Increased risk of infection in bereaved older adults: from broken heart to broken immune system

 Running Head: Bereavement, ageing and immune system

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**Abstract**

Bereavement, the loss of someone close, is frequently followed by grief and can have serious implications for physical and mental health, from the increased symptoms of depression and anxiety, sleep disturbances and indigestion, and more serious physical health consequences such as cardiovascular and immune related illness. Another key factor associated with a deterioration of the body’s defence mechanisms, such as the immune system, is ageing. This review has as its focus the combined effects of bereavement and ageing on immune function. First, the relationship between bereavement and increased mortality is examined, followed by its link to various physical and mental health morbidities. Second, the effects of ageing *per se* on immune functions are considered. Finally, the joint impact of both ageing and bereavement are discussed, focussing on recent studies of immune function after bereavement in young and older adults.

*Keywords:* Bereavement; Ageing; Immune Response

**1. Bereavement and grief**

Grief is a complex reaction to the loss of someone close, a relationship or an attachment ([1](#_ENREF_1)). It triggers physiological, behavioural and cognitive responses. Whereas previously regarded as a negative adjustment, associated as it often is with the inability to cope with daily activities and mundane demands, it is now appreciated as an essential aspect of human experience ([2](#_ENREF_2)). Grief should be considered in terms of the nature of the relationship lost ([3](#_ENREF_3)). Although the loss of a very close friend or relative can occur at any point in life, the probability of such loss increases with age, and the nature of the relationship with the person lost vary across different age groups. For example, 3-4% of children 18 years old and younger have experienced a loss of one of their parent ([4](#_ENREF_4)). On the other hand, in those over 65, bereavement is most frequently due to the loss of a spouse, often a life-time partner who has over years provided love, companionship, and critical social support; it has been estimated that in the USA, around 45% of older adults are widows and 15% are widowers ([5](#_ENREF_5)). It is not easy to compensate for the loss of such a life-time partner, as it is unlikely that a similar relationship can be established ([2](#_ENREF_2)). It is perhaps not surprising, then, that spousal loss almost invariably compromises mental and physical health ([6](#_ENREF_6)). Bereavement can be characterised as a chronic stress, given that its impact is rarely transient and usually long-lasting. Accordingly, like most chronic stress exposures it is likely to be associated with deterioration in well-being. Here, we first explore the association between bereavement and increased mortality, and then the link between bereavement and physical and mental health. We then consider the role of impaired immune function consequent on ageing and argue that there is an additive effect of ageing and bereavement on immunity which greatly increases the risk of infection.

**2. Bereavement and mortality**

An association between bereavement and increased mortality is strongly supported by the studies that compare adults bereaved of a spouse with age- and sex-matched married controls, taking into account possible confounding factors such as socio-economic status, lifestyle factors shared with their spouse, presence of chronic illness that prevents some bereaved individuals from easily finding another partner, and accident-caused bereavements that might eventually be responsible for the death of the bereaved partner ([7](#_ENREF_7)). Although such study designs are unable to definitively ascribe causality, there is now a clear consensus that bereavement is associated with increased mortality ([8](#_ENREF_8)). Some frequently reported factors related to mortality risk after bereavement are gender, ethnicity, cause of the death of the spouse, as well as the time elapsed since bereavement (9). For example, it has been reported that there is a higher risk of bereavement-related mortality in Whites than in Blacks ([9](#_ENREF_9)), and in widowers as opposed to widows ([10](#_ENREF_10)). It has also been observed that the risk of mortality in the first week following bereavement is 6.6-fold higher for widowers, and 9.6-fold higher for widows relative to non-bereaved age-matched controls ([11](#_ENREF_11)). It has also been reported that 30% of men and 15% of women died following bereavement with the highest risk of mortality occurring between 7-12 months after bereavement ([12](#_ENREF_12)). More recent studies have shown significantly higher odds of mortality in the first 3 months of widowhood when compared to the matched married controls, which seemed to be unrelated to socio-economic status ([13](#_ENREF_13)), while also confirming the importance of controlling for gender ([14](#_ENREF_14)), geographic region and age when examining mortality risk ([15](#_ENREF_15)). Further, individuals bereaved as a result of a spouse's suicide are more likely to take their own life than die from other causes ([16](#_ENREF_16)). Finally, it has been shown that this so called ‘widowhood effect’, the increase in the mortality of those recently Bereaved of a spouse, is frequently related to the death from immune related diseases, such acute illness caused by pathogens or sepsis, or chronic, autoimmune diseases such as chronic obstructive pulmonary disease , diabetes, or cancer ([9](#_ENREF_9)). This would suggest that bereavement may be compromising the immune system, an issue we shall return to later.

**3. Bereavement effects on physical and mental health**

It is well established that after the loss of a close relative or a friend, those bereaved report a variety of health problems. Most commonly reported symptoms range from insomnia, dizziness, headache, to indigestion ([7](#_ENREF_7), [17](#_ENREF_17)), implying that bereavement has a powerful psychosomatic impact. Although grief can remain evident as long as 30 months following bereavement ([18](#_ENREF_18)), common manifestations of the health effects of grief, such as the increased use of medications, more frequent hospital and GP visits, and poorer general health ratings, usually recover to levels comparable with those reported by non-bereaved controls two months following bereavement ([19](#_ENREF_19)). There are, however, exceptions. In a clinical study of sleep quality and duration in individuals over 60 years of age that were bereaved for between two months and one year, sleep disturbance was positively associated with the levels of reported grief, but there was no relationship with time passed since the bereavement ([20](#_ENREF_20)). Poor sleep is now implicated in range of adverse health outcomes, including prolonged activation of the sympathetic nervous system, hypertension, increased inflammation, and diabetes ([21](#_ENREF_21)). Another important effect of bereavement on physical health may be the exacerbation of symptoms of already existing disorders. For example, worsening of diabetes in bereaved patients has been reported ([22](#_ENREF_22)).

**4. Ageing effect on immune system**

Ageing has well-established effects on structural and functional aspects of the immune system. With old age comes a reduced capacity to combat viral and bacterial pathogens such as influenza viruses and pneumococcus pneumonia bacteria. Although a number of immune cells remains largely unaffected by ageing ([23](#_ENREF_23)), an age-related deterioration of immunity , termed immunosenescence, has been reported for a number of functional characteristics in both the innate and adaptive branches of the immune system. For example, Natural Killer (NK) cells, key effectors in the first line of defence against viral infections and tumour cells, show decreased cytotoxicity per cell ([24](#_ENREF_24)) and impaired secretion of the cytolytic molecule perforin in the area of the immunological synapse ([25](#_ENREF_25)). Macrophages, another cellular component of innate immunity, are phagocytic cells involved in variety of immunological, inflammatory and metabolic processes ([26](#_ENREF_26)). As another component of the fast-acting innate immunity, they are also affected with age, showing poorer phagocytic ability, decreased secretion of different cytokines and chemokines, and the delayed wound healing with ageing ([26](#_ENREF_26)). Neutrophils are another category of phagocytic cells essential for eradicating rapidly dividing pathogens such as bacteria and fungi ([27](#_ENREF_27)). The function of these cells has been shown to be affected by ageing on several levels: phagocytosis, superoxide production, chemotaxis, and apoptosis ([28](#_ENREF_28)), leaving them unable to fight infections such as pneumonia, one of the major causes of morbidity and mortality among older adults ([29](#_ENREF_29)).

The adaptive branch of the immune response is also known to be affected by ageing, as manifest in thymic involution, reduction in output of naïve T cells capable of reacting to novel antigens, and simultaneous oligoclonal expansion of memory lymphocytes unable to provide adequate protection (reviewed in ([30](#_ENREF_30))). Increases in infection rates seen in older adults is often associated with the lifetime increase in antigenic load, believed to be related to the existence of the chronic persistent viral infections such as Cytomegalovirus ([31](#_ENREF_31)). These infections lead to the expansion of particular, generally dysfunctional cells within cytotoxic CD8+ T range of cells, which serve to narrow the available immunological space for development of those T cells capable of recognising novel antigens.

In addition, the effectiveness of many vaccinations, as measured as the specific antibody response, is also diminished in the elderly. This is considered to be the outcome of a phenomenon termed replicative senescence, whereby activated lymphocytes are unable to proliferate and, accordingly, unable to create sufficient numbers of effector cells ([32](#_ENREF_32)). This would indirectly lead to a decreased antibody response to vaccination in older adults, especially as replicative senescence affects T helper cells which are important for supporting B cells in antibody production.

Decreased immune function in the elderly is often followed by increased inflammatory status, a phenomenon known as inflammaging. Inflammaging is characterised by a higher relative ratio of circulatory pro-inflammatory (e.g. IL-1, TNF-α, IL-12) to anti-inflammatory (e.g. IL-4 and IL-10) cytokines, and increased cytokine-induced reactive oxygen species production, which in turn stimulates further release of pro-inflammatory cytokines, starting *circulus vitiosus* that leads toward a chronic inflammatory state ([33](#_ENREF_33)). A higher presence of pro-inflammatory cytokines will also affect the hypothalamic-pituitary-adrenal axis (HPA) and increase the availability of cortisol ([33](#_ENREF_33)), a stress hormone with an anti-inflammatory effect that will attempt to counterbalance the inflammatory effects of cytokines ([33](#_ENREF_33)). At the same time, dehydroepiandrosterone sulphate (DHEAS), another HPA axis hormone secreted from the adrenal gland, considered to counteract cortisol’s effects on innate immunity ([34](#_ENREF_34)), is decreased with age ([35](#_ENREF_35)). Ultimately, the result is a higher cortisol:DHEAS ratio with age, whereby the immunosuppressive effects of cortisol overcome the immuno-enhancing effects of DHEAS ([34](#_ENREF_34)).

**5. Bereavement and the risk of infection**

It is now well established that chronic stress can have deleterious effects on various aspects of the immune system. These include, but are not limited to the shift from Th1 to Th2 phenotype followed by the changes in cytokine expression ([36](#_ENREF_36)), reduced NK cell cytotoxicity ([37](#_ENREF_37)), thymic involution ([38](#_ENREF_38)), and impaired vaccination response ([39](#_ENREF_39)). One model of chronic stress frequently used in the literature is that of older spousal caregivers of dementia patients. It has been shown that these are particularly vulnerable individuals where the effects of the chronic stress of caregiving impair various aspects of the immune system when compared with their age- and sex-matched non-caregiving counterparts ([40-46](#_ENREF_40)). It is also possible in some instances that care-giving effects may only be manifest in older individuals. For example, s-IgA secretion rates were lower only in the eldest (aged 63 years) of three distinct age cohorts of informal caregivers relative to controls ([47](#_ENREF_47)), and it has also been shown that older caregivers mount a poorer antibody response to influenza and pneumococcal vaccinations, a diminished NK cell response to cytokine stimulation, poorer control of latent viral infections such as Epstein Barr virus, and delayed wound healing (reviewed in ([48](#_ENREF_48))).

Bereavement is another chronic stress exposure that is associated with immunity; however, it appears that this effect varies between different age cohorts. For example, in some bereaved adults, psychological morbidity more frequently emerges as an important factor that influences weakening of the immune system after bereavement. Although preserved immunity has been reported in a group of the middle aged widows compared to the non-bereaved controls ([49](#_ENREF_49)), those bereaved who reported more depressive symptoms exhibited poorer NK cell function and impaired response to mitogen stimulation than those without such symptoms ([49](#_ENREF_49)). Young men diagnosed with human immunodeficiency virus type 1 (HIV-1) infection showed decreased NK cell cytotoxicity and lymphocyte proliferative responses to mitogen following bereavement, although those with better active coping skills showed better immunity function ([50](#_ENREF_50)). Finally, there was no decrease in neutrophil phagocytosis and superoxide production in a group of healthy younger bereaved adults when compared to matched controls ([51](#_ENREF_51)). Similarly, this group of bereaved individuals had comparable stress hormone (cortisol and DHEAS) levels to those of the control group.

On the other hand, the bulk of the evidence indicates that bereavement in older individuals has a negative influence on immunity. For example, compared to non-bereaved control, older widows had a poorer NK cell function ([52](#_ENREF_52)), while both male and female older bereaved showed poorer neutrophil superoxide production ([53](#_ENREF_53)), when compared to a non-bereaved control group. The latter group of the bereaved also showed a higher cortisol:DHEAS ratio, suggesting the presence of an imbalance in immune-modulating hormones that has negative effects on an immune response overall ([51](#_ENREF_51)). Higher cortisol levels were observed in the bereaved six months after the death of a spouse occurred following prolonged expected bereavement, with levels of cortisol being higher in bereaved women than in bereaved men ([54](#_ENREF_54)). Another cortisol-related symptom with observed health implications is the flattened profile of its release throughout the day ([55](#_ENREF_55)). Reduced cortisol levels in the morning, decreased cortisol awakening response and a flatter diurnal profile have been observed with ageing and in young adults reporting poorer dietary habits ([56](#_ENREF_56)). This is even more pronounced in the bereaved suffering from Complicated Grief syndrome, where the inability to recover from a loss beyond six months after bereavement is related not only to the maladaptive thoughts, emotional dysfunction and social isolation, but also to a flatter cortisol profile during the day, even when compared to the bereaved individuals with a Non-Complicated Grief ([57](#_ENREF_57)). A similar negative effect on the HPA axis was observed after a spousal bereavement with reported lower morning cortisol levels and flatter daily cortisol rhythm In terms of the adaptive immune system, in the period following bereavement, older adults showed decreased lymphocyte response to phytohaemagglutinin (PHA) ([58](#_ENREF_58)), lower antibody responses to two different influenza strains in older adults (mean age 75 years) ([39](#_ENREF_39)), and down-regulated expression of those genes that are involved in the B cell immunity ([59](#_ENREF_59)).

Stress activates the HPA axis and subsequently induces the secretion of cortisol, a hormone with immune-modulatory effects ([60](#_ENREF_60)). Cortisol is a glucocorticoid and therefore mainly immunosuppressive, whereas DHEAS, also secreted by the adrenal gland, is considered to be immune-enhancing ([34](#_ENREF_34)). As with ageing, an imbalance between these two hormones, i.e., a high cortisol:DHEAS ratio can arise in response to stress ([61](#_ENREF_61), [62](#_ENREF_62)) and have negative implications for immunity. For example, our previous research in older adults showed a higher cortisol:DHEAS ratio in bereaved participants when compared to age- and sex-matched controls ([53](#_ENREF_53)). Indeed, with ageing generally, levels of DHEAS decline whereas cortisol continues to be produced ([35](#_ENREF_35)), thus resulting in a higher cortisol:DHEAS ratio. This could explain why psychosocial influences on immune function are more likely to emerge in older populations.

**6. Conclusion**

In summary, this review presents support of the notion that both the chronic stress of bereavement and ageing negatively affect wellbeing. This is illustrated by the association between bereavement and increased mortality and its link to poor physical and mental health. Further, since ageing *per se* has detrimental effect on many functions of the immune system, it seems likely that the particularly salient effect of bereavement in older adults is a consequence of the combined action of ageing and bereavement. Although the mechanisms are yet to be elucidated, it is possible that an imbalance in stress hormone levels, in particular the decrease in DHEAS that occurs with ageing, is at least partly responsible. As always, a better understanding of the processes by which bereavement affect health in older adults can provide a better insight into potential intervention approaches.

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