Published in final edited form as:
Neurosci Biobehav Rev. 2010 September ; 35(1): 33–38. doi:10.1016/j.neubiorev.2009.09.003.

Close Relationships, Inflammation, and Health

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Abstract

KIECOLT-GLASER, J.K., J-P. Gouin, and L. Hantsoo, *Close Relationships, Inflammation, and Health*. NEUROSCI BIOBEHAV REV XX(X) XXX-XXX, 2009.- Different aspects of personal relationships including social integration, social support, and social conflict have been related to inflammation. This article summarizes evidence linking the quality and quantity of relationships with gene expression, intracellular signaling mechanisms, and inflammatory biomarkers, and highlights the biological and psychological pathways through which close relationships impact inflammatory responses. Relationship conflict and lower social support can effectively modulate proinflammatory cytokine secretion both directly (via CNS/neural/endocrine/immune biobehavioral pathways), and indirectly, by promoting depression, emotional stress responses, and detrimental health behaviors. Accordingly, thorough assessments of health behaviors and attention to key methodological issues are necessary to identify the contributions of relationships to inflammation, and thus we highlight procedural issues to be considered in the design of studies. Despite some notable methodological challenges, the evidence suggests that learning more about how close relationships influence inflammation will provide important new insights into the ways that relationships impact health.

Keywords

social support; social integration; personal relationships; social conflict; marriage; stress; interleukin-6; C-reactive protein; psychoneuroimmunology; proinflammatory cytokines; depression

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The close link between personal relationships and immune function is one of the most robust findings in the psychoneuroimmunology (PNI) literature (Kiecolt-Glaser et al., 2002; Kiecolt-Glaser and Newton, 2001). Mechanistic data from PNI studies have bolstered epidemiological evidence linking supportive relationships with lower rates of morbidity and

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mortality (Seeman, 1996). In the past decade PNI researchers have focused considerable attention on inflammation, one aspect of immune function, because of the growing evidence that inflammation is central to many diseases. This article summarizes evidence linking inflammation and health, and highlights the pathways through which close personal relationships impact inflammatory responses. We then review recent findings on personal relationships and inflammation, and end by underscoring key methodological issues.

Inflammation and Health

Local inflammation is a vital immune response triggered by infection and injury. Inflammatory responses promote the destruction and clearance of viral and bacterial pathogens, and enhance wound healing. Proinflammatory cytokines attract immune cells to sites of infection or injury, activating them to respond to the insult. While acute, local inflammation is beneficial, chronic low grade inflammation may have detrimental health consequences.

Inflammation is a robust and reliable predictor of all-cause mortality in older adults. C-reactive protein (CRP) and proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) are prognostic for cardiovascular disease, type II diabetes, arthritis, osteoporosis, Alzheimer's disease, and periodontal disease (Ershler and Keller, 2000; Kiecolt-Glaser et al., 2002). More globally, chronic inflammation has been suggested as one key biological mechanism that may fuel declines in physical function leading to frailty, disability, and, ultimately, death (Ershler and Keller, 2000).

Different mechanisms are likely responsible for the diverse associations among inflammation, disease-specific processes, and poor health. In cardiovascular disease, inflammatory processes may induce endothelial dysfunction; when arterial endothelium is exposed to proinflammatory cytokines, expression of adhesion molecules is upregulated, increasing cellular adhesion and accelerating arterial stiffening (Ridker, 2009). Further, CRP downregulates endothelial nitric oxide synthase, which may lead to impaired vasodilation (Ridker, 2009). In type II diabetes, excessive macronutrient intake induces a proinflammatory state; increased TNF-α and IL-6 may suppress insulin signal transduction, impairing control of blood sugar levels (Dandona et al., 2004). In addition, inflammation is considered a risk factor for most cancers because of the evidence that proinflammatory cytokines influence tumor promotion, survival, proliferation, invasion, angiogenesis, and metastases (Aggarwal et al., 2006). While inflammation is clearly associated with these diseases, there may not be causal links in each case; inflammation may reflect the presence of other associated risk factors or underlying disease processes such as obesity, or it could be part of the disease course itself (Dandona et al., 2004).

Psychosocial stress can directly provoke proinflammatory cytokine production in the absence of infection or injury. Norepinephrine-dependent adrenergic stimulation activates transcription factor nuclear factor kappa B (NF-κB), an intracellular signaling molecule that activates gene expression of several inflammatory mediators (Bierhaus et al., 2003). Accordingly, norepinephrine's well-documented responsivity to stress (Kiecolt-Glaser et al., 1997) provides a direct route for translating interpersonal stress into inflammation.

Proinflammatory cytokines are elevated following menopause or andropause even in the absence of infection, trauma, or stress (Ershler and Keller, 2000); however, any of these conditions can further enhance expression of IL-1, IL-6, and TNF-α (Ershler and Keller, 2000). Thus, older adults are already at greater risk, and stress- and depression-related alterations compound risk.

Pathways From Personal Relationships To Health: Depression, Stress, and Inflammation

Depression is reliably associated with relationship conflict and lower social support, providing one psychological mechanism through which close relationships influence inflammation (Graham et al., 2007). There is a robust association between inflammation and depression not only in clinically depressed samples, but also in community-based samples (Howren et al., 2009); some non-replications may be due to confounding factors such as body mass index (BMI) or medication use (Glassman and Miller, 2007; Howren et al., 2009). Moreover, there is some evidence that depression may sensitize the inflammatory response, thus effectively promoting larger cytokine increases in response to stressors or antigen challenge (Glaser et al., 2003; Pace et al., 2006). Additionally, depression and stress contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing; all processes that can fuel sustained proinflammatory cytokine production (Glaser and Kiecolt-Glaser, 2005). Furthermore, depression alters inflammation-relevant health behaviors; for example, disturbed sleep, a common correlate of depression and stress, promotes IL-6 production (Vgontzas et al., 2004).

Given the association between depression and inflammation, recent research has explored underlying mechanisms. Findings that pharmacologically-induced inflammation can produce symptoms of depression indicate that the relationship between inflammation and depression is bidirectional. Administration of proinflammatory cytokines in rodents induces sickness behavior, a cluster of symptoms resembling human depression (Dantzer et al., 2008). In healthy volunteers, mood is worse and proinflammatory cytokine production is higher following administration of cytokines, endotoxin or vaccinations (Raison et al., 2006); imaging reveals that resultant low mood is associated with reduced connectivity of brain areas implicated in depression, a mechanism modulated by peripheral IL-6 (Harrison et al., 2009). Cytokines can alter serotoninergic systems by upregulating indoleamine 2,3-dioxygenase (IDO), which in turn turned reduces tryptophan production, and ultimately brain serotonin levels. (Dantzer et al., 2008).

By promoting depression and emotional stress responses, relationship conflict and lower social support can effectively modulate secretion of proinflammatory cytokines both directly (via CNS/neural/endocrine/immune biobehavioral pathways), and indirectly, through behavioral changes. Through these pathways, depression and stressful interpersonal experiences contribute to both acute and chronic proinflammatory cytokine production (Kiecolt-Glaser et al., 2005; Kiecolt-Glaser et al., 2003). Certainly, the pathways linking social processes, inflammation, and health are complex. While interpersonal stress may impact depressive symptoms, and via this mechanism exacerbate inflammation, other relationship variables such as social integration or relational discord may also moderate the associations between personal relationships, inflammation, and health outcomes.

Social Relationships and Inflammation

Different aspects of relationships, including social integration, social support, and social conflict have been related to inflammatory processes. Social relationships impact gene expression, intracellular signaling mechanisms, and inflammatory biomarkers. These associations have been observed across the life span in both healthy participants and individuals with chronic medical conditions.

Three types of research design have been used to study the impact of relationships on inflammation: 1) correlational studies that relate self-reported relationship quality and/or quantity to inflammation, 2) observational studies that compare individuals undergoing a major interpersonal stressor, family dementia caregiving, to noncaregiving controls, and 3)

experimental studies of married couples that evaluate the impact of laboratory-induced interpersonal conflict and support.

Correlational studies relating self-reported relationship quality/quantity and inflammation—Social integration refers to the extent of ties to friends, family, and the community. Social integration, as assessed by marital status, number of close friends and relatives, and participation in religious activities, clubs, and voluntary associations was inversely related to plasma levels of IL-6 and CRP. Individuals with larger social networks and more frequent social contacts had lower IL-6 and CRP than individuals with smaller social networks. However, this relationship was observed only among older men (Ford et al., 2006; Loucks et al., 2006). Among older adults, married men had lower CRP levels than previously married men, as well as married and unmarried women; the size of the effect of marriage on CRP was comparable to that of other traditional risk factors such as smoking, hypertension, and obesity (Sbarra, 2009). Notably, these CRP differences were not explained by mood, stress, loneliness, or social support, and none of these variables moderated the association between marital status and CRP levels (Sbarra, 2009). Furthermore, in a genome-wide DNA microarray study, genes under-expressed by socially isolated individuals involved anti-inflammatory response elements and genes over-expressed involved proinflammatory response elements, compared to individuals who reported less social isolation (Cole et al., 2007). Additionally, diminished glucocorticoid sensitivity may promote chronic low grade inflammation. Among socially isolated individuals, diminished regulation of leukocyte trafficking by cortisol was observed, compared to more socially integrated individuals (Cole, 2008).

Social support represents the perceived availability of help when it is needed (Graham et al., 2007). Pregnant women reporting lower levels of social support during their third trimester had higher CRP throughout the pregnancy, compared to women with better social support (Coussons-Read et al., 2007). Among older women, trusting and satisfying relationships with others, and concerns with others' welfare were related to lower IL-6 (Friedman et al., 2005). In ovarian cancer patients, the more frequent use of instrumental support and greater perceptions of closeness and intimacy in personal relationships were associated with lower plasma IL-6. (Lutgendorf et al., 2000; Costanzo et al., 2005). Similarly, the proinflammatory transcription factor Nf-κB, was overexpressed in ovarian tumors of patients who reported both high levels of depression and low levels of social support, compared to their counterparts without these risk factors (Lutgendorf et al., 2009).

Social conflict and interpersonal stress have been associated with inflammation. In a six-month longitudinal study of adolescent females, greater interpersonal stress was associated with larger lipopolysaccharide (LPS)-stimulated IL-6 production and bigger NFκB increases over time (Miller et al., 2009). Among adults diagnosed with rheumatoid arthritis, greater daily interpersonal stress was also related to higher LPS-stimulated IL-6 production (Davis et al., 2008). Similarly, adolescents who reported more daily interpersonal stressors had higher CRP plasma levels than those with less interpersonal stress (Fuligni et al., 2009).

Correlational studies suggest that social isolation, lack of social integration, and interpersonal conflict are associated with higher IL-6 and CRP. Importantly, even small increases in biomarkers associated with stress may have health implications. CRP levels above 3 mg/L indicate high relative risk for cardiovascular disorder, independent of other known risk factors (Ridker, 2009). In large longitudinal studies of initially healthy individuals, elevated IL-6 (mean 1.81 pg/mL vs. 1.46 pg/mL) and CRP levels (median 4.2 mg/L vs. 2.8 mg/L) independently predicted risk of cardiovascular events, compared to other risk factors (Ridker et al., 2000a; Ridker et al., 2000b). Epidemiological studies have linked

social isolation, low social support, and high levels of social conflict with morbidity and mortality, and inflammation provides one obvious mechanism (Graham et al., 2007).

Observational studies with dementia family caregivers—Providing care for a family member with dementia is a chronic interpersonal stressor with consequences for caregivers' mental and physical health. Caregivers deal with many dementia-related behaviors: diminished cognitive function, wandering, impaired self-care, and personality changes. The situation is most acute for spousal caregivers, because their main source of interpersonal support has instead become their prime source of stress.

Caregiving can exacerbate age-related increases in inflammation. Community women who were caregivers had higher plasma IL-6 levels than either women who were anticipating a housing relocation or community controls, despite the fact that caregivers were 6 to 9 years younger than women in the other two groups (Lutgendorf et al., 1999). In further work, age was significantly correlated with IL-6 in caregivers but not controls, suggesting that older caregivers may be at risk for a rapid transition into what has been termed the frailty syndrome (von Kanel et al., 2006).

Indeed, a six-year longitudinal study revealed that caregivers' average rate of increase in IL-6 was about four times as large as that of noncaregivers (Kiecolt-Glaser et al., 2003). Even after their spouse's death, bereaved spousal caregivers' mean annual rate of change in IL-6 did not differ from current caregivers, and these patterns of change were not explained by differences in health or medication status. Caregivers' social networks shrink over the course of caregiving; bereaved caregivers' self-rated loneliness remains similar to that of current caregivers for several years or more after the death of the impaired spouse, undoubtedly contributing to the enduring IL-6 differences (Kiecolt-Glaser et al., 2003).

Diminished sensitivity to the anti-inflammatory properties of glucocorticoids provides one potential mechanism through which chronic interpersonal stressors such as caregiving promote chronic low grade inflammation. Caregiving for a child with cancer has been associated with diminished inhibition of LPS-stimulated IL-6 production following glucocorticoid administration (Miller et al., 2002). Among individuals who were caring for a family member with cancer, CRP increased and glucocorticoid sensitivity decreased in the year following the first radiotherapy treatment (Rohleder et al., 2009). Additionally, genes underexpressed by family cancer caregivers included glucocorticoid response elements, while genes overexpressed included NF-κB response elements, compared to noncaregiving controls (Miller et al., 2008).

Compared to similar older adults without caregiving responsibilities, caregivers have an increased risk for infectious disease (evidenced by poorer vaccine responses) as well as delayed wound healing (Glaser and Kiecolt-Glaser, 2005), additional processes that can fuel sustained proinflammatory cytokine production, as described earlier. In sum, dementia caregiving strains family relationships, resulting in depression as well as inflammation. The IL-6 differences described by multiple laboratories provide one viable mechanism that could explain caregivers' substantial differences in mortality (Schulz and Beach, 1999).

Experimental studies of laboratory-induced marital conflict—A series of well-controlled laboratory studies have shown that hostile behavior during marital conflict augments adverse immune and endocrine changes, including enhanced norepinephrine production (Kiecolt-Glaser and Newton, 2001). Indeed, less hostile couples showed roughly the same increment in IL-6 over 24 hours following either a social support or conflict interaction (65% vs. 70%), while IL-6 production for the more hostile couples jumped from

45% to 113% (Kiecolt-Glaser et al., 2005). Thus, relationships characterized by hostility and conflict could have negative health consequences.

Health Behaviors and Other Methodological Issues

Supportive relationships can substantially influence inflammation by facilitating health promoting behaviors, while relationship conflict or termination can provoke detrimental health behaviors including less physical activity, disturbed sleep, unhealthy diets, and greater use of alcohol and other drugs (Eng et al., 2005). Thorough assessments of health behaviors and attention to key methodological issues are necessary to identify the contributions of relationship quality and distress to inflammation, and thus to health.

Physical Activity—People who describe themselves as physically active have lower levels of inflammation than their sedentary counterparts (Kasapis and Thompson, 2005). When physical or cardiorespiratory fitness is assessed rigorously and objectively by maximal exercise testing, fitness is inversely associated with inflammation, even after adjusting for confounds including age, smoking, medications, and visceral fat (Kasapis and Thompson, 2005).

Although regular physical activity lowers inflammation, acute exercise transiently boosts production and release of IL-6 from skeletal muscles; the IL-6 that is released during physical activity inhibits TNF-α production and induces IL-10 production, one of exercise's anti-inflammatory mechanisms (Kasapis and Thompson, 2005). Because exercise can induce substantial transient cytokine changes, research participants should not exercise on a day before blood is drawn.

Sleep—Disrupted sleep can dysregulate proinflammatory cytokine production, altering both the normal diurnal patterns and total production (Vgontzas et al., 2004). Modest sleep deficits produced significant overall IL-6 increases in the following 24 hours in young, healthy, normal sleepers (Vgontzas et al., 2004); these data likely represent the best case scenario, with larger changes likely in older and/or less healthy individuals.

Diet and Meal-Related Influences—Higher intakes of a “Westernized” diet (red and processed meats, sweets, desserts, French fries, and refined grains) have been associated with higher CRP, IL-6, E-selectin, sICAM-1, and sVCAM-1 (Lopez-Garcia et al., 2004). These data are not surprising given recent evidence that fast-food-type meals high in saturated fats acutely enhance inflammation. For example, IL-6 levels were more than twice as high 10 hours after a breakfast high in saturated fat compared to a healthier alternative (Poppitt et al., 2008). Furthermore, proinflammatory responses to meals high in saturated fats are exaggerated by obesity, pushing elevated levels even higher (O'Keefe et al., 2008). Either fasting morning blood samples or feeding a standardized meal can circumvent these problems.

Adiposity—Obesity has been characterized as a state of chronic inflammation because of the elevated plasma levels of IL-6, TNF-α, and CRP (Dandona et al., 2004). In fact, adipocytes (fat cells) are capable of producing and secreting IL-6 and TNF-α; up to 30% of IL-6 may be derived from adipose tissue (Dandona et al., 2004). Thus, even when adiposity is below the threshold for obesity, it can influence inflammation.

Furthermore, obesity may exaggerate inflammatory responses to stressors. For example, women with greater central adiposity produced larger inflammatory responses to a laboratory stress task than their leaner counterparts (Brydon et al., 2008). In accord with these data, glucocorticoid inhibition of inflammatory cytokine production following acute

stress was lower in men with a higher BMI than in their leaner counterparts (Wirtz et al., 2008).

BMI can be misleading for some individuals like body builders who can have higher BMIs but little body fat, and it does not provide data on central adiposity. Both waist circumference and the waist/hip ratio are common techniques for assessing central adiposity (Brydon et al., 2008). Sagittal abdominal diameter (SAD) measurements are relatively simple, and can provide data on the total amount of abdominal fat. The utility of SAD as a noninvasive central adiposity measure has been demonstrated by validational studies using computerized axial tomography (CT) and dual-energy X-ray absorptiometry (DEXA) (Clasey et al., 1999).

Alcohol and smoking—Moderate alcohol intake is associated with lower levels of systemic inflammatory markers than non-drinking and heavy drinking. Smoking is reliably associated with heightened inflammatory responses (Hamer and Stamatakis, 2008).

Medications and Chronic Health Problems—Many medications directly and indirectly influence inflammation. The statins, originally developed for cholesterol treatment, have well-documented anti-inflammatory effects. Others include antidepressants, systemic and respiratory steroids, nonsteroidal anti-inflammatories, estrogens, immunomodulators, immunosuppressants, antirheumatic medications, chemotherapy and other anti-cancer medications, diabetes medications, anti-hypertensives, as well as many others. Furthermore, dietary intake and/or supplements like omega-3 and curcumin can also impact inflammation as well as mood (Kiecolt-Glaser et al., 2007).

An older adult who is not taking any medication is a relative rarity, and limiting a sample to such individuals would not provide representative data. Accordingly, after setting exclusion criteria, medication use and chronic health problems need to be routinely considered as potential confounders, and variables representing use of particular medications need to be evaluated statistically for their impact (Kiecolt-Glaser et al., 2007).

Experimental Design and Logistical Issues

In contrast to the rapid increase in cortisol and catecholamines, serum IL-6 does not rise immediately in response to a laboratory stressor. Several researchers have suggested that assessment 90-120 minutes after the stressor initiation may be necessary to observe changes (Pace et al., 2006). Indeed, some studies that have not shown significant changes ended data collection earlier. In this context, blood sample processing cannot wait until data collection is complete, because time passage before samples are processed and frozen can substantially influence cytokine concentrations (Thavasu et al., 1992).

Both IL-6 and TNF-α have distinct diurnal cycles, e.g., normal IL-6 values at 9:00 PM are more than twice as large as those at 9:00 AM (Vgontzas et al., 2004). To control for diurnal variation, all blood samples from a given population should be drawn within the same window of time. Night or swing shift workers may provide unrepresentative data because of altered diurnal cycles.

We have summarized key methodological issues that are important for consideration when designing studies addressing relationships and inflammation. Although there are certainly some notable methodological challenges, the evidence suggests that learning more about how close relationships influence inflammation will provide important new insights into the ways that relationships impact health.

Acknowledgments

Work on this paper was supported in part by NIH grants AG029562, CA126857, CA131029, AT003912, UL1RR025755, and CA16058.

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