

Section VI  
Health Disorders and Specialties

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## Psychoneuroimmunology of Interpersonal Relationships: Both the Presence/Absence of Social Ties and Relationship Quality Matter

Lisa M. Jaremka, Heather M. Derry, and  
Janice K. Kiecolt-Glaser

Being socially connected has health benefits. For example, married people had lower premature all-cause mortality rates, higher 5-year cancer survival rates, and fewer chronic health conditions than their non-married counterparts (Johnson, Backlund, Sorlie, & Loveless, 2000; Schoenborn, 2004; Sprehn, Chambers, Saykin, Koniski, & Johnstone, 2009). In addition, people with more diverse social ties had lower premature all-cause mortality rates and a better prognosis following a myocardial infarction or stroke than people who were less socially integrated (Colantonio, Kasl, Ostfeld, & Berkman, 1993; Holt-Lunstad, Smith, & Layton, 2010; Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984). On the other hand, distressing interpersonal relationships enhance risk for a variety of health problems such as coronary heart disease, delayed wound healing, metabolic syndrome, and premature all-cause mortality (Holt-Lunstad et al., 2010; Kiecolt-Glaser et al., 2005; Orth-Gomér et al., 2000; Whisman, 2010). Importantly, the links between close relationships and health remain after controlling for important sociodemographic and health-relevant risk factors.

Growing evidence suggests that immune function may be one potential pathway linking close relationships and health (Robles & Kiecolt-Glaser, 2003); proper immune function is essential to health (Glaser & Kiecolt-Glaser, 2005). Indeed, inflammation and other forms of immune dysregulation increase risk for premature all-cause mortality and a variety of diseases including cardiovascular disease, cancer, and metabolic syndrome (Ershler & Keller, 2000; Hansson, 2005; Hotamisligil, 2006; Nabipour, Vahdat, Jafari, Pazoki, & Sanjdideh, 2006; Parkin, 2006). Studies addressing inflammation, herpesvirus latency, vaccine responses, and wound healing can provide windows into how close interpersonal relationships impact immune function.

In this chapter, we suggest that the mere presence of close relationships confers immunological benefits. Next, we investigate the quality of these relationships and argue that distressing relationships dysregulate immune function, whereas supportive relationships may be immunoprotective. We also discuss the immunological consequences of relationship loss, and conclude by suggesting areas for future research. Throughout this review, we focus on the empirical adult human literature addressing close relationships and immune function.

### Presence/Absence of Relationships

Marriage, many adults' most intimate and close relationship, appears to benefit immune function. For example, married older adults had more vigorous antibody responses to an influenza virus vaccine than their non-married counterparts (Phillips et al., 2006), reflecting an adaptive vaccine-related immune response (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996). Several inflammatory protein markers (e.g., fibrinogen) were lower in married men compared with non-married men (Engström, Hedblad, Rosvall, Janzon, & Lindgärde, 2006). Furthermore, men with lower levels of these inflammatory protein markers had a lower risk of coronary events and stroke over an 18-year period (Engström et al., 2006). Chronic systemic 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 (Ershler & Keller, 2000; Hansson, 2005; Harris et al., 1999; Hotamisligil, 2006), suggesting one mechanism underlying the health benefits of marriage.

The immunological benefits evident in the marital literature also extend to other relationships. For instance, social integration, the number and/or diversity of a person's social ties, appears to be immunoprotective. Among a nationally representative sample of adults, more socially integrated individuals had lower levels of systemic C-reactive protein (CRP), an inflammatory marker linked to cardiovascular disease, than less socially integrated individuals (Ford, Loucks, & Berkman, 2006). Consistent with this data, additional studies demonstrated that people who were more socially integrated had lower systemic inflammation, as indexed by CRP and interleukin-6 (IL-6), than those who were less socially integrated (Heffner, Waring, Roberts, Eaton, & Gramling, 2011; Koenig et al., 1997; Lutgendorf, Russell, Ullrich, Harris, & Wallace, 2004; Shankar, McMunn, Banks, & Steptoe, 2011). In addition, compared to people more socially isolated, those who were more socially integrated had larger antibody responses to an influenza virus vaccine (Pressman et al., 2005). One intriguing study demonstrated that nasal inoculation with a rhinovirus (the common cold virus) produced clinically verified common colds less frequently among people with more diverse social ties than those with less diverse social ties (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). Accordingly, being married or having numerous social ties is linked to

lower systemic inflammation, more adaptive vaccine responses, and less susceptibility to the common cold.

Some studies suggest that the immune-relevant effects of being married and socially integrated may be stronger for men than for women. In a population-based study, married men exhibited significantly lower levels of systemic CRP compared to unmarried men, married women, and unmarried women (Sbarra, 2009). Compared to their less socially integrated counterparts, more socially integrated men had lower systemic CRP and IL-6; inflammation and social integration were unrelated among women (Loucks, Berkman, Gruenewald, & Seeman, 2006; Loucks et al., 2006). Thus, multiple studies show that the immune benefits of being in or out of a relationship are most evident among men.

## Quality of Relationships

### The negative side of relationship quality

While the presence of a spouse generally benefits immune function, a marriage wrought with conflict and discontent can take a toll. For example, people in poorer-quality relationships are more stressed and depressed than those in better quality relationships; both stress and depression dysregulate immune function (Jaremka, Lindgren, & Kiecolt-Glaser, 2013). Indeed, compared to more happily married people, people in distressed relationships had smaller antibody responses to an influenza virus vaccine (Phillips et al., 2006). Furthermore, individuals in more distressed marriages had higher Epstein-Barr virus (EBV) antibody titers than those in less distressed marriages (Kiecolt-Glaser et al., 1987, 1988). Because herpesviruses, including EBV and cytomegalovirus (CMV), are better able to reactivate and replicate when the cellular immune system is compromised, higher antibody titers to a latent herpesvirus reflect poorer cellular immune system control over viral latency (Glaser & Jones, 1994).

Observational studies of marital conflict discussions provide a unique window into the effects of marital distress on immune function; behavioral coding systems assess actual relationship behaviors, and thus do not rely on self-reported marital quality. A provocative study using this paradigm demonstrated that wound healing, an immunologically-mediated event, was slower after a marital disagreement than a socially supportive discussion (Kiecolt-Glaser et al., 2005). 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 (Hansson, 2005; Hotamisligil, 2006; Nabipour et al., 2006; Parkin, 2006), local inflammation at the wound site is adaptive and critical to effective wound healing. These results show that marital conflict produces clinically meaningful stress-induced immune dysregulation, as evidenced by differences in wound repair.

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 (Kiecolt-Glaser et al., 2005). Furthermore, whereas 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 (Kiecolt-Glaser et al., 2005). Indeed, repeated hostile interactions may cause long-lasting immunological alterations and poor health over time.

Although older couples displayed fewer negative behaviors during marital discussions than younger couples, older adults' negative relationship behaviors were still linked to poorer immune function (Kiecolt-Glaser et al., 1997). These results suggest that the immune system does not habituate to negative social interactions over time. Because aging enhances immune dysregulation, negative marital interactions may be particularly detrimental among older adults (Fagundes, Gillie, Derry, Bennett, & Kiecolt-Glaser, 2012).

Divorce, a clear hallmark of distress in a marriage, also has negative immunological consequences. Recently separated/divorced women had higher EBV antibody titers compared to sociodemographically matched married women (Kiecolt-Glaser et al., 1987). Interestingly, EBV antibody titers were highest for women whose spouses initiated the separation (Kiecolt-Glaser et al., 1988).

Lonely people feel socially isolated from those around them and are at increased risk for depression (Cacioppo, Hawkley, & Thisted, 2010). Indeed, loneliness is an interpersonally distressing state that dysregulates immune function (Jaremka, Lindgren, et al., 2013). Lonelier people had higher EBV, CMV, and human herpesvirus 6 (HHV-6) antibody titers than less lonely people (Dixon et al., 2006; Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985; Jaremka, Fagundes, Glaser, et al., 2013). Lonelier people had smaller antibody responses to an influenza virus vaccine than those who were less lonely (Pressman et al., 2005). In addition, compared with people who were more socially connected, lonelier individuals exhibited upregulation of proinflammatory genes and downregulation of anti-inflammatory genes (Cole et al., 2007). Recent data also demonstrated that loneliness exacerbates stress-related immune dysregulation. Among healthy adults and post-treatment breast cancer survivors, systemic inflammation was higher after an acute laboratory stressor among those experiencing greater loneliness compared with those who were less lonely (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Jaremka, Fagundes, Peng, et al., 2013).

The immunological consequences of distressing relationships may be particularly strong for women compared with men (Kiecolt-Glaser & Newton, 2001). For example, marital stress was associated with heightened systemic inflammation in young women but not young men (Whisman & Sbarra, 2012). A marital conflict discussion led to greater negative affect and immune dysregulation among women compared with men (Kiecolt-Glaser et al., 1993; Mayne, O'leary, McCrady, Contrada, & Labouvie, 1997). Negative affect can dysregulate immune function (Jaremka,

Lindgren, et al., 2013), and women may be more emotionally affected by marital conflict than men (Kiecolt-Glaser et al., 1993; Mayne et al., 1997). Taken together, these results could help explain elevated immune dysregulation among women in distressing relationships.

In sum, distressing relationships clearly dysregulate immune function, and initial evidence suggests that these effects may be most prominent for women. One interesting question is whether the immunological consequences of distressing relationships are driven by negative features of the relationship, a lack of positive features, or a combination of the two. Research about the positive side of relationship quality begins to address this question.

### The positive side of relationship quality

Initial evidence suggests that supportive marriages confer immunological benefits (Kiecolt-Glaser & Newton, 2001), potentially because they buffer against stress and depression (Cohen & Wills, 1985). For example, couples who displayed more cognitive engagement during a marital conflict discussion had lower systemic IL-6 responses than those displaying less cognitive engagement (Graham et al., 2009). People with rheumatoid arthritis, an inflammatory disease, had less disease activity in response to stressful life events if they were in better-quality marriages than if their marriages were more distressed (Zautra et al., 1998). In addition, rheumatoid arthritis patients reporting better marital quality at study entry had lower systemic inflammation 6 months later, suggesting that positive relationships can benefit immune function over time (Kasle, Wilhelm, McKnight, Sheikh, & Zautra, 2010).

Other supportive relationships may also confer immunological benefits. Although a full review of the social support literature is outside the scope of this chapter, we highlight select findings about immune function and perceived social support, the perception that close others are available for support in times of need (for a recent review, see Uchino, Vaughn, Carlisle, & Birmingham, 2012). The majority of perceived social support research suggests that people who feel more supported have better immune function than those who feel less supported. For example, people reporting more supportive relationships had lower systemic inflammation, as indexed by IL-6 and IL-8, than those with less supportive relationships (Friedman, 2011; Friedman et al., 2005; Marsland, Sathanoori, Muldoon, & Manuck, 2007). People with more social support had larger antibody responses to pneumococcal pneumonia, hepatitis B, and influenza virus vaccines than those with less social support (Gallagher, Phillips, Ferraro, Drayson, & Carroll, 2008a, 2008b; Glaser et al., 1992; Phillips, Burns, Carroll, Ring, & Drayson, 2005). In addition, people who felt more supported had lower EBV and HHV-6 antibody titers than those with less social support (Dixon et al., 2006; Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Interestingly, one study suggested that the relationship between social support and herpesvirus antibody titers may be strongest for higher-socioeconomic-status (SES) people. Among higher-SES women, those with more support from

friends had lower EBV antibody titers; no effect was found for lower-SES women (Fagundes, Bennett, et al., 2012).

### Relationship Loss

The death of a spouse, family member, or friend is a profoundly stressful experience that often causes intense distress (Bodnar & Kiecolt-Glaser, 1994; Zisook et al., 1994). In this way, loss is a unique type of relationship stress. Thus, it is not surprising that the death of a loved one dysregulates immune function. For instance, people who experienced the death of a spouse in the past year had smaller antibody responses to an influenza virus vaccine than those who were currently married (Phillips et al., 2006). Bereaved spouses also exhibited heightened levels of systemic inflammation, as measured by IL-6 and interleukin-1 receptor antagonist (IL-1ra), compared to non-bereaved controls (Schultze-Florey et al., 2012). Husbands' immune responses to three different mitogens decreased substantially following their wives' deaths (Schleifer, Keller, Camerino, Thornton, & Stein, 1983). Mitogen responses may provide an analog to understanding white blood cells' ability to replicate or proliferate when challenged. Accordingly, husbands' immune responses reflected decrements in cellular immunity from pre- to post-bereavement.

Providing care for a loved one with Alzheimer's disease or a related dementia is a stressful experience. Indeed, some caregivers describe their loved ones' loss of mental function as a process of living bereavement (Schulz et al., 2003). In addition, caregivers report more loneliness, stress, and depression than non-caregivers (Kiecolt-Glaser et al., 2003, 1991). Consequently, dementia caregiving enhances risk for immune dysregulation. For instance, Alzheimer's disease caregivers had higher levels of systemic inflammation than non-caregivers (Damjanovic et al., 2007; Lutgendorf et al., 1999; von Känel et al., 2006). In addition, spousal and offspring dementia caregivers had higher herpes simplex virus type 1 (HSV-1) and EBV antibody titers than non-caregivers (Glaser & Kiecolt-Glaser, 1997; Kiecolt-Glaser et al., 1987). Compared to non-caregivers, spousal dementia caregivers had smaller antibody responses to an influenza virus vaccine and diminished antibody responses over time to a pneumococcal pneumonia vaccine (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000; Kiecolt-Glaser et al., 1996). In addition, one provocative study demonstrated that a punch biopsy wound took longer to heal among spousal and offspring dementia caregivers compared with non-caregivers (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995).

The immunological consequences of caregiving are also evident among people caring for a loved one with other chronic medical conditions. For instance, primary caregivers for a family member with brain cancer had higher systemic CRP and upregulated pro-inflammatory transcription factors compared with non-caregivers (Miller et al., 2008). In addition, parents caring for a child with a

developmental disability had smaller antibody responses to a pneumococcal polysaccharide vaccine than non-caregivers (Gallagher, Phillips, Drayson, & Carroll, 2009).

Longitudinal data provide additional evidence that the chronic stress of caregiving dysregulates immune function over time. Compared to non-caregivers, spousal dementia caregivers had larger EBV antibody titer increases over time (Kiecolt-Glaser et al., 1991). Primary caregivers for a family member with cancer had larger systemic CRP increases over time than non-caregivers (Rohleder, Marin, Ma, & Miller, 2009). Spousal dementia caregivers' average rate of increase in systemic IL-6 over 6 years was about four times as large as that of non-caregivers (Kiecolt-Glaser et al., 2003). Interestingly, 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 also did not differ between current and former caregivers, suggesting that psychological recovery from relationship loss may be critical to immune system recovery over time.

### Future Directions

Distressing relationships negatively affect immune function (Jaremka, Lindgren, et al., 2013). However, some people may be more resilient in the face of stress than others. Indeed, psychological resources (e.g., self-esteem) may buffer against the negative effects of relationship distress. For example, 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 (Ford & Collins, 2010). This study suggests that, compared to their lower-self-esteem counterparts, people with higher self-esteem may interpret ambiguous interpersonal situations as less threatening. Exploring whether these self-esteem differences translate into altered stress-related immune function is an interesting research direction.

The presence/absence of relationships versus the quality of those relationships appears to affect men and women differently. Compared to women, men reap more immunological benefits from being married. On the other hand, women are more sensitive to marital quality and thus experience more immune dysregulation when marriages take a negative turn (Kiecolt-Glaser & Newton, 2001). These findings may help explain gender-based health differences; men's health benefits more from being married, whereas women's health is more closely tied to marital quality (House, Robbins, & Metzner, 1982; Kiecolt-Glaser & Newton, 2001). It remains unclear whether these gender differences extend to non-marital relationships; the loneliness and social support literatures largely do not report gender differences, either because they do not exist or because they were not studied. In either case, a full exploration of gender differences is necessary in order to understand the immunological consequences of close relationships.

Preliminary evidence suggests that social interactions via social media websites (e.g., Facebook) can be both positive and negative. For example, frequent Facebook users experienced more supportive interactions than non-frequent users (Ellison, Steinfield, & Lampe, 2007; Muise, Christofides, & Desmarais, 2009), but they also experienced more jealousy (Muise et al., 2009). One interesting question is understanding whether the affective consequences of social-media-based relationships have immunological consequences.

Relationships may affect immune function differently in older versus younger adults. Both social integration and relationship quality likely evolve with age. Social networks of older adults contain fewer peripheral relationships than those of younger adults, and older adults view emotionally close relationships as more important than novel friendships (Fung, Carstensen, & Lang, 2001). Thus, older and younger adults appear to view relationships differently, which may have immune consequences. Longitudinal studies may be useful in answering whether age-related relationship changes alter immune function.

## Conclusion

In sum, being married and having diverse social ties confer immunological benefits. On the other hand, distressing relationships have negative immunological consequences. Furthermore, immune dysregulation is evident among people experiencing relationship loss, either through the death of a spouse or providing care for a loved one with a deteriorating medical condition. Because immune function is essential to health, these studies may provide mechanistic insight into the ways that relationships affect health.

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