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Relationships and Inflammation across the Lifespan: Social Developmental Pathways to Disease

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Abstract

There are well documented links between close relationships and physical health, such that those who have supportive close relationships have lower rates of morbidity and mortality compared to those who do not. Inflammation is one mechanism that may help to explain this link. Chronically high levels of inflammation predict disease. Across the lifespan, people who have supportive close relationships have lower levels of systemic inflammation compared to people who have cold, unsupportive, conflict-ridden relationships. Not only are current relationships associated with inflammation, but past relationships are as well. In this article, we will first review the literature linking current close relationships across the lifespan to inflammation. We will then explore recent work showing troubled past relationships also have lasting consequence on people's inflammatory levels. Finally, we will explore developmental pathways that may explain these findings.

There are well documented links between close relationships and physical health, such that those who have supportive close relationships across their lifespan have lower rates of morbidity and mortality compared to those who do not (Berkman & Syme, 1979; Brummett et al., 2001; Gilbert et al., 2009; House, 1988; Orth-Gomer & Johnson, 1987; Repetti, Taylor, & Seeman, 2002; Tomaka, Thompson, & Palacios, 2006; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Researchers are beginning to understand the underlying mechanisms behind these findings (Uchino, 2006).

People who have supportive close relationships have lower levels of systemic inflammation compared to people who have cold, unsupportive, conflict-ridden relationships (Kiecolt-Glaser, Gouin, & Hantsoo, 2009). Not only do current relationships affect inflammation, but past relationships do as well (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Kiecolt-Glaser, et al., 2009). In this paper, we first review the literature linking current close relationships across the lifespan to inflammation. We then explore recent work suggesting troubled past relationships also have lasting consequences for people's inflammatory levels. Finally, we evaluate developmental pathways that may explain these findings.

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Inflammation

Acute inflammation is an important immune response to infection or injury. However, chronic low grade inflammation is involved in many age-related diseases (Harris et al., 1999; Ishizuka, Nagata, Takagi, & Kubota, 2009; Lin et al., 2008; Sin & Man, 2007). Both acute and chronic stressors can boost inflammation. For example, experimental stressors such as the Trier Social Stress Test (TSST) reliably increase inflammation (Pace et al., 2006; Steptoe, Hamer, & Chida, 2007). Furthermore, acute naturalistic stressors, such as preparing for a medical exam or giving an oral presentation, enhance inflammation (Heinz et al., 2003; Maes et al., 1998). Accordingly, those who are more chronically stressed have higher levels of inflammation compared to those who are less stressed (Kiecolt-Glaser et al., 2003).

Relationships and Inflammation across the Lifespan

Close relationships can be a source of stress; they can also buffer against stress (Cohen, 2004). People who believe others will provide necessary resources for them are better able to cope with stressful situations compared to their counterparts who do not hold these beliefs. However, troubled interpersonal relationships provoke psychological stress that may have short and long-term health consequences (Cohen, 2004). Accordingly, interpersonal relationships can both dampen and enhance psychological stress, which may have important implications for inflammation. There is considerable evidence across the lifespan to support this link.

Current Relationships and Inflammation

Inflammation is quite low during childhood and adolescence, however, interpersonal stress still influences inflammatory markers. For example, troubled parent-child relationships can promote inflammation. In a prospective study, asthma-related inflammatory markers esoinophil cationic protein (ECP) and stimulated interleukin-4 (IL-4) were higher six months later among children with more stressed parents at baseline compared to children with less stressed parents. Children's own stress levels did not predict their inflammatory levels (Wolf, Miller, & Chen, 2008). Stressed parents are not able to provide the same level of care and support to their children as unstressed parents (Moss, Rousseau, Parent, St-Laurent, & Saintonge, 1998; Weinraub & Wolf, 1983). These findings highlight the importance of parental relationships for inflammation.

Interpersonal stress has also been linked to enhanced inflammation in adolescence. Nuclear factor κB (NF-κB) transcription is an intracellular signaling molecule that regulates proinflammatory cytokine gene expression (Straub & Härle, 2005). In a prospective study, healthy adolescent girls who reported more interpersonal stress at the onset of the study had higher levels of NF-κB and stimulated interleukin-6 (IL-6) six months later compared to those reporting less stress (Miller, Rohleder, & Cole, 2009). In another study, adolescents who reported more frequent negative interpersonal interactions had higher C-reactive protein (CRP; a downstream marker of inflammation) levels eight months later compared to adolescents who reported fewer negative interactions (Fuligni et al., 2009). These associations existed in both studies even after investigators controlled for general psychological distress.

The association between interpersonal relationships and inflammation persists in adulthood. Marriage represents the most significant relationship for most adults; spouses can provide an important source of social support for each other (Kiecolt-Glaser & Newton, 2001; Litwak et al., 1989). On average, those who are married have higher levels of social support than those who are not (Dehle, Larsen, & Landers, 2001). Married individuals' mortality rates are lower than those of their unmarried counterparts (Lillard & Waite, 1995). In a population

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based study of community dwelling older adults, being married was associated with reduced CRP for both sexes; these effects were particularly pronounced in men (Sbarra, 2009). The absolute magnitude of the risk reduction for married men was equivalent to being a nonsmoker, having normal blood pressure, and having a healthy BMI (Sbarra, 2009).

While marriage typically has positive health benefits, marital quality has important health implications (Kiecolt-Glaser & Newton, 2001). Marital interaction studies have provided some of the best work demonstrating the importance of marital quality. Hostile marital interactions have particularly important negative physiological consequences. In one study in which couples engaged in a supportive discussion and a marital problem discussion across two separate sessions, those couples who were more hostile produced more IL-6 after the conflict discussion than the supportive discussion (113% vs. 45%).In contrast, less hostile couples' IL-6 production was similar after both discussions (70% vs. 65%) (Kiecolt-Glaser et al., 2005).

Another study addressed how being more cognitively engaged (operationalized by a greater use of cognitive processing words) during a marital disagreement altered inflammatory responses. More cognitively engaged individuals produced less IL-6 and tumor necrosis-alpha (TNF-α) over the next 24 hours after a disagreement compared to less cognitively engaged individuals (Graham et al., 2009). Additionally, those who were more cognitively engaged had lower absolute levels of IL-6 and TNF-α than those who were less cognitively engaged.

Marital stress may be particularly detrimental when combined with other health risk factors. For example, there was a stronger association between marital stress and CRP for women with larger waists than smaller waists (Shen, Farrell, Penedo, Schneiderman, & Orth-Gomer, 2010). This is important because abdominal fat is a prime source for inflammation (Després & Lemieux, 2006). Higher levels of CRP raises the risk of cardiovascular disease (Kardys et al., 2006), and thus the combination of marital stress and greater abdominal fat may be particularly prognostic for heart problems.

The association between interpersonal stress and inflammation has been documented among older adults as well. For example, older women who had more satisfying interpersonal relationships had lower IL-6 than those who had less satisfying relationships (Friedman et al., 2005). This is particularly notable because inflammation is most health relevant for older adults (Hamerman, Berman, Albers, Brown, & Silver, 1999). Chronic stress intensifies age-related increases in proinflammatory cytokines (Kiecolt-Glaser, et al., 2003). Furthermore, chronic stress and inflammation accelerate cellular aging (Damjanovic et al., 2007; Epel et al., 2004). In light of these age-related effects, troubled relationships in older adulthood may be particularly problematic.

Those who have chronically elevated proinflammatory cytokines are at greater risk for cancer, cardiovascular disease, type II diabetes, osteoporosis, periodontal disease, and rheumatoid arthritis (Ershler & Keller, 2000). A few studies have directly examined links between relationships and inflammation among those with health problems. Women with ovarian cancer who reported greater social support had lower IL-6 levels compared to women who reported less social support (Costanzo et al., 2005). Furthermore, gynecologic cancer survivors who sought more support at diagnosis had lower IL-6 one year later compared to those who sought less support (Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000). Older rheumatoid arthritis patients who reported more negative interpersonal events had higher levels of IL-6 compared to those who reported fewer negative interpersonal events (Davis et al., 2008).

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Past Relationships and Inflammation

Not only are current relationships linked to inflammation, but past relationships are as well. In a longitudinal prospective study of almost 1000 people, those who were neglected during the first decade of their life showed higher levels of CRP at age 32 compared to those who were not neglected. Indeed, the findings suggested that more than 10% of adult low-grade inflammation can be attributed to child maltreatment (Danese, Pariante, Caspi, Taylor, & Poulton, 2007). Middle-aged adults who had harsh family environments as children had higher CRP than those from more benign family environments (Taylor, Lehman, Kiefe, & Seeman, 2006).

The association between early life experiences and elevated inflammation even exists among older adults. In a study of healthy older adult family dementia caregivers and noncaregivers whose average age was 70, those who experienced emotional, physical, or sexual abuse as children were more likely to have higher IL-6 and TNF-α levels, as well as shorter telomeres compared to those who were not abused (Kiecolt-Glaser et al., 2011). Importantly, this association was detectable even among distressed dementia caregivers. Troubled early relational experiences have been linked to cancer and heart disease in adulthood (Felitti et al., 1998; Fuller Thomson & Brennenstuhl, 2009; Korkeila et al., 2010). Inflammation may be one possible mechanism underlying these links.

Developmental Links to Elevated Inflammation

At any age, relationships can impact both psychological and immunological function. Early relational experiences may be particularly important. However, researchers have yet to establish *why* early relational experiences have these long-term consequences. Inflammation may be an important physiological mechanism that explains these links. Establishing the pathways through which early relationships are linked to inflammation in adulthood is crucial to understand and improve health outcomes.

Attachment

Attachment theory provides a useful organizing framework to understand links between troubled early relational experiences and adult inflammation. Attachment theory suggests people who have responsive and supportive care providers during childhood develop a sense of security; therefore, they believe others can be counted on for support in times of need. However, people who have unresponsive and unsupportive caregivers develop a sense of insecurity that persists in adulthood (Hazan & Shaver, 1987; Mikulincer & Shaver, 2009; Thompson, 1999).

Considerable research suggests there are two habitual patterns of attachment insecurity: attachment avoidance and attachment anxiety. Attachment avoidance refers to the degree to which people limit closeness with others. Avoidantly attached people are uncomfortable depending on others for support. Attachment anxiety refers to the degree to which individuals chronically seek reassurance that people love and care for them. Anxiously attached people constantly worry about being rejected and abandoned compared to those who are less anxiously attached people (Brennan, Clark, & Shaver, 1998; Fraley & Shaver, 2000). As outlined below, attachment insecurity may contribute to elevated inflammation by producing greater physiological stress sensitivity, poorer relationship quality, more depressive symptoms, and more maladaptive health behaviors.

Consistent with the attachment framework, there has been work showing that those who are insecurely attached are more physiologically reactive to stress compared to their secure counterparts (Diamond & Fagundes, 2010; Diamond, 2001). In turn, those who are insecurely attached are more physiologically reactive to stress than those who are secure.

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Insecurely attached individuals (especially those who are anxiously attached) have greater cortisol increases in response to stress than their secure counterparts, reflecting more pronounced hypothalamic pituitary adrenal axis (HPA) activity (Diamond, Hicks, & Otter-Henderson, 2008; Laurent & Powers, 2007; Rifkin-Graboi, 2008). These cortisol data are in accord with both human and animal work that has shown that poor early parental experiences are also linked to more pronounced stress-induced glucocorticoid production (Heim et al., 2000; Heim, et al., 2008; Sanchez, 2006). Although cortisol acutely inhibits inflammation (Barnes, 1998; Brattsand & Linden, 1996), chronically high cortisol levels can *sometimes* lead to glucocorticoid insensitivity. Glucocorticoid insensitivity allows immune cells to produce proinflammatory cytokines in an unregulated environment, thereby raising inflammation (Miller, Cohen, & Ritchey, 2002).

Further evidence consistent with attachment theory, insecurely attached adults (both anxious and avoidant) have higher sympathetic activity in response to both interpersonal and non-interpersonal stressors than their secure counterparts (Diamond, Hicks, & Otter-Henderson, 2006; Roisman, 2007). Insecurely attached individuals (especially those who are anxiously attached) also have lower resting parasympathetic activity compared to those who are secure (Diamond & Hicks, 2005; Izard et al., 1991), a pattern of autonomic activity that is consistent with alterations in inflammation. Sympathetic activation results in the production of the stress hormones, catecholamines, epinephrine and norepinephrine. Norepinephrine induces NF-κB (Straub & Härle, 2005). Consequently, norepinephrine enhances the production of proinflammatory cytokines (Bierhaus et al., 2003). The parasympathetic nervous system promotes relaxation and restoration (Thayer, 2009). parasympathetic activity results in lower levels of inflammation via cholinergic anti-inflammatory pathways that facilitate acetylcholine release (Tracey, 2009). Stimulation of immune cells' alpha-7 nicotinic acetylcholine receptors inhibits proinflammatory cytokine production (Tracey, 2009).

One study demonstrated a direct link between adult attachment insecurity and inflammation. Researchers assessed the relationship between attachment insecurity and inflammation among married adults by assessing couples who engaged in a supportive discussion and a marital problem discussion across two separate sessions. Those who were more insecurely attached (specifically avoidantly attached) produced more IL-6 following the conflict interaction compared to those who were securely attached. This was not the case during the supportive interaction (Gouin et al., 2009). Therefore, more insecurely attached people showed a greater inflammatory response following conflict than their securely attached counterparts.

Presumably, attachment insecurity is associated with more pronounced inflammation after a stressor because of greater autonomic reactivity to the stressor. However, there are no studies to show that the association between attachment insecurity (or adverse early relational experiences) and elevated inflammation exist *because* of more pronounced autonomic stress reactivity. Evaluating this pathway by assessing autonomic activity during the stressor is an important direction for future research.

In addition to being more physiologically sensitive to stress as adults, children who have troubled relationships with parents and other adults with whom they are close are less likely to develop social and emotional skills that are crucial for establishing a lifetime of supportive close relationships. Insecure adults are more likely to perceive less support, report more relationship conflict, and have poorer quality marriages than secure adults (Fraley & Shaver, 2000; Mikulincer & Shaver, 2009; Williams & Risking, 2004). Accordingly, in addition to being more sensitive to stress in adulthood, those who had troubled relationships as children may *also* have elevated inflammation as adults because

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they are more likely to have more conflict-ridden relationships in adulthood than their secure counterparts. This pathway suggests that the association between early relationships and inflammation may be partially explained by subsequent poor relational experiences. In order to test this pathway, researchers should take into account current relationship functioning when examining links between past relationships and inflammation.

Individuals who are insecurely attached have more depressive symptoms in adulthood compared to their secure counterparts, especially when confronted with romantic breakups, divorces, deaths, and illnesses compared to their secure counterparts (Fagundes, 2011; Fraley & Bonanno, 2004; Rodin et al., 2007; Sbarra, 2006). People with depressive disorders have elevated proinflammatory cytokine production compared to those without depressive disorders (Boyle, Jackson, & Suarez, 2007; Irwin, 2002; Kiecolt-Glaser, et al., 2003; Musselman et al., 2001; Zorrilla et al., 2001). Even minor elevations in depressive symptoms are associated with higher levels of proinflammatory cytokines (Lutgendorf et al., 1999). In a prospective study, IL-6 was higher six years later among healthy older adults who had higher levels of depressive symptoms at baseline compared to those with lower levels of depressive symptoms at baseline (Cremeans-Smith, Soehlen, Greene, Alexander, & Delahanty, 2009). Therefore, the association between attachment insecurity and elevated inflammation may be partially explained by depressive symptoms.

People who smoke, have problems sleeping, and maintain an unhealthy diet have higher inflammation than their counterparts who practice good health behaviors (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006; Kangavari et al., 2004; Kiecolt-Glaser, 2010; Van Der Vaart et al., 2005). Troubled early relationship experiences increase the risk of smoking in adolescence and adulthood (Anda et al., 1999). Insecurely attached children, adolescents and adults have more sleep problems than those who are secure (Benoit, Zeanah, Boucher, & Minde, 1992; Carmichael & Reis, 2005; Scharfe & Eldredge, 2001). Insecurely attached individuals are also more likely to have eating disorders than their secure counterparts (Cole-Detke & Kobak, 1996). Therefore, the association between troubled childhood relationships and inflammation may also be explained by health behaviors. In order to test this pathway, researchers should take health behaviors into account when examining links between early relational experiences and inflammation.

Epigenetics

Epigenetics offers another possible mechanism linking troubled early relationships to inflammation. Epigenetics refers to modifications in DNA and its associated histone proteins that help regulate gene transcription (Jones & Takai, 2001). DNA methylation is the most likely epigenetic mechanism underlying gene-environment interactions (Crews, 2010). Researchers have proposed that DNA methylation may underlie many of the associations between adverse early life events and subsequent mental and physical health problems (McGowan et al., 2009).

Early relational experiences may alter the expression and DNA methylation of certain genes linked to inflammation. Compared to rat pups raised by mothers who showed better maternal care (indexed by more licking, grooming, and arched back nursing), those raised by mothers who showed poorer maternal care had altered histone acetylation and transcription factor (NGFI-A) binding to the glucocorticoid receptor gene promoter in the hippocampus. In turn, these rats showed more pronounced HPA axis stress responses in adulthood compared to the offspring of mothers who showed better maternal care (Weaver et al., 2004). Similar associations have been identified in human populations. For example, methylation of the exon 1_F NR3C1 promoter was higher, and hippocampal NR3C1 gene expression was lower, in male suicide victims with troubled childhood relationships compared to controls (McGowan, et al., 2009). Lower Nr3c1 gene expression has been

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linked to more pronounced HPA axis activity (Ridder et al., 2005). Recall that chronically elevated glucocorticoids can sometimes lead to glucocorticoid insensitivity and enhance inflammation.

Toll-like receptor 4 (TLR4) provides another likely epigenetic marker linking early relationships to elevated inflammation. Those with higher levels of TLR4 mRNA are more likely to have excessive inflammation compared to those with lower levels. Adolescents who were raised in lower SES environment as children had higher levels of TLR4 mRNA compared to their higher SES counterparts (Miller & Chen, 2007). Lower SES children are more likely to have troubled relationships with their parents than their higher SES children (Herrenkohl & Herrenkohl, 2007). Future work should examine if those who had troubled early relationships have higher levels of TLR4 mRNA compared to their counterparts who had healthy early relationships.

Limitations and Future Directions

In sum, our model suggests that troubled early relationships are linked to attachment insecurity, dysregulated autonomic and HPA function, poor adult relationships, more depressive symptoms, poor health behaviors, and a proinflammatory epigenetic phenotype. In turn, those who experienced troubled early relationships have higher levels of inflammation as adults compared to those who had healthy relationships. However, researchers have yet to test these pathways. In order to do this, researchers must simultaneously assess multiple psychological, physiological, and epigenetic factors with relatively large samples to establish meditational models. This is a critical direction for future research.

Furthermore, studies investigating links between troubled early relationships and poor subsequent psychological and physiological outcomes have relied heavily on retrospective designs. By relying on these designs, we cannot say with certainty that past relationships experiences *lead* to attachment insecurity and elevated inflammation in adulthood. In order to strengthen causal inference, future work using prospective longitudinal designs are needed. Furthermore, one concern with retrospective data is that participants could be biased reporters. However, adults generally underreport rather than over-report troubled childhood relationships (Dill, Chu, Grob, & Eisen, 1991).

Research examining links between past relationships and inflammation has focused on how poor relationships in *early* childhood contribute to current inflammation. This may be for good reason, as adolescent and adults' psychological and physiological profiles are not as malleable to long-term changes as children's (Repetti, et al., 2002). However, poor past adult relationships may also have long-term consequences. For example, an abusive marriage may have long-term consequences well after it ends. People with poor past adolescent or adult relationships may be at risk for heightened inflammation due to the same psychological and physiological pathways that make those with poor early relational experience in childhood vulnerable. Examining how past relationships at different developmental stages across the lifespan are linked to psychological processes, inflammation, and disease would be an interesting avenue for future research.

Finally, caution is warranted when drawing general conclusions about links between relationships and inflammation based on studies showing associations between relationships and a single marker of inflammation. This is especially important when mapping relational processes onto specific diseases because certain markers of inflammation are more strongly linked to certain diseases than others. For example, there is much more evidence linking CRP to cardiovascular disease than other inflammatory markers (Lagrand et al., 1999; Stumpf & Hilgers, 2009; Taubes, 2002). In order for researchers to make general

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conclusions about relationships and inflammation, multiple inflammatory markers should be examined.

Conclusion

Close relationships matter. Not only do close relationships shape people's emotions, they affect the very physiological processes that underlie disease. Close relationships across the lifespan contribute to elevated inflammation--now a well regarded risk factor for disease. Accordingly, close relationship research is not just an intellectual pursuit. Understanding how people form healthy attachments, perceive support, interact positively with others, and cope with losses is essential if we are to gain a comprehensive understanding of the social developmental pathways that contribute to disease.

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