[118,119]</sup> Additional evidence suggests that IFN- $\alpha$  treatment-related depression produced more somatic depressive symptoms than traditional major depression,<sup>[120]</sup> at least during the initial phase of treatment. Cognitive-affective symptoms appear to develop shortly thereafter and may be more responsive to antidepressant treatment.<sup>[121,122]</sup> On the other hand, a TNF- $\alpha$  inhibiting medication improved psoriasis patients' depressive symptoms, independent of disease improvement.<sup>[123]</sup> Accordingly, research suggests that cytokine administration can promote depression, and anti-inflammatory medications may decrease depressive symptoms. Furthermore, immune-challenge paradigms are most clearly linked to depression-related somatic symptoms (e.g., sickness behaviors); the effects of immune-challenge paradigms on the core cognitive-affective symptoms of depression, such as suicidal ideation and guilt, requires further examination.<sup>[124]</sup>

If stress and depression elevate inflammation, then treatments designed to reduce stress and depression should reduce inflammation. Consistent with this possibility, CRP decreased following antidepressant medication for a subset of people with major depressive disorder, and the anti-inflammatory effects of the medication were most reliable for those who benefited

psychologically from treatment.<sup>[125,126]</sup> People who do not benefit from antidepressants often have persistently higher IL-6 than those who do benefit, suggesting one potential way to identify people who will respond to antidepressants.<sup>[114,125]</sup> Nonprescription pharmacological treatments may also improve depression and thus reduce inflammation. For example, growing evidence suggests that omega-3 fatty acids may have antidepressant effects.<sup>[127,128]</sup> In addition, omega-3 supplementation reduces inflammation.<sup>[129,130]</sup>

Behavioral data further suggest that lowering distress reduces inflammation. For instance, a compassion meditation intervention reduced emotional distress and IL-6 for people who practiced more frequently than less frequently.<sup>[131]</sup> In addition, the regular practice of yoga was related to lower baseline and stress-induced inflammation.<sup>[132]</sup> Exercise also has well-documented anti-inflammatory and antidepressant effects.<sup>[133,134]</sup> Some evidence even suggests that exercise interventions may be as effective as antidepressive medications in alleviating major depression for some individuals.<sup>[135]</sup>

In sum, the relationship between distress and inflammation is bidirectional. Cytokine administration and other immune-challenge studies suggest that inflammation induces sickness behaviors such as anhedonia and lethargy. Studies demonstrating that depression interventions reduce inflammation support the argument that depression enhances inflammation.

## FUTURE DIRECTIONS

Stress, depression, and troubled relationships reliably increase inflammation. However, it is possible that some stressors are more potent than others and are thus more strongly linked to inflammation. For example, loneliness threatens the need to belong, a fundamental need that is at the core of human nature, and thus should impact immune function across cultures and demographic groups.<sup>[136,137]</sup> On the other hand, threats to social harmony are particularly relevant in Eastern cultures<sup>[138]</sup> and thus may be more strongly related to inflammation among Eastern compared to Western cultures.

Stress and depressive symptoms often remain elevated after a stressful event ends.<sup>[64,139]</sup> In addition, psychological recovery may be impacted by the length and intensity of the stressor, depressive episode, or troubled relationship. Accordingly, another intriguing question is how long inflammation remains elevated after a stressor ends and how this relates to psychological recovery. Furthermore, it is possible that older adults may be particularly influenced by the long-lasting inflammatory consequences of stress and depression.<sup>[140]</sup>

Depression and loneliness exacerbate stress-induced inflammation.<sup>[82,83]</sup> However, some people may be more resilient in the face of stress than others. Indeed, psychological resources (e.g., self-esteem) and interpersonal resources (e.g., social support) may buffer the negative impacts of stress.<sup>[141]</sup> For example, people with higher

self-esteem perceived a timed and evaluated performance task as less stressful than those with lower self-esteem.<sup>[142]</sup> In response to being told that a potential dating partner left the study early, higher self-esteem participants explained the other person's behavior with more benign (e.g., the other participant was sick) than malevolent (e.g., the other participant did not like me) attributions.<sup>[143]</sup> These studies suggest that, compared to their lower self-esteem counterparts, people with higher self-esteem may experience less stress in response to an objective stressor and may interpret ambiguous situations as less threatening. A novel new direction is to explore whether self-esteem differences in stress perceptions translate into altered stress-related inflammatory responses.

Researchers are beginning to understand the relationships between stress-induced health behaviors and inflammation. For example, people often eat poorly and stop exercising when they are stressed or depressed,<sup>[71,144]</sup> both food and exercise influence inflammation.<sup>[133,145]</sup> Researchers in these areas can investigate multiple hypotheses about the relationships among distress, health behaviors, and inflammation. For instance, stress and depression may affect inflammation because they cause poor health behaviors. Another possibility is that poor health behaviors exacerbate stress-induced inflammation.

Understanding the relationships between inflammation and interventions to reduce stress and depression is a burgeoning area of research.<sup>[125,126,146]</sup> Because some people respond to behavioral and pharmacological treatments differently than others,<sup>[125]</sup> exploring the relationship between psychological symptom improvement and decreased inflammation is important. Furthermore, the strongest evidence demonstrating that inflammation causes depression has focused on somatic symptoms (e.g., "sickness behaviors" such as lethargy). Mechanistic insight may be gained if researchers can determine whether depression-related inflammatory changes are related to reduced "sickness behaviors," cognitive-affective symptoms such as suicidal ideation and guilt, or a combination of these factors.

In sum, research reliably demonstrates that inflammation is linked to stress, depression, and troubled relationships. Because elevated inflammation is a risk factor for poor health,<sup>[14-17,85,86,89]</sup> these studies may provide mechanistic insight into the ways that stress, depression, and troubled relationships affect health.

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