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Marriage, Divorce, and the Immune System

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This article reviews evidence from several lines of work to describe how marriage and divorce can provoke health-relevant immune alterations, including ways that marital closeness can be perilous for health and divorce can be beneficial. The multiple stresses of a troubled relationship are depressogenic, and the development of a mood disorder sets the stage for psychological and biological vulnerability. Depression provides a central pathway to immune dysregulation, inflammation, and poor health; gender-related differences in depression and inflammation can heighten risk for women compared to men. Sleep and obesity can simultaneously feed off depression as they promote it. In addition, spousal similarities in health behaviors, gene expression, immune profiles and the gut microbiota offer new ways to consider the health advantages and risks of marriage and divorce, providing new perspectives on couples' interdependence, as well as new directions for research.

Keywords: marriage, gut microbiome, depression, inflammation, interdependence

Many epidemiological studies convey the same message: marriage is good for health, and divorce threatens mental and physical well-being (Holt-Lunstad, Smith, & Layton, 2010; Sbarra, Law, & Portley, 2011). However, a closer look at individual variation provides a far more nuanced view. Indeed, turbulent marriages can breed depression and impair health, but marital closeness and happiness can also pose risks when couples share unhealthy behaviors (Kiecolt-Glaser & Wilson, 2017). Separation and divorce may leave lasting scars on a small minority, but most recover their health and well-being quickly (Bourassa, Sbarra, & Whisman, 2015).

This article addresses the immune system's starring role to consider how marriage and divorce can provoke health-relevant immune alterations, beginning with an overview of the endocrine and immune changes following hostile marital interactions that can be observed even in very early marriage. The immune system's responsivity to stress and depression-reactive pathways (through the sympathetic and parasympathetic nervous systems, and the hypothalamic–pituitary–adrenal and sympathetic–adrenal–medullary axes) provides multiple avenues for behavioral modulation of immune function. In addition, spousal similarities in sleep, diet, gene expression, immune profiles, and the gut microbiota offer new ways to consider the health benefits and perils of marriage and divorce. Depression provides a central pathway to immune dysregulation, inflammation, and poor health, and sleep and obesity can simultaneously feed off depression as they promote it. Factors associated with women's greater risk are described, as well as new directions for research.

Marriage

Newlyweds

Newlyweds' high marital satisfaction makes them a valuable study population for understanding the dynamics that lead to marital success or distress (Karney & Bradbury, 1995). One study that used an intensive screening process with stringent inclusion criteria produced a sample of 90 newlywed couples with an average age of 25 who had exceptional physical and mental health (Kiecolt-Glaser et al., 1993). The couples' 24-hr admission to a hospital research unit allowed for intensive endocrine and immune data collection.

Early in the day, couples' 30-min discussion of a disagreement was videotaped, and the ratings of these "con-

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flict" session tapes provided data on negative or hostile behaviors like sarcasm and disgust, in addition to nonverbal behaviors such as eye rolling or a hostile tone of voice (Heyman, 2001). Many researchers have found that conflict behaviors are stable and reliable; unhappy couples act much more negatively toward their partners, and, when their partner is hostile, they are far more likely to reciprocate than happy couples (Heyman, 2001). Compared to positive or supportive behaviors, hostile behaviors discriminate much better between happy and unhappy couples (Rivers & Sanford, 2018; Sanford, Backer-Fulghum, & Carson, 2016), and hostile behaviors are also much stronger predictors of physiology and marital distress (Kiecolt-Glaser & Newton, 2001). To permit unobtrusive endocrine sampling during the marital problem discussion, a long polyethylene tube was attached to a heparin well, allowing nurses to draw blood samples out of subjects' sight; samples obtained before, midway, and 15 min after the couples' discussion provided data on short-term endocrine reactivity (Malarkey, Kiecolt-Glaser, Pearl, & Glaser, 1994).

Hostile behaviors during the marital problem discussion were associated with marked increases in norepinephrine, epinephrine, and adrenocorticotropic hormone (ACTH) that persisted after the discussion ended. These stress-responsive hormones typically show *acute* responses to novel or stressful events. Unwinding quickly after a stressor, that is, returning to one's endocrine baseline, reduces the physiological fallout. However, stressors that elicit greater distress may continue to elevate stress hormones, and these effects can persist even after repeated exposures (Miller, Chen, & Zhou, 2007). Aliquots from each of the hourly blood samples (8:00 a.m. to 10:00 p.m.), pooled because of financial constraints, provided a single summary daytime hormone value from a day that included a conflict (Kiecolt-Glaser et al., 1996). These pooled samples provide desirable information on tonic or resting levels of stress hormones, augmenting the prior data on phasic or acute changes: The links between behavior and these summary daytime endocrine data were much stronger and more consistent among wives than husbands for cortisol, epinephrine, and norepinephrine (Kiecolt-Glaser et al., 1996). Wives' cortisol and norepinephrine values were higher in this 14-hr daytime sample when their husbands withdrew following wives' negative behavior, but husbands' endocrine data were not associated with this interaction sequence. Paralleling these data, this negative/withdraw pattern has been associated with declines in wives' (but not husbands') marital happiness (Heavey, Layne, & Christensen, 1993).

Cortisol, ACTH, epinephrine, and norepinephrine impact the immune response (Glaser & Kiecolt-Glaser, 2005); thus, it was not surprising that newlyweds' hostile conflict behaviors had immunological correlates as well. In the blood samples obtained at the start and finish of their 24-hr visits, more hostile newlyweds demonstrated greater maladaptive change across multiple immune assays from one morning to the next relative to their less hostile counterparts, and women showed greater immune dysregulation than men (Kiecolt-Glaser et al., 1993). Furthermore, when these couples were followed up with 2 years later, spouses in distressed marriages had larger declines on immune assays than those in happy marriages (Jaremka, Glaser, Malarkey, & Kiecolt-Glaser, 2013).

In summary, despite the fact that these were very happy newlyweds, hostile behaviors during marital conflict produced persistent alterations in endocrine and immune function (Kiecolt-Glaser et al., 1993, 1996; Malarkey et al., 1994). Women showed greater endocrine and immune change than men during and after marital conflict. These patterns were especially notable because of couples' high levels of marital satisfaction, and the newlyweds' pristine physical and mental health.

Older Couples

The newlywed study illustrated key pathways through which marital behavior could alter the immune response, and, ultimately, health; nevertheless, the findings could have underestimated a troubled marriage's real cost, because these healthy young newlyweds would be at low risk for any actual health consequences. Additionally, marital conflict occurs less frequently and is less intense in very early marriage (Storaasli & Markman, 1990), and could thus have muted endocrine and immune responses. Alternatively, the relative novelty of such conflicts for these newlyweds might have provoked larger responses; in this scenario, older couples' responses to conflict might be muted, because of their greater familiarity with such disagreements in their long-term marriages (Birditt, Brown, Orbuch, & McIlvane, 2010).

Accordingly, endocrine and immune responses to marital problem discussions were assessed in older couples (M_{age} = 67) who had been together for 42 years, on average (Kiecolt-Glaser et al., 1997). Among women, intensification of hostile conflict behaviors and lower marital satisfaction accounted for 16% to 21% of the variance in the increased cortisol, ACTH, and norepinephrine during the conflict discussion. However, men's changes in these hormones were not associated with hostile behavior or marital satisfaction. Both men and women who had poorer immune responses across several immune markers were more hostile during the problem-solving task; in addition, they described their typical marital arguments as more hostile than those who had better immune response data. This study illustrated how hostile marital discussions can alter immune and endocrine function even among older couples in longer term relationships, consistent with the evidence that stressors can continue to raise stress hormones even after repeated exposures (Miller et al., 2007). What is more, the risks can be

substantially heightened by the age-related increases in inflammation discussed below.

Heart Rate Variability and Inflammation

Stress and depression can imbalance the autonomic nervous system, simultaneously amplifying sympathetic nervous system activity while lowering parasympathetic (vagal) activation. Lower heart rate variability (HRV, a measure of parasympathetic activation) is an early cardiovascular hazard marker, as well as a valuable predictor of cardiovascular problems. Moreover, lower HRV is related to heightened inflammation (Frasure-Smith, Lesperance, Irwin, Talajic, & Pollock, 2009). Parasympathetic activity decreases during normal aging (Antelmi et al., 2004), and these decrements appear to be linked to age-related inflammatory increases (Tracey, 2009). Inflammatory markers including tumor necrosis factor alpha and interleukin-6 (IL-6) have been implicated in a variety of age-linked diseases and disorders including Type 2 diabetes, cardiovascular disease, stroke, osteoporosis, arthritis, cancer, frailty, and functional decline (Michaud et al., 2013).

Among 114 young couples (average age of 29, married 1–3 years), higher resting HRV (greater parasympathetic activity) was correlated with better marital quality (Smith et al., 2011). Furthermore, HRV decreased in women, but not men, following a negative interaction task (Smith et al., 2011). Paralleling these cross-sectional data, increases in marital satisfaction and support over 10 years were related to higher HRV among a sample of 907 midlife and older adults drawn from the Midlife in the United States study; increased marital strain over 10 years was associated with lower HRV (Donoho, Seeman, Sloan, & Crimmins, 2015). Thus, lower marital satisfaction and greater marital strain would also be expected to boost inflammation.

In accord with these HRV findings, hostile marital behavior heightened inflammation in couples (M_{age} = 37, married an average of 13 years) who had spent 24 hr on a hospital research unit on two occasions in a study addressing inflammation and wound healing (Kiecolt-Glaser et al., 2005). Their first visit included a supportive interaction, and in their second visit they tried to resolve a marital disagreement. The IL-6 production of the less hostile couples was roughly the same across both visits, but more hostile couples' IL-6 jumped from 45% after the supportive visit to 113% after the conflict visit.

Subsequent studies have linked troubled marriages with heightened inflammation (Donoho, Crimmins, & Seeman, 2013; Kiecolt-Glaser, Jaremka, et al., 2015; Shen, Farrell, Penedo, Schneiderman, & Orth-Gomer, 2010; Uchino et al., 2013; Whisman & Sbarra, 2012). Recent work has also found partners' HRV synchrony to be relevant for inflammation: When couples' moment-to-moment HRV changes tracked more closely together during conflict, they had higher levels of three inflammatory markers across the day (Wilson et al., 2018). In addition, higher trait hostility in one spouse was associated with higher C-reactive protein in his or her partner (Smith, Uchino, Bosch, & Kent, 2014). Furthermore, marital discord's notable consequences include an amplified risk for inflammation-related disorders including depression, cardiovascular disease, metabolic syndrome, diabetes, and poorer wound healing (Beach, 2014; Gallo et al., 2003; Joseph, Kamarck, Muldoon, & Manuck, 2014; Kiecolt-Glaser et al., 2005; Orth-Gomer et al., 2000; Troxel, Matthews, Gallo, & Kuller, 2005; Whisman, Li, Sbarra, & Raison, 2014). The laboratory HRV and inflammatory data provided the mechanistic evidence that showed how troubled marriages can impact health and the community and epidemiological studies have confirmed and extended the laboratory findings. Although the emphasis thus far has been on the risks of marital turmoil, close and supportive marriages can carry risks as well, described below.

Partner Convergence: Gene Expression, Immune Profiles, and the Gut Microbiome

Recent studies have provided mechanistic insights into spouses' shared disease risk. Researchers have demonstrated coregulation of couples' cortisol levels (Laws, Sayer, Pietromonaco, & Powers, 2015; Liu, Rovine, Klein, & Almeida, 2013; Saxbe & Repetti, 2010). This convergence could have consequences for gene expression, immune function, and the gut microbiota. For example, gene expression, shaped by both genetic and environmental regulators, plays a fundamental role in determining traits and phenotypes. In this context, it is significant that gene expression patterns in husbands and wives exhibited noteworthy transcriptional similarity, with much smaller variances in couples than random pairs across a sizable number of genes (Tang & Zhang, 2016).

Another research team, using a systems-level approach to determine cellular immune profiles for 670 healthy people, found that couples living together had 50% less immunological variation than between unrelated pairs (Carr et al., 2016). Cohabitation had the strongest influence on the profiles, and the cohabitation effect was independent of age, and included stimulated cytokine production. In fact, the authors concluded that living together had a very strong relationship to immune system parameters, surpassing the large immune changes produced by acute and untreated gastroenteritis. These transcriptional and immune profile similarities in couples reflect their shared living environment and concordant health behaviors (Carr et al., 2016; Tang & Zhang, 2016). The immune system serves as a major communication path between the brain and the gut (Dinan & Cryan, 2017), and the gut microbiome appears to play a central mediational role while influencing both. What is more, growing evidence has implicated the gut micro-

biome in mental and physical health (Dinan & Cryan, 2017).

In this context, the fact that cohabiting couples' gut microbiotas are also more similar to each other than unrelated partners can be seen in a new light (Rothschild et al., 2018). Physical interaction promotes microbial sharing, and touching, kissing, and sex ensure microbial transfers. Importantly, genetics have only a minor influence on the gut microbiota's composition (Rothschild et al., 2018). In contrast, environmental factors (diet, drugs, and anthropometric measurements) account for over 20% of interperson gut microbiota variability. Indeed, even after controlling for age, gender, diet, and host genetics, microbiota data accounted for substantial variability in body mass index (25%), fasting glucose (22%), high-density lipoprotein (36%), waist circumference (29%), waist–hip ratio (24%), and lactose consumption (36%; Rothschild et al., 2018).These microbiota influences have real-world correlates. For example, even when people eat identical foods, their blood glucose responses are highly variable, reflecting the microbiota's mediation (Zeevi et al., 2015).

Couples' microbiota similarities reflect the partners' behavioral concordance in key health behaviors that influence the microbiome—diet, exercise, sleep, smoking, and alcohol consumption (Gilbert et al., 2018; Kiecolt-Glaser & Wilson, 2017; Liu, 2017). Health habits are "contagious" within couples, and improvement in one spouse often follows after the partner has made a healthy change, while unhealthy behaviors promote the same in the partner. Consequently, there are sizable spousal ties among a range of health-related markers, for example, spousal linkages have been demonstrated for adiposity measures, blood pressure, heart rate, and two inflammatory markers, C-reactive protein and fibrinogen (Davillas & Pudney, 2017). Marital mood contagion has been extensively documented, and distress or depression in one spouse can evoke related emotional responses in their partner. Having a spouse with serious and persistent mental health issues such as depression increases the risk for the partner (Benazon & Coyne, 2000; Kiecolt-Glaser & Wilson, 2017). In fact, increased risk has been documented across a very wide range of diseases and disorders including asthma, allergies, peptic ulcer disease, hypertension diabetes, metabolic syndrome, hypertension, arthritis, cancer, and cognitive functioning (Kiecolt-Glaser & Wilson, 2017).

Separation and Divorce

Amplifying risk. Separated and divorced individuals have a heightened risk for physical and mental illness compared to their married counterparts (Sbarra & Nietert, 2009). To explain this amplified risk, early cross-sectional research focused on immune alterations. For example, compared to their married counterparts, men who had separated/divorced within the last 3 years had higher levels of depressive symptoms and described themselves as lonelier; in addition, the separated/divorced men had poorer immune function and more recent illnesses (Kiecolt-Glaser et al., 1988). Those separated/divorced men whose wives had initiated the separation (and thus presumably had less control) were more distressed and had poorer health than the initiators.

Emotional distress following divorce is relatively short-lived for most people, and only a minority account for most of the heightened risk following divorce (Sbarra, Emery, Beam, & Ocker, 2014; Sbarra, Hasselmo, & Bourassa, 2015). Among 38 women who had been separated/divorced for up to 6 years, those who had been separated within the prior year had poorer immune function across multiple assays, and they also described themselves as more depressed and lonelier than their 38 married community counterparts (Kiecolt-Glaser et al., 1987). However, other factors besides the recency of the separation are influential; continued preoccupation with the former spouse can also prolong distress-related symptoms (Sbarra et al., 2015). The recurrent thoughts may be negative or positive—fury or longing—but, in either case, these intrusive, ruminative thoughts perpetuate negative emotions. Greater marital-related rumination was associated with poorer immune function among the separated/divorced women (Kiecolt-Glaser et al., 1987).

Similarly, in a novel laboratory study, 70 recently separated or divorced adults who reported more divorce-related emotional intrusions had higher resting blood pressure (Sbarra, Law, Lee, & Mason, 2009). When asked to think about their separation experiences, the blood pressure of the more distressed men shot up into the hypertensive range. Intrusive thoughts can spike sympathetic nervous system activity (Ottaviani et al., 2016), as illustrated by the blood pressure changes in this study (Sbarra et al., 2009).

Although divorce typically provokes short-term increases in distress, it can also be beneficial. For example, women in very low-quality marriages experienced heightened life satisfaction following divorce (Bourassa, Sbarra, et al., 2015). Without regular exposures to marital stressors, this heightened life satisfaction could also serve to promote better quality sleep, more exercise, and a healthier diet. Additionally, better social integration has been associated with a more favorable immune profile following marital separation (Hasselmo et al., 2018).

The newlyweds, 10 years later: A longitudinal perspective on divorce. Declines in self-rated marital quality are predictable during early marriage, and roughly a third of the couples will divorce during the first 4 years (Kurdek, 1991). For this reason, early predictors of later marital dissatisfaction and divorce were examined in a 10-year follow-up study of the 90 newlywed couples described previously (Kiecolt-Glaser et al., 1993, 1996; Malarkey et al., 1994). Importantly, current marital status was determined for 100% of the original sample, with follow-up data

collected from all participants who were still married (Kiecolt-Glaser, Bane, Glaser, & Malarkey, 2003). Similar to other newlywed samples, only 3% had reported marital distress when studied in their first year of marriage.

Stress hormones, assessed in the first year of marriage, demonstrated robust relationships with subsequent marital satisfaction and divorce. Following the Year 1 problem-solving discussion, the postdisagreement epinephrine levels collected at the initial visit were 34% higher in couples who later divorced than in those who remained married 10 years later. Importantly, these hormonal alterations were not restricted to the couples' interactions; among couples who later divorced, epinephrine was 22% higher throughout the day (8:00 a.m. to 10:00 p.m.), and both norepinephrine and epinephrine were 16% higher at night (11:00 p.m. to 7:00 a.m.) than among those who were still married 10 years later.

Similarly, Year 1 stress hormones were associated with marital quality 10 years later in couples who were still married. The postconflict Year 1 ACTH levels of women who were dissatisfied with their marriage 10 years later were twice as large as those of women who were satisfied; furthermore, troubled couples' postconflict norepinephrine levels had been 34% higher than those of untroubled couples. These elevations were not simply a transient response to conflict; indeed, those couples who were dissatisfied with their marriage 10 years later had also produced 24% more norepinephrine across the day, and, what is more, 17% more throughout the night when they were still newlyweds, compared to those who continued to report high levels of marital satisfaction 10 years later. Compared to couples who were untroubled at the 10-year assessment, troubled couples had shown more hostile behavior as newlyweds.

The heightened Year 1 epinephrine and norepinephrine production among newlyweds who were later dissatisfied and/or divorced demonstrates sympathetic nervous system overactivity, as well as a hormonal route to inflammation. Norepinephrine induces a molecular signaling pathway that regulates proinflammatory cytokine gene expression, and thus, the newlyweds' norepinephrine overproduction during both waking and sleeping hours provided a persistent upstream inflammatory stimulus (Straub & Härle, 2005). Indeed, the newlyweds' norepinephrine data dovetail with the evidence linking divorce with heightened inflammation (Sbarra, 2015) and shorter telomeres (Whisman, Robustelli, & Sbarra, 2016). These data show one clear biological path to the increased risk for early death seen in separated and divorced individuals (Sbarra & Nietert, 2009).

Even though the overall risk for early mortality rises following divorce, large-scale divorce studies find that the majority of people are resilient, experiencing only short-term disruptions in functioning that last for a few months up to a year (Malgaroli, Galatzer-Levy, & Bonanno, 2017; Mancini, Sinan, & Bonanno, 2015). However, 10% of the participants in a longitudinal population-based study became depressed postdivorce; this subgroup had a significantly greater risk for early mortality when compared to the resilient group or married people (Malgaroli et al., 2017). Individual differences associated with poorer outcomes have included a ruminative response style, lower perceived control, and higher levels of negative affect (Bonanno, Westphal, & Mancini, 2011); these individual differences have also been associated with heightened sympathetic reactivity as well as greater immune dysregulation (Kiecolt-Glaser et al., 1987, 1988; Sbarra et al., 2009).

Depression as a Central Pathway to Immune Dysregulation and Poor Health

Marital distress can provoke heightened depressive symptoms as well as syndromal depression (Beach, 2014). The relationship is bidirectional: distressed marriages boost depressive symptoms, and depression promotes poorer marital quality (Beach, 2014). Importantly, depression can have long-lasting consequences well beyond its resolution. Marital relationships can be impaired for years following an acute depressive episode (Bothwell & Weissman, 1977; Levkovitz, Lamy, Ternochiano, Treves, & Fennig, 2003). Both previously and currently depressed individuals reported more stressors, both major and minor, than people without a similar history, and past and current depression also heightened emotional responsivity to stressors (Hammen, 1991; Husky, Mazure, Maciejewski, & Swendsen, 2009; O'Grady, Tennen, & Armeli, 2010). Consistent with this heightened response to stressful events, marital dissolution was associated with a greater likelihood of subsequent depression only among those individuals who had a depressive episode prior to divorce (Sbarra et al., 2014). Furthermore, depression can harm a person's closest relationships; in one study, the family functioning of those with a past or current depressive episode was poorer than those who had no history of depression, even years after remission of their depressive episode (Herr, Hammen, & Brennan, 2007).

Depression Primes Inflammatory Responsiveness

What is more, depression can also leave multiple adverse physiological changes in its wake. Current depression is associated with increased sympathetic activity, as well as lower parasympathetic activity (Frasure-Smith et al., 2009). Parasympathetic activity (HRV) decreases with increasing depression severity, such that more severe depression has a greater impact on HRV (Kemp et al., 2010). The relationships between parasympathetic activity and inflammation are stronger among depressed than nondepressed individuals (Frasure-Smith et al., 2009). Additionally, although antidepressant treatment reduces depressive symptoms, it does not change HRV (Kemp et al., 2010). Consequently, per-

sistently lower HRV could contribute to heightened inflammation and larger inflammatory stress responses.

Depression and stress can also prime inflammatory responsiveness, stimulating larger cytokine spikes following exposure to pathogens and stressors (Glaser, Robles, Sheridan, Malarkey, & Kiecolt-Glaser, 2003; Kiecolt-Glaser, Derry, & Fagundes, 2015). This maladaptive heightened responsiveness has been documented in patients with major depression, as well as among individuals with higher levels of depressive symptoms (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013; Pace et al., 2006; Weinstein et al., 2010). Importantly, the pathway between depression and inflammation is bidirectional, and thus exaggerated inflammatory responses increase the risk for depression (Kiecolt-Glaser, Derry, et al., 2015). Accordingly, a past or current mood disorder could act synergistically with stress and marital discord to heighten inflammation and heightened inflammation can lead to depression.

Depression, Sleep, and Obesity

Disturbed sleep, a cardinal depressive symptom, increases the risk for depression twofold (Irwin, 2015). Sleep loss stimulates inflammation, thus promoting depression (Irwin, 2015). In turn, heightened inflammation disrupts normal sleep patterns (Lopresti, Hood, & Drummond, 2013). Persistent insomnia is a potent risk factor for depression; although the risk is greatest for those with a depression history, continuing insomnia is sufficient to provoke heightened depressive symptoms even among those without a mood disorder history (Irwin, 2015). In this context it was noteworthy that the sleep quality scores of 138 recently separated individuals fell within the range normally observed in major depression—5 *SD* above the average for healthy adults Furthermore, sleep complaints predicted heightened blood pressure three months later in this group (Krietsch, Mason, & Sbarra, 2014).

Stressful marital interactions can provoke ruminative thinking, especially when a partner is sleeping next to the source of their discontent (Troxel, 2010). Not surprisingly, rumination and intrusive thoughts can, in turn, fuel insomnia (Troxel, 2010). In married couples, shortened sleep promoted larger inflammatory responses during a marital conflict discussion the next day (Wilson et al., 2017).

Depression increases the risk of obesity by 58% (Luppino et al., 2010). Additionally, depression stimulates increases in visceral fat (Vogelzangs et al., 2008). Marital distress promotes depression as well as metabolic responses that directly foster weight gain and heighten visceral fat accumulation (Kiecolt-Glaser, Jaremka, et al., 2015). These data have health implications; abdominal adiposity (visceral fat) is the keystone for the metabolic syndrome, and both marital discord and depression have been implicated in its development (Pan et al., 2012; Troxel et al., 2005; Whisman & Uebelacker, 2012; Whisman, Uebelacker, & Settles, 2010).

Gender Differences

Gender differences in studies of marital distress and health have been most evident in the limited number of laboratory studies that have used behavioral coding of interactions along with assessments of endocrine and immune reactivity (Kiecolt-Glaser & Newton, 2001). In contrast, a meta-analysis of marital quality and health showed small and nonsignificant gender differences, although the direction was toward greater magnitude for women (Robles, Slatcher, Trombello, & McGinn, 2014). However, both psychological and biological studies that have addressed depression and inflammation in the broader literature suggest that women would be at greater risk in poor marriages than men.

Depression clearly serves as a key pathway between marital distress and health, but the causal relationships may differ for men and women (Fincham, Beach, Harold, & Osborne, 1997). In this context, the evidence that women have higher rates of depression than men has obvious implications for marriage-related health outcomes (Derry, Padin, Kuo, Hughes, & Kiecolt-Glaser, 2015). Depression's close ties to inflammation (Kiecolt-Glaser, Derry, et al., 2015) may be particularly relevant to women for several reasons. First, inflammation-induced mood and behavior changes appear to be more prominent among women than men (Derry et al., 2015). Additionally, prior depression, somatic symptomatology, interpersonal stressors, childhood adversity, obesity, and physical inactivity are all factors that elevate inflammation, and women have disproportionately higher representation than men in each of these domains (Derry et al., 2015). Relationship-related distress has stronger ties to inflammation among women than men (Derry et al., 2015), and the relationship between depression and marital quality is stronger among women than men (Whisman, 2001).

In addition to these gender-related differences in depression and inflammation, women also show greater emotional reactivity to negative marital interactions than men (Kiecolt-Glaser & Newton, 2001), and wives have more detailed and vivid memories of marital disagreements than their husbands (Ross & Holmberg, 1990). More broadly, women also have better memories for nonmarital emotional events than men; women's superior memory for emotional stimuli is related to greater overlap in brain regions that are sensitive to current emotion and also facilitate subsequent memory (Canli, Desmond, Zhao, & Gabrieli, 2002). Furthermore, women also report that they reminisce more frequently about important relationship events and spend more time thinking about their marital relationships than men

(Burnett, 1987; Ross & Holmberg, 1990), processes that would serve to strengthen memories.

In fact, women are more likely to ruminate then men; rumination is an important predictor of becoming depressed as well as remaining depressed (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Memories of stressful experiences can themselves continue to evoke stress-related physiological changes (Ottaviani et al., 2016), and thus women's stronger and more enduring memories would help to sustain maladaptive physiological changes, that would, in turn, promote both depression and inflammation.

Couples' Interdependence

Interdependence theory posits that partners affect each other's functioning through multiple potential psychological and physiological pathways. This interdependence can have far-reaching effects, persisting even when couples no longer have ongoing interactions. For example, data from a multinational older adult sample showed that a deceased spouse's quality of life prior to death predicted the subsequent quality of life in the surviving partner (Bourassa, Knowles, Sbarra, & O'Connor, 2016). In fact, the studies reviewed in this article suggest that couples' interdependence has broad and deep roots, casting a long shadow.

On the biological side, couples' convergence in health behaviors, immune profiles, and microbiota provide new ways to look at the health consequences of marriage and its disruption. How long a couple lives together and the extent to which they share health behaviors undoubtedly influences the extent of similarity, but no studies have addressed the time course in each of these domains. Following separation and divorce, expartners undoubtedly maintain some residual biological similarity for an unknown period of time.

On the psychological side, the multiple stresses of a troubled marriage are depressogenic, and the development of a mood disorder sets the stage for psychological and biological vulnerability. A mood disorder history signifies a high-risk phenotype for emotional and physiological stress sensitivity in tandem with a greater risk for troubled relationships (Hammen, 1991; Husky et al., 2009; Kiecolt-Glaser, Habash, et al., 2015; Kiecolt-Glaser, Jaremka, et al., 2015; O'Grady et al., 2010). Persistent depression-related HRV alterations following a depressive episode (Kemp et al., 2010) would foster heighted inflammation and inflammatory stress responses, which could, in turn, promote depression (Kiecolt-Glaser, Derry, et al., 2015). Furthermore, it is reasonable to assume that this heightened emotional and physiological stress sensitivity could continue to have repercussions even after a marriage has ended.

Although prior depression is sufficient to increase risk, it is not a necessary condition. The 90 newlywed couples described earlier had been carefully screened to eliminate anyone with a current or past mood disorder history. Nonetheless, newlyweds whose marriages would later be troubled or end in divorce had notably higher levels of epinephrine and norepinephrine during both waking and sleeping hours in their first year of marriage (Kiecolt-Glaser et al., 2003). These hormones have a one to two minute half-life, such that the rapid turnover or decay quickly reduces any acute spikes unless there is further stimulation. Accordingly, the persistent epinephrine and norepinephrine elevations reveal how a troubled marriage heightens sympathetic nervous system activity (Kiecolt-Glaser et al., 2003). The longer term immunological fallout would include amplified inflammation, and, in turn, shorter telomeres (Kiecolt-Glaser & Glaser, 2010). In fact, the newlywed study demonstrated how hostile behavior can begin driving adverse endocrine and immune changes very early in the marriage—before spouses reported dissatisfaction with their partner.

Future Research Directions

Much remains to be learned. For example, the absence of immune data from same-sex couples reflects the broader heteronormative perspective throughout the relationship literature, an important limitation. However, the fact that same-sex couples have greater health behavior concordance than different-sex couples (Holway, Umberson, & Donnelly, 2017) leads to interesting questions about same-sex couples' similarities in gene expression, immune profiles, and gut microbiota. Greater health behavior concordance might also reflect greater risk when one partner is stressed or depressed.

As is true for same-sex couples, the literature addressing both marriage and immune function is largely silent with regard to socioeconomic status (SES) differences. Certainly, the link between low SES and poorer health is well-documented, and dovetails with the evidence that the chronic stress of low SES degrades marital quality (Neff & Karney, 2017). For example, the health of low SES people suffered more from marital conflict and benefited less from marital bliss than those of higher SES (Choi & Marks, 2013). Thus, SES could interact with marital quality to affect health in multiple ways.

Close relationships can provoke changes in many facets of the immune system, but the magnitude and/or duration of immune change necessary to produce clinically significant shifts remains largely unknown—mirroring a broader question in the basic science endocrine and immune literatures. For example, it is clear that heightened inflammation carries multiple risks in probabilistic terms, but, like high blood pressure, the threshold for the development of clinical disease depends on many other factors.

Relatedly, it seems reasonable to assume that improvements in marital quality could propel positive physiological and health changes, but data are limited. In one provocative

study, a couples' relationship education program altered cortisol responsiveness to marital conflict but not to a nonmarital laboratory stressor, and these effects were mediated by improvements in relationship quality (Ditzen, Hahlweg, Fehm-Wolfsdorf, & Baucom, 2011). Other researchers showed reductions in health services utilization following couples therapy (Madsen, Tomfohr-Madsen, & Doss, 2017). Further intervention and prevention research that addresses changes in physiology and health care would be valuable.

Partners influence each other's mood and health behaviors, producing both direct and indirect downstream effects on the immune system, and these changes can create longer term risks and benefits, resonating through autonomic, endocrine, gut microbiome, and immune system pathways. The potential long-term persistence of these changes suggests there may be new layers of meaning in the phrase "till death do us part."

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