CHAPTER 2

Resilience and Immune Function in Older Adults

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ABSTRACT

Normal aging is marked by dysregulated immune function or immunosenescence. However, there is considerable variation in the degree to which adults are susceptible or resilient to immune dysregulation and disease. Stress is an important factor that can further alter the aging immune system. In this chapter, we review research that shows how stress can enhance age-related immune dysregulation in a variety of clinically relevant ways. We then explore what factors promote resilience to the negative immunological consequences of stress and aging. Finally, we take a lifespan perspective to examine evidence to suggest that some of the most important factors that augment or assuage an older adult's capacity for resilience to age and stress-related immune dysregulation develop long before he or she reaches older adulthood.

Humans are living longer than ever before. More than 12% of the U.S. population is older than the age of 65 years, and those who live at the age of 65 years can expect to live an additional two decades (Kung, Hoyert, Xu, & Murphy, 2008). Decreased infant mortality, better nutrition, and improved medical and environmental conditions are largely responsible for these dramatic increases. Accordingly, aging researchers have become increasingly interested in the notion of "successful aging." Although there are many definitions for what constitutes

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successful aging, they all include freedom from chronic illness and disease, and thus successful aging is clearly dependent on a healthy immune system.

Normal aging is marked by dysregulated immune function or immunosenescence. The average life expectancy for most of our evolutionary history was only 40–45 years (Aw, Silva, & Palmer, 2007). One of the biggest threats to reaching reproductive age was infectious disease. Consequently, strong immune responses early in life were essential for human survival (Aw et al., 2007). However, there was no evolutionary pressure to maintain strong immune responses after reproductive age. Accordingly, the immune system is susceptible to becoming increasingly dysregulated with age (Aw et al.).

As we age, cell-mediated immunity decreases (Vedhara & Irwin, 2005). Cell-mediated immunity protects the body against fungi, viruses that have invaded the cells, parasites, foreign tissues, and cancer (Vedhara & Irwin). Cellular immune decrements predict disease morbidity and mortality (Vedhara & Irwin). Aging is also characterized by elevated systemic inflammation (Vedhara & Irwin). Immune dysregulation is partly responsible for the higher prevalence of diseases such as cancer, heart disease, and infectious diseases found among older adults.

There is considerable variation in the degree to which adults are susceptible or resilient to immune dysregulation and disease. Resilience can be defined as the ability to maintain a stable equilibrium (Bonanno, 2004). Older adults who are resilient to premature immune dysregulation age more successfully than their counterparts. Understanding why some older individuals are more resilient to age-related immune dysregulation than others may help researchers identify the biological mechanisms that underlie healthy aging.

Stress is an important factor that can further alter the aging immune system. Psychological stress can diminish the strength of immune responses to vaccines, slow wound healing, reactivate latent viruses, enhance inflammation, and shorten telomeres (Glaser & Kiecolt-Glaser, 2005). Stress is particularly detrimental to older adults because they already have maladaptive age-related immune changes. Over the past three decades, there has been considerable work demonstrating that stress exacerbates age-related immune alterations.

In this chapter, we review research that shows how stress can enhance age-related immune dysregulation in a variety of clinically relevant ways. We then explore what factors promote resilience to the negative immunological consequences of stress and aging. Finally, we examine emerging evidence to suggest that some of the most important factors that augment or assuage older adults' capacity for resilience to age and stress-related immune dysregulation develop long before they reach older adulthood.

THE IMMUNE SYSTEM, STRESS, AND OLD AGE

Dementia family caregiving is an excellent model to study how a severe and chronic stressor alters older adults' immune function. Studies comparing older adult dementia family caregivers with age-matched noncaregiving controls have provided a wealth of information about (a) how stress exacerbates age-related declines in immunity and (b) what factors promote resilience to age-related immune decrements. Individuals with neurodegenerative diseases such as Alzheimer's disease and dementia often exhibit problem behaviors such as wandering, incontinence, and cognitive disturbance (Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991). Caregivers must provide around the clock care. In addition to this demand, they also experience a type of "living bereavement" as they watch their partners slowly lose their personality and intellect (Kiecolt-Glaser et al., 1991). Older adult caregivers have poorer antibody responses to vaccination, poorer control of latent herpes viruses, slower wound healing, and higher systemic inflammation than their noncaregiver peers (Glaser & Kiecolt-Glaser, 2005).

Vaccination Response

Among adults aged 65 years or older, influenza and pneumonia infections are the fourth leading cause of death (Mustanski & Thompson, 2006). The Centers for Disease Control and Prevention (CDC) recommends that individuals aged 50 years or older receive a protective pneumococcal pneumonia vaccination and yearly influenza vaccinations. In order for a vaccine to protect against disease and illness, one must mount and maintain an adequate antibody response to the vaccine. Aging impacts parts of the immune system that facilitate the antibody response following immunization. People must be able to induce a strong antibody and T-cell response in order for their vaccine to be effective (Kiecolt-Glaser et al., 2003). Older adults show impaired activation and proliferation of T cells (Vedhara & Irwin, 2005). Stress can further exacerbate these age-related decrements.

Caregivers have poorer influenza vaccine responses than noncaregivers. In one study, among those individuals who showed a clinically significant antibody response, caregivers had lower antibody titers than controls. Furthermore, age intensified the effect of chronic stress on the vaccine response (Kiecolt-Glaser et al., 2003). In individuals older than 70 years, only 26% of caregivers had an adequate response compared to 60% of controls. These immunological differences were not explained by depression, even though caregivers were more depressed than controls. Another study demonstrated similar results; 16% of caregivers in contrast to 39% of controls showed a clinically significant antibody response to the influenza vaccine (Vedhara et al., 1999). Furthermore, caregivers' daily salivary cortisol output was greater than controls. Cortisol can modulate cell-mediated immunity, and thus caregivers' higher salivary cortisol is consistent with their poorer vaccine responses.

Researchers have also examined links between caregiver status and vaccine responses to the pneumococcal pneumonia vaccine (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000). Pneumococcal pneumonia is caused by bacteria, and unlike the previously mentioned influenza vaccine, it is independent of T-cell activation. In a study comparing current and former caregivers to controls, all groups had similar pneumococcal pneumonia antibody titers before, and 2 and 4 weeks following vaccination (Glaser et al., 2000). However, at 3- and 6-month follow-up visits, current caregivers' overall vaccine-specific antibody titers were lower than those of former caregivers and controls. Accordingly, the stress associated with caregiving reduced the longer term protection of the pneumococcal pneumonia vaccine (Glaser et al., 2000).

In summary, caregivers respond more poorly to both viral and bacterial vaccines compared to age-matched controls. These findings suggest that the stress associated with caregiving diminishes the body's ability to mount an effective immune response to vaccines beyond age-related declines in immune function.

Control of Latent Viruses

Herpesviruses are able to evade destruction by the immune system and thus remain in a latent state after the primary infection. The cellular immune system, which controls these latent viruses, can be compromised with age. After people are infected with one of the herpesviruses, they carry the virus(es) with them for the rest of their lives. These viruses usually lay dormant and are asymptomatic. However, reactivation may occur when the cellular immune response is compromised or less competent, as is the case with older adults. With a less competent cellular immune response, herpesviruses can replicate more readily, as reflected by increased antibody production.

Control over latent viruses is maintained by T lymphocytes, or T cells, components of the cellular immune system (Vedhara & Irwin, 2005). Older individuals have poorer control over latent viruses than their younger counterparts because of age-related decrements in the cell-mediated immune response (Vedhara & Irwin). In response to reactivation of latent herpesviruses, the immune system produces antibodies. Higher antibody titer levels reflect greater reactivation of the virus. Older adults have higher levels of Epstein-Barr virus (EBV) IgG antibody than younger adults (Glaser et al., 1985). Additionally, higher concentrations of cytomegalovirus (CMV) mRNA, another member of the herpesvirus family, were detected more frequently in the urine of older adults, compared to younger adults (Stowe et al., 2007).

Latent herpesviruses have clinical relevance, and poorer control over these viruses can have clinical consequences. Latent herpesvirus reactivation is associated with increased morbidity and mortality among organ transplant

recipients and HIV patients. Herpesvirus reactivation may also lead to disease development. For instance, shingles, a consequence of varicella-zoster virus (VZV) reactivation, is more prevalent among older individuals. Shingles can be extremely painful for older adults (Glaser & Jones, 1994).

Stress can promote reactivation of latent herpesviruses. In one study, investigators examined dementia spousal caregivers and matched controls (average age is 67 years) over a 1-year period to understand how chronic stress affected EBV reactivation. Dementia caregivers had higher EBV antibody titers compared to matched controls (Kiecolt-Glaser et al., 1991). In addition, caregivers' peripheral blood lymphocytes proliferated less readily in response to mitogenic stimulation than controls (Kiecolt-Glaser et al., 1991). Accordingly, the stress associated with caregiving exacerbated age-related declines in cell-mediated immunity.

Another study addressed the relationship between caregiver status and herpes simplex virus (HSV)-1 (Glaser & Kiecolt-Glaser, 1997). Caregivers had higher HSV-1 antibody titers than controls. However, caregivers' and controls' antibody titers showed the same ability to neutralize the latent virus, suggesting that chronic stress decreases control over viral reactivation, but does not modulate the antibody function. Furthermore, caregivers had poorer in vitro memory T-cell proliferation to HSV-1 infected cells compared to controls (Glaser & Kiecolt-Glaser, 1997). These findings also suggest that chronic stress impairs older adults' ability to control reactivation of a latent herpesvirus over and above their natural age-related declines.

Inflammation

Inflammation is part of the body's initial and nonspecific response to invasion by foreign pathogens. The inflammatory response promotes the destruction and clearance of foreign particles and facilitates wound healing. Proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) are chemical signals that increase immune cell trafficking to infection sites. Acute local inflammation in response to infection or trauma is beneficial; however, chronic low-grade inflammation can be maladaptive. Among older adults, having higher levels of inflammation is a risk factor for morbidity and mortality among older adults. (Vedhara & Irwin, 2005).

Sickness behaviors, fatigue, and depressive symptoms, which impair older adults' quality of life, can be consequences of inflammation. Physically ill humans and animals exhibit sickness behaviors when they are exposed to an infection. Sickness behaviors are functional in that they help sick individuals to restructure their perceptions and actions in order to conserve energy and resources (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Although feeling tired and lethargic is a normal and adaptive response to an acute infection, persistent low-grade

inflammation has been linked to fatigue and depression (Dantzer et al., 2008). Depression and fatigue can be side effects of long-term low-grade inflammation; they represent a maladaptive version of inflammatory induced sickness behaviors (Dantzer et al.). Higher levels of inflammation have also been associated with frailty and disability in older adults (Ershler & Keller, 2000).

Elevated inflammation is associated with cardiovascular disease, type 2 diabetes, Alzheimer's disease, osteoporosis, rheumatoid arthritis, periodontal disease, and cancer (Ershler & Keller, 2000). Peripheral proinflammatory cytokines rise with age. Compared to younger adults, elderly adults have higher levels of proinflammatory cytokines and C-reactive protein (CRP; Ershler & Keller). Given the role inflammation plays in contributing to these diverse negative mental and physical health outcomes, it is important to understand the factors that contribute to elevated inflammation among older adults.

Stress-induced changes in the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis impact inflammation. Activation of the sympathetic branch of the ANS enhances inflammation. Stress heightens production of the catecholamines epinephrine and norepinephrine by the sympathetic nervous system. Norepinephrine induces nuclear factor-kappa B (NF-κB) transcription, which enhances proinflammatory cytokine production (Bierhaus et al., 2003).

Several mechanisms work to limit the inflammatory response to stress. The parasympathetic branch of the ANS works in opposition to the sympathetic branch. Stress reduces parasympathetic activity. Higher parasympathetic activity can lower inflammation by inhibiting proinflammatory cytokine production (Tracey, 2009). Therefore, the combination of lower parasympathetic activity and higher sympathetic activity results in elevated inflammation.

Cortisol is also produced in response to stress. Although cortisol acts to inhibit proinflammatory cytokine release in the short term, chronically elevated levels of cortisol can *sometimes* lead to glucocorticoid insensitivity. Glucocorticoid insensitivity allows immune cells to produce proinflammatory cytokines in an unregulated environment, thereby raising inflammation (Miller, Cohen, & Ritchey, 2002).

Considerable evidence suggests that the chronic stress of caregiving for an impaired family member can enhance inflammation. For example, older women who were dementia family caregivers had higher IL-6 levels than older women who were planning a housing relocation as well as nonmoving and noncaregiving controls (Lutgendorf et al., 1999). These findings were particularly provocative because the caregivers were approximately 6–9 years younger than the women in the other two groups (Lutgendorf et al., 1999). Another study showed that caregivers had higher levels of IL-6 than age-matched controls (von Känel et al., 2006).

Caregiving stress may also accelerate age-related increases in inflammation. Caregivers had a fourfold higher rate of increase in IL-6 across a span of 6 years

compared to noncaregivers (Kiecolt-Glaser et al., 2003). Importantly, epidemiological studies have found that individuals with IL-6 levels in the highest quartile (more than 3.19 pg/ml) had a twofold greater risk of mortality compared to those with lower levels of IL-6. Accordingly, these data suggest that caregivers would reach this risky IL-6 level, on average, by the age of 75, whereas noncaregivers would not do so until the age of 90 years.

Heightened inflammation can persist even after caregiving ends. Former caregivers continued to have a mean annual increase in IL-6 compared to current caregivers even several years after the death of the spouse (Kiecolt-Glaser et al., 2003). Accordingly, when older adults experience chronic stress over a long time, they may not be able to recover even when the stressor ends.

Wound Healing

Wound healing is an important response to trauma. Proper wound healing is critical for maintaining good health because it reestablishes the body's first line of defense against foreign pathogens. The inflammatory phase, which begins soon after trauma, is important for all other phases (Christian, Graham, Padgett, Glaser, & Kiecolt-Glaser, 2006). Proinflammatory cytokines prepare injured tissue for repair by enhancing phagocytic cell recruitment and activation (Lowry, 1993). In addition, proinflammatory cytokines regulate fibroblasts and epithelial cells in order to remodel damaged tissue (Lowry).

Wound healing occurs in phases. Healing begins with an inflammatory phase in which immune cells clear bacteria and debris from the wound site. In the proliferative phase, phagocytes migrate to the site and proliferate to facilitate regrowth of tissue and capillaries. The final step of wound remodeling restores tissue structure and function. Throughout this cascade, proinflammatory cytokines play a role in protecting against infection and enhancing phagocytic cell recruitment (Glaser et al., 1999). Successful healing at one stage depends on adequate completion of the preceding stage.

Older adults' wounds do not heal as fast as younger adults, putting them at increased risk for infection and associated health risks. Older adults suffer from greater rates of morbidity and mortality following surgery (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). Further, inadequate wound healing leads to poor surgical outcomes and stressful postoperative pain (Kiecolt-Glaser et al., 1998). Impaired wound healing may be one mechanism by which older adults' recovery is delayed (Kiecolt-Glaser et al., 1998).

Chronic stress further impairs wound healing among older adults. In one study, caregivers and noncaregiving controls were given a punch biopsy wound and subsequently monitored to compare differences in healing over time. Caregivers took an average of 9 days longer to heal than the noncaregivers,

regardless of age (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). Further, it appeared that the chronic stress of caregiving disrupted the early inflammatory phase of wound healing. The greatest differences in wound size between caregivers and noncaregivers occurred early in the healing process.

In another study, researchers used a suction blister procedure to examine how stress contributes to the initial phase of wound healing. Higher levels of perceived stress were associated with lower production of inflammatory cytokines IL-1 and IL-8 at a suction blister wound site in the first 24 hours of wound healing (Glaser et al., 1999). This first phase of wound healing is a critical period that may predict delays in the rest of the wound healing process. Accordingly, chronic stress interferes with older adults' ability to heal wounds in a timely manner, increasing the risk of infection. Given the immune dysregulation that occurs with age, delays in wound healing may increase the risk of negative health consequences by enhancing infection risk.

These findings may have important implications for older adults who undergo surgery. Older adults are at heightened risk for surgical complications compared to younger adults, partially caused by infections (Kiecolt-Glaser et al., 1998). Furthermore, stress enhances surgery-associated risks among older adults. When researchers classified younger and older surgical patients based on preoperative anxiety, high anxious older adults experienced more disability days and complications than their younger and less anxious counterparts (Linn & Jensen, 1983).

Telomeres

Stress may also facilitate cell aging by reducing telomere length. A telomere is a group of nucleoprotein complexes that caps chromosomes to protect and stabilize their integrity across the lifespan (Epel et al., 2004). Each time a cell replicates, telomeres shorten. Telomere length is a proxy for a cell's biological age; cells with shorter telomeres reach the critical minimum length more rapidly and subsequently die more quickly than cells with longer telomeres (Epel et al.). Shorter telomeres have also been linked to mortality (Epel et al.). In addition, stress-related changes in inflammation can impact telomere length (Kiecolt-Glaser et al., 2011).

Chronic stress shortens telomere length. In a landmark study, Epel and colleagues (2004) examined the relationship between perceived stress and telomere length in mothers who provided care for a chronically sick child and mothers who raised a healthy child (Epel et al., 2004). Longer duration of caregiving predicted shorter telomere length and other markers of cellular aging, independent of chronological age. Greater perceived stress also predicted greater cellular aging for both caregivers and controls. In fact, those who reported high stress had shorter telomeres, representing 9–17 years of additional cellular aging compared

to the low stress group (Epel et al.). Consequently, the chronicity and perceived magnitude of a stressor are important factors in determining its influence on cellular aging. Stress may actively age the immune system by contributing to age-related reductions in telomere length. This could have major implications for disease and mortality among older adults.

RESILIENCY

We reviewed a large body of evidence suggesting that aging is related to increased immune dysregulation, and stress exacerbates this process. However, not everyone experiences age-related immune decrements at the same rate. Understanding what factors promote and hinder resilience in the face of stress and age-related immune system declines may help older adults age more successfully.

The field of psychoneuroimmunology has focused most of its attention on how psychological factors (i.e., stress and depression) impair immune function. There is a good reason for this; the primary pathways through which the psyche directly influences immune function are negative. Stress-related increases in autonomic and HPA activity alter immune function. However, psychological factors can buffer the negative impact of stress. Likewise, practicing good health behaviors can boost better immune function and possibly buffer stress-related immune alterations (Figure 2.1).

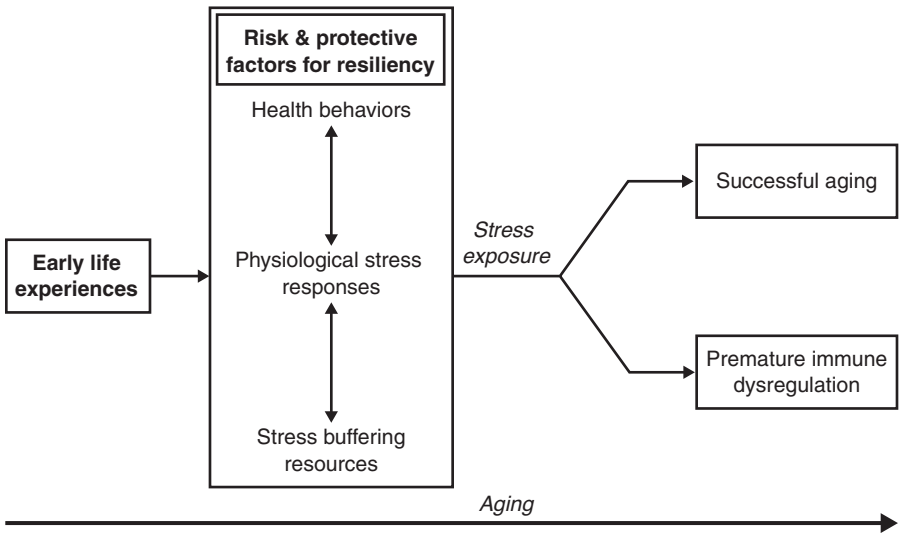

FIGURE 2.1 Developmental pathways to resilience in older adulthood.

Social Support

Considerable evidence suggests that those who report receiving more support from others enjoy better mental and physical health (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Older adults who have healthy relationships with family and friends have lower rates of morbidity and mortality than those who do not (Uchino et al., 1996). Importantly, social support may be one possible mechanism for these findings as it can buffer the negative physical and mental effects of stress.

Older adults face unique hurdles in their ability to maintain social relationships. People often lose parts of their social network when they retire. Furthermore, frail older adults are less mobile and thus less able to engage in certain social activities (Charles & Carstensen, 2010). Mortality increases with age, and thus older adults are more likely to lose key social support figures such as friends, siblings, and their spouse than younger adults (Charles & Carstensen). However, older adults are also more likely to strengthen and optimize the social ties they do have (Charles & Carstensen). On average, older adults report greater satisfaction with their relationships than younger adults (Charles & Carstensen).

Although social support is important in and of itself, it can also buffer the negative immunological consequences of caregiving. In one study, caregivers who perceived more support and closeness had better augmentation of natural killer (NK) cell activity to interferon-gamma and recombinant IL-2 (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). NK cells are an important function of the innate immune system that kill viruses and plays a role in tumor rejection. Data from a longitudinal study suggested that older caregivers who had lower social support were more likely to show more immunological declines across several different measures of cellular immunity 1 year later (Kiecolt-Glaser et al., 1991).

Social support can also influence inflammation. Among women with advanced stage ovarian cancer, those who reported higher levels of social support had lower plasma levels of IL-6 (Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000). The relationship between social support and inflammation may be exacerbated by health behaviors such as sleep. Women who reported poorer sleep and poorer social relationships had higher levels of IL-6 than those who only had one of these risk factors (Friedman et al., 2005). Thus, social networks and perception of support have been associated with a number of different aspects of immune function in older adults.

Exercise

Physical activity can lower inflammation. In a randomized trial, older adults (aged 60–83 years) who participated in a cardiovascular exercise program for 10 months had lower CRP and less total and central trunk adiposity than those who participated in noncardiovascular flexibility training (Vieira et al., 2009).

Furthermore, reduced trunk fat was associated with reduced CRP (Vieira et al.). Other studies have also found an association between physical activity level and lower levels of IL-6 and CRP (Ford, 2002).

Exercise may also reduce the physiological consequences of stress. Some evidence suggests that individuals who are physically fit may have a smaller inflammatory response to acute mental stress than those who are not (Hamer & Steptoe, 2007). Thus, exercise helps to maintain immunological homeostasis. Exercise is also associated with increased IL-10, an anti-inflammatory cytokine (Jankord & Jemiolo, 2004).

Sleep

Sleep is essential for a healthy immune system. In a longitudinal study of older adults, better sleep quality was associated with lower levels of IL-6, and shorter sleep latency was linked to decreased CRP. Those with sleep problems had higher inflammation than those who do not. In fact, as few as 4 hours of sleep loss resulted in greater NF-κB activation (a pathway that prompts inflammatory cytokine release) and higher morning levels of IL-6 and TNF-α, compared to a night of uninterrupted sleep (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006).

Nutrition and Weight

Large-scale epidemiological studies demonstrate a strong relationship between diet and inflammation. Diets high in refined grains, processed meat, sugar, and saturated and trans-fatty acids and low in fruits, vegetables, and whole grains promote inflammation (Kiecolt-Glaser, 2010). High-fat meals can increase glucose levels and triglycerides, which stimulate the production of IL-6 and CRP (Kiecolt-Glaser). In contrast, higher fruit and vegetable intake is associated with lower inflammation, which may counteract the proinflammatory responses to high-saturated fat meals (Kiecolt-Glaser).

Abdominal fat is a prime source for inflammation. Accordingly, those who are overweight, especially in the abdominal region, have higher inflammation and more disease (Després & Lemieux, 2006). Because both diet and stress impact the immune system, the interaction between these two factors is likely to be a provocative area of research in the future.

Behavioral Interventions

Interventions may buffer stress-induced immune dysregulation. Spousal dementia caregivers who participated in a nonrandomized stress management intervention were more likely to have a fourfold antibody increase 6 weeks postvaccination, compared to control caregivers who did not receive the intervention (Vedhara et al.,

2003). Furthermore, caregivers in the intervention group did not differ from noncaregiving controls in terms of their antibody response to the influenza vaccine (Vedhara et al., 2003). Although these results suggest that behavioral interventions may lessen stress-induced vaccine impairments, they must be interpreted cautiously because participants were not randomly assigned to conditions.

Stress-reducing interventions may also enhance latent antibody virus control and NK cell activity. In a randomized controlled trial, researchers examined whether older adults who received training in progressive relaxation or had social contact with a college student had changes in HSV-1 antibody titers compared to older adult controls. Older adults who were assigned to the relaxation condition had lower HSV-1 antibody titers following the intervention, whereas those who were assigned to the college social contact group and the control group had no changes in antibody titers (Kiecolt-Glaser et al., 1985). Individuals in the relaxation condition also exhibited higher NK cell activity up to 1 month after the end of the intervention. Taken together, these two studies suggest that psychological interventions may have positive effects on the immune response in older adults.

Relaxation exercises may buffer against immune dysregulation. *Tai Chi* is an exercise that incorporates light aerobic activity, relaxation, and meditation. In a study that randomly assigned older adults to either a 25-week Tai Chi intervention or a health education course, those who were assigned to the Tai Chi intervention had greater cell-mediated immunity to VZV than those assigned to the health education intervention (Irwin, Olmstead, & Oxman, 2007). Cell-mediated immunity to VZV was assessed by measuring the frequency of peripheral blood mononuclear cells (PBMCs) and CD4+CD45RO+T cells or memory T cells that proliferate in response to VZV antigen. Compared to preintervention levels, the Tai Chi group also reported improved physical functioning, decreased pain, increased vitality, and improved mental health after the intervention.

Similar to Tai Chi, yoga is an accessible form of exercise that confers immunological benefits. In a randomized study of chronic heart failure patients, those who participated in an 8-week yoga class, in addition to receiving standard medical treatment for heart failure, had reduced IL-6 and CRP from pretreatment to postreatment. However, IL-6 and CRP levels did not change among those who only received standard medical care for heart failure (Pullen et al., 2008). Yoga is also effective in healthy populations and may bestow advantages with experience. One study compared markers of inflammation in novice and expert yoga practitioners. Serum IL-6 was 41% lower in expert yoga practitioners, compared to novice practitioners (Kiecolt-Glaser et al., 2010). In addition, the novice group was 4.75 times as likely to have detectable CRP levels

compared to the expert group (Kiecolt-Glaser et al., 2010). Different inflammatory responses to stress may account for disparities between novice and expert yoga practitioners. Indeed, following an acute stressor, stimulated IL-6 production in the expert group was lower compared to the novice group, suggesting that extended yoga practice may buffer stress-induced proinflammatory cytokine elevations (Kiecolt-Glaser et al., 2010).

EARLY ADVERSITY

Although several factors offer protection against the effects of stress and immune dysregulation in older adults, the skills and behaviors that lead to resilience develop long before one reaches old age. In particular, early developmental experiences can "set the stage" for either vulnerability or resilience in later life. Early adversity is a risk factor for poorer health among older adults (Hertzman, 1999). Dysregulated immune function may be one biological pathway that explains these links.

Early life adversities can leave individuals more vulnerable to dysregulated immune function in older adulthood (Hertzman, 1999). For example, in a study of healthy older adult family dementia caregivers and noncaregivers, average age of 70 years, those who experienced emotional, physical, or sexual abuse as children were more likely to have higher IL-6 and TNF-α levels (Kiecolt-Glaser et al., 2011). These findings may help explain some of the well-known associations between child adversity and poor physical health in old age.

Early adversity has also been linked to cellular aging. Recall that telomere length is a proxy for cellular aging. Healthy older caregivers (average age of 70 years) who were abused as children had shorter telomeres than those who were not abused. Importantly, the difference between abused and nonabused older adults translated into a 7- to 15-year lifespan difference. These associations were detectable even among distressed dementia caregivers (Kiecolt-Glaser et al., 2011).

Researchers have yet to establish *why* early adverse experiences have such profound effects. Identifying the pathways through which troubled early life experiences are linked to poor immune function in older adulthood may be crucial to understanding the developmental antecedents of resilience for age-related immune dysregulation. Those with adverse early experiences may be particularly vulnerable because they have multiple risk factors that enhance immune dysregulation.

Early adversity makes people more physiologically reactive to stress (Repetti, Taylor, & Seeman, 2002). Those who experienced early life adversities have more pronounced stress-induced HPA and sympathetic responses than those who had happy childhoods (Hertzman, 1999; Repetti et al., 2002). A physiological profile

characterized by elevated stress-induced sympathetic and HPA activity can lead to dysregulated immune function (Bierhaus et al., 2003; Miller et al., 2002).

Adverse early life experiences also influence the degree to which one perceives events as stressful (Hertzman, 1999; Repetti et al., 2002). Adults who experienced adverse childhood experiences report more frequent daily hassles throughout their life than those who did not have these experiences (Luecken, Kraft, Appelhans, & Enders, 2009). They are also more likely to perceive events in ambiguous situations as more stressful than their counterparts (Luecken et al., 2009). Accordingly, adults who had troubled childhoods experience more severe and frequent stress than those who had happy childhoods.

Those who experienced early adverse events also cope with stress less effectively than others. Early adversity is linked to poorer emotional control and worse social skills (Hertzman, 1999). Accordingly, compared to their counterparts, those with troubled childhoods have less emotional and social resources available to manage stress. Not surprisingly, these individuals are more likely to smoke, abuse alcohol, and eat unhealthy than people who had happy childhoods (Repetti et al., 2002). These factors also contribute to dysregulated immunity later in life.

Caution is warranted when drawing conclusions about relationships between early adversity and resilience because the majority of studies linking adverse early experiences to physical health have used retrospective designs. Accordingly, we cannot say with certainty that early adversity *leads* to less resilience. Although challenging, future work using prospective designs are needed in order to strengthen causal inference.

In summary, compared to adults who had happy upbringings, those who had troubled childhoods experience more stress throughout their lives and cope with it less effectively; accordingly, resilient outcomes are much more difficult to obtain for these individuals. Chronic stress throughout life may prematurely age the immune system, making these individuals particularly vulnerable to immune dysregulation later in life. The "wear and tear" hypothesis suggests that stress has a cumulative effect on the aging process (McEwen, 1998). Although the body can recover from transient stressors, chronic stressors progressively impair the body's ability to maintain normal function over time. Chronic overactivation of the ANS and HPA axis increases allostatic load that is the long-term "cost" associated with frequent and prolonged adaptation to stress (McEwen). People who experience more frequent and prolonged stress throughout life more quickly accumulate allostatic load and have poorer health later in life (Hertzman, 1999). Accordingly, the "wear and tear" hypothesis suggests that resilience to immune dysregulation and disease in old age begins at a very young age. Early adversity puts people at risk for a combination of risk factors that impede resilience to immune dysregulation.

The majority of stress interventions have focused on older adults. This is for good reason because older adults are more at risk for the negative immunological consequences of stress. However, interventions aimed at reducing stress among younger individuals may be particularly beneficial as well. If the long-term consequences of stress are largely cumulative, and one's capacity to manage stress develops in early childhood, then one way to enhance resilience later in life may be to promote resilience early in life. Accordingly, a promising direction for future research is to design and evaluate stress interventions for younger individuals.

CONCLUSION

Immune dysregulation occurs naturally with age and can be exacerbated by stress. In particular, caregiving stress has been associated with impaired immune function including decreased antibody response to vaccination, poor control over latent viruses, delayed wound healing, and elevated inflammation. Additionally, chronic stress may actively age the immune system. Despite these challenges, individuals can promote resilience by practicing good health behaviors, learning to manage stress, and fostering healthy relationships. These practices are best developed well before one reaches old age because the negative consequences of stress may be cumulative. Accordingly, dysregulated immunity in old age can represent a lifetime of psychological and psychophysiological alterations. To understand and promote resilience in old age, aging research must take a lifespan approach to understand and promote a healthy immune system at all ages.

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