Matters of the Heart: Grief, Morbidity, and Mortality

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Abstract
Spousal bereavement is associated with elevated risk of morbidity and mortality. Several well-regarded multidisciplinary research teams have investigated the biopsychosocial processes underlying why widows and widowers are at elevated physical-health risk. Here, we review research from multiple investigators showing that, on average, widows and widowers exhibit maladaptive patterns of autonomic, neuroendocrine, and immune activity compared with matched comparison subjects. Widows and widowers also exhibit poorer health behaviors than they did before their spouse’s death, and the considerable variation in postloss psychological-adjustment trajectories among widows and widowers likely corresponds to physical-health risk trajectories. Yet there is little biobehavioral research on patterns of change in physical-health risk after the death of a spouse. We summarize recently published work demonstrating how attachment theory can characterize and predict individual differences in physical-health biomarkers, highlighting the need for a biopsychosocial approach to understanding and characterizing postloss trajectory patterns. We conclude by discussing the possibility that this line of inquiry could help researchers, and ultimately providers, identify adjustment trajectories earlier and thus deliver appropriate interventions when they are most needed.

Keywords
health, bereavement, attachment theory, immune system, heart disease

When friends and family members use the term “broken-hearted” to describe a widow or widower, they are usually referencing the intense emotional pain experienced after the death of a spouse (Stroebe, Schut, & Stroebe, 2007). Indeed, the loss of a spouse takes a considerable emotional toll, ranking first on the Social Readjustment Rating Scale (Holmes & Rahe, 1967). In addition to the mental-health toll, broken-hearted widows and widowers are at risk for premature morbidity and mortality, especially as it relates to cardiovascular events (Moon, Glymour, Vable, Liu, & Subramanian, 2014). The focus of our recent work has been to understand why individuals who are spousally bereaved are at heightened risk of morbidity and mortality (Chirinos, Ong, Garcini, Alvarado, & Fagundes, 2019; Fagundes et al., 2019; Fagundes et al., 2018; Knowles, Ruiz, & O’Connor, 2019).

Health Behaviors
Bereavement is associated with negative changes in routine health behaviors, one probable mechanism underlying the link between grief and poor health. Poor dietary behaviors characterize many people who are widowed (Stahl & Schulz, 2014). Widows and widowers consistently report eating alone, skipping meals, and eating more commercial meals in the first year after loss; there is a strong positive relationship between bereavement and nutritional risk (Stahl & Schulz, 2014). Alcohol consumption also increases among bereaved spouses (Stahl & Schulz, 2014). During the first year of bereavement, relative to matched comparison subjects, widows and widowers also report sleep problems, including difficulty falling asleep and staying asleep; they are also more sedentary (Stahl & Schulz, 2014).

Autonomic and Neuroendocrine Dysregulation
Psychological stress promotes the fight-or-flight response resulting in activation of the autonomic nervous system...
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**Autonomic activity**

The autonomic nervous system has two main divisions: the sympathetic and parasympathetic branches. The sympathetic nervous system regulates the fight-or-flight response, whereas the parasympathetic division helps maintain homeostasis and conserve resources (Thayer & Lane, 2000). Lower resting parasympathetic activation is associated with worse physical and mental health and is assessed by measuring heart rate variability (HRV). Heart rate rises and falls with one's breath, an oscillatory pattern called *respiratory sinus arrhythmia*. The parasympathetic nervous system controls respiratory sinus arrhythmia and partially controls heart rate because the vagus innervates the sinoatrial node, which is the heart’s pacemaker (see Fig. 1, left side). We can capture a vagally mediated heart rate by measuring HRV at the frequency of people’s respiration rate (8-25 cycles per min) or by evaluating beat-to-beat HRV. Although there are other sources of HRV that are not attributed to vagally mediated parasympathetic influences, when referencing HRV below, we are referring to indices of vagally mediated HRV because of its links to mental and physical health (Thayer & Lane, 2000).

Because lower HRV is prognostic for disease, we surmised that HRV could be a potential mechanism linking and hypothalamic-pituitary-adrenal (HPA) axis. When the sympathetic nervous system is activated as part of a coordinated stress response, the catecholamines epinephrine and norepinephrine boost heart rate, blood pressure, and blood glucose levels. Generally, in response to stress, activity in the parasympathetic nervous system decreases (Gianaros & Wager, 2015).
bereavement and cardiovascular risk (Thayer & Sternberg, 2006). We recently demonstrated that spousally bereaved older adults have lower resting HRV than age-matched control subjects (Fagundes et al., 2018). Excellent work from other groups has provided additional evidence for the role of HRV in the context of bereavement. In a study examining within-persons differences in depression among bereaved individuals, O’Connor, Allen, and Kaszniak (2002) showed that those who exhibited more depressive symptoms had lower HRV than widows and widowers who reported less depressive symptoms, which suggests that HRV may serve as a biomarker of poor mental health among widows and widowers (O’Connor et al., 2002). Bereavement has also been linked to elevated catecholamines and higher blood pressure, showing that sympathetic activity is elevated among widows and widowers (Buckley et al., 2011). One condition that is of considerable interest to cardiologists and grief researchers alike is takotsubo. Known colloquially as “broken-heart syndrome,” takotsubo is characterized by considerable emotional distress. Both the sympathetic and parasympathetic nervous system have been linked to the pathogenesis of takotsubo syndrome (Nordcliffe-Kaufmann et al., 2016).

**Neuroendocrine activity**

Cortisol is a glucocorticoid produced in the adrenal glands in response to stress or low blood glucose (Gianaros & Wager, 2015). As seen on the right-hand side of Figure 1, the corticotropin-releasing hormone (CRH) is secreted when the brain signals a stress response, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, the adrenal cortex secretes cortisol. Compared with individuals who have average levels of grief, participants with complicated grief, a former psychiatric diagnosis, show lower levels of morning cortisol and a flatter cortisol slope across the day, two indicators of dysregulated neuroendocrine function (O’Connor, Wellisch, Stanton, Olmstead, & Irwin, 2012). Morning cortisol levels are higher among women grieving the death of their spouse compared with nongrieving women (Irwin, Daniels, Risch, Bloom, & Weiner, 1988). Chronic secretion of cortisol impairs immune cells’ ability to kill pathogens (Gianaros & Wager, 2015); furthermore, although generally anti-inflammatory, chronically high cortisol levels can sometimes lead to glucocorticoid insensitivity, thereby raising systemic inflammation (Miller, Cohen, & Ritchey, 2002).

**Immune Activity**

Some of the foundational studies in the field of psychoneuroimmunology, the discipline concerned with brain–immune interactions, compared bereaved individuals with matched control subjects. A psychoneuroimmunologist often performs functional assays to measure how immune cells in both the innate and adaptive immune system react to challenge. White blood cells mediate the innate immune response, which plays an initial role when the body is exposed to a pathogen (Kusnecov & Anisman, 2014). The innate immune system is activated within minutes to hours after exposure to an antigen; however, it is nonspecific and thus is not always able to eliminate a pathogen. The adaptive immune system takes much longer to respond effectively but is antigen specific and develops a memory for long-term protection from reinfection. Functional methods are used to show that stressors, such as bereavement, impair responses from T and B Cells (an aspect of the adaptive immune system), as well as natural killer cells and neutrophils (components of the innate immune system illustrated on the bottom left of Fig. 1; Kusnecov & Anisman, 2014). A recent meta-analysis showed that functional markers of both the innate immune system and the adaptive immune system are impaired among individuals who are bereaved (Knowles et al., 2019).

Proinflammatory cytokines (bottom of Figure 1) such as interleukin-6 and tumor necrosis factor-α are chemical signals that increase immune-cell trafficking to infection sites. Acute local inflammation in response to an initial infection or trauma can be beneficial; however, chronic low-grade inflammation can contribute to a variety of diseases in older adulthood, such as Type 2 diabetes, Alzheimer’s disease, osteoporosis, rheumatoid arthritis, periodontal disease, some cancers, and cardiovascular disease. In the context of bereavement, the link between cardiovascular disease and inflammation is of particular interest.

Researchers evaluate levels of proinflammatory cytokines by either assessing circulating levels of cytokines or by stimulating certain immune cells (e.g., monocytes/macrophages and T cells; Knowles et al., 2019). Most commonly, serum or plasma levels of circulating proinflammatory cytokines are evaluated. There is now considerable work showing that bereaved individuals have higher levels of circulating inflammatory biomarkers, and other markers of immune dysregulation, than age-matched comparisons. Widows and widowers had higher plasma levels of specific cytokines if they also carried a specific proinflammatory gene polymorphism (Schultze-Florey et al., 2012). Although this review is focused on spousal bereavement, some of the studies on circulating levels of inflammation and bereavement combined different forms of bereavement into one group; these studies show similar results (Cohen, Granger, & Fuller-Thomson, 2015).

Another approach to measuring inflammation that is more time consuming, but likely more indicative of a typical proinflammatory response, is to stimulate (challenge) specific immune cells, such as monocytes/macrophages
and T cells. By exposing the white blood cells to a bacterial pathogen, a procedure called *ex vivo stimulation*, we recently demonstrated that bereavement is associated with the capacity of immune cells to produce inflammatory cytokines when challenged (Fagundes et al., 2018). This method more likely represents the in vivo context in which the immune system produces cytokines in response to stress or infection (Korenromp et al., 2011). Specifically, widows and widowers showed enhanced proinflammatory cytokine production by in vitro lipopolysaccharide-stimulated peripheral blood leukocytes than did matched comparison subjects (Fagundes et al., 2018). When examining between-persons differences among widows and widowers, we found that individuals with higher grief severity had higher levels of proinflammatory T-cell-derived cytokines than those with less grief severity (Fagundes et al., 2019). We also examined the association between depressive symptoms and inflammation because we wanted to know whether the well-established relationship between elevated inflammation and greater depressive symptoms existed among widows and widowers (Kiecolt-Glaser, Derry, & Fagundes, 2015). We found that those who experienced higher levels of depression exhibited elevated levels of T-cell-derived proinflammatory cytokines compared with those who had lower levels of depressive symptoms. However, depression did not explain the relationships with grief and proinflammatory cytokines (Fagundes et al., 2019).

In the broader psychoneuroimmunology literature, there is evidence that levels of inflammation predict future psychopathology. Because depression and inflammation interact through a bidirectional feedback loop (Kiecolt-Glaser et al., 2015), widows and widowers’ levels of inflammation at one time point may predict future postloss adjustment at another time point, an important area for future investigation.

**Individual Differences**

In the bereavement literature, the vast majority of research on biomarkers of risk and health has focused on differences between bereaved and matched comparison subjects. Yet there is considerable adjustment variation among widows and widowers. Widows and widowers consistently fall under one of five different psychological-adjustment trajectories over the first 2 years after their spouse’s death (Bonanno, Wortman, & Nesse, 2004; see Fig. 2). Thus, bereavement poses unique problems for interventionists (Bonanno et al., 2002) because they have no way of knowing which trajectory profile a widow or widower will most likely fall into until the trajectory unfolds, making intervention efforts problematic (Robbins & Kubiak, 2014). Research that identifies a widow or widower’s most probable long-term trajectory shortly after the loss would be a major advance. Stable individual differences in personality constructs are likely sources of information to predict future grief trajectories.

Attachment theory provides a theoretical framework for understanding individual differences in grief reactions after the death of a spouse (Shaver & Tancred, 2001). There are two patterns of attachment insecurity: attachment anxiety and attachment avoidance. People with high attachment anxiety use *hyperactivating* emotional-coping strategies that accentuate the stress response. People with high attachment avoidance are uncomfortable depending on others and use *deactivating* coping strategies in an attempt to inhibit stress. In the adult attachment literature, people who are low on both attachment anxiety and attachment avoidance are considered securely attached (LeRoy et al., 2020). We cross-sectionally assessed widows and widowers within approximately 3 months after the death of their spouse to determine whether individual differences in attachment patterns predicted self-reported health and inflammation (as evaluated by ex vivo cytokine production). Attachment anxiety was associated with increased ex vivo stimulated monocyte production of proinflammatory cytokines. Likewise, attachment anxiety was associated with poorer self-reported mental and physical health. Bereaved spouses (death of spouse within approximately 3 months) who had higher levels of attachment anxiety reported poorer mental and physical health (i.e., less energy, poorer emotional functioning, poorer social functioning, and poorer self-rated health; LeRoy et al., 2020). Attachment anxiety was also associated with greater ex vivo cytokine production. In contrast, attachment avoidance was not associated with inflammation; however, compared with individuals low on attachment avoidance, those high on attachment avoidance reported better self-reported mental and physical health (LeRoy et al., 2020). Importantly, these data were cross-sectional; it will be important for future work to determine whether these individual differences predict trajectories in grief, self-reported health, and biomarkers of physical-health risk over 1 to 2 years after the loss.

In addition to identifying stable individual-differences characteristics of risk, a more fine-grained understanding of widows’ and widowers’ lived experiences would inform prediction and intervention efforts. Our understanding of the behaviors, emotions, and contextual influences underlying physical and mental health after the death of a spouse is limited because the methods used have relied on snapshots of grief (often assessed retrospectively) and stress physiology. Yet according to the dual-process model of coping with bereavement, grief is a dynamic process during which widows and widowers vacillate between coping with restoration-oriented...
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Stroebe & Schut, 2010). Mobile health-sensor technologies can now collect contextual and physiological data in one's natural environment noninvasively and with little burden; these methods may be particularly useful for evaluating the dynamic processes associated with grief. Using this data, inference algorithms could then generate estimates of context, behavior, and stress physiology to better predict a widow's or widower's health risk and future adjustment trajectory. This information would be particularly helpful to intervention scientists because of the now well-established literature showing that

stressors and loss-oriented stressors (Stroebe & Schut, 2010). Mobile health-sensor technologies can now collect contextual and physiological data in one's natural environment noninvasively and with little burden; these methods may be particularly useful for evaluating the dynamic processes associated with grief. Using this data, inference algorithms could then generate estimates of context, behavior, and stress physiology to better predict a widow’s or widower’s health risk and future adjustment trajectory. This information would be particularly helpful to intervention scientists because of the now well-established literature showing that

Fig. 2. Factors influencing physical- and mental-health outcomes in spousally bereaved individuals over time. After the death of the spouse, bereaved individuals experience a number of emotional, behavioral, and physiological changes. Stress related to bereavement (a), including loss-oriented and restoration-oriented stressors, may encourage negative health behavior, disrupt homeostasis within physiological systems, or create emotional instability. All of these impacting elements affect and are affected by each other. Months or years later (b), individuals who still exhibit high levels of depressive or grief symptoms are at increased risk for cardiovascular disease, depression, or grief-related disorders. Preexisting factors (c) such as attachment patterns influence how susceptible individuals are to physiological, behavioral, and emotional dysregulation as a result of bereavement-related stress. High attachment anxiety is a risk factor for poor emotional and physical health. The five grief trajectories identified by Bonanno, Wortman, and Nesse (2004) are represented in (d), with pink and blue representing individuals who are symptomatic and nonsymptomatic 18 months after their loss.
widows and widowers have different intervention needs based on their characteristics and adjustment trajectories (Bonanno et al., 2002). For example, we now know that the vast majority of widows and widowers should not receive psychotherapy focused on grief work, but a minority of widows and widowers do benefit from this treatment (Bonanno et al., 2002). Further, because widows and widowers must attend to new daily tasks and cope with new stressors, interventions focused on specific skills training, changes in health behavior, or stress reduction are likely warranted. We argue that a personalized approach to care during this difficult period is an important next step.

Conclusion

Spousal bereavement increases the risk for poor health outcomes, as it is accompanied by alterations in mood, behavior, and disruptions to physiological and immunological systems. We surmise that these systems affect and are affected by negative health behaviors and emotional distress; together, these interacting factors potentiate risk for heart disease and depression. Individual differences among widows and widowers may help to identify individuals who require formal intervention. Future work should distinguish comprehensive patterns of risk and resilience to target individualized treatments toward vulnerable individuals.

Recommended Reading


Transparency

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