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**Stress and Exercise: getting the balance right for aging immunity**

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#### **ABSTRACT**

Age-related immunological and endocrinological changes may have implications for resilience to stress in older adults. We hypothesise that the combination of adrenopause and immunesenescence may leave this population particularly vulnerable to the negative effects of stress on immunity. We propose that exercise may be an effective intervention to limit the impact of stress on immunity in chronically stressed older populations.

#### **Summary for Table of Contents Page**

Exercise may be an effective intervention to limit the impact of stress on immunity in chronically stressed older populations.

#### **Key words**

aging, cortisol, DHEA, exercise, immune, stress.

## INTRODUCTION

Average life expectancy in the developed world is increasing at a rate of 2 years per decade and, if this continues, then by the year 2020 one in five of the population will be aged 65 years and over. Despite the increase in average lifespan, the period of illness experienced at the end of life has not reduced significantly in the last 50 years (1). Susceptibility to infectious disease increases with age (Table 1), and infection related mortality accounts for almost 1 in 7 deaths amongst those aged over 85 years (9). These data reflect a decline in the efficiency of the immune response with age, a well documented process termed immunosenescence. In addition, there are age-related alterations to the Hypothalamic-Pituitary-Adrenal (HPA) axis, a key effector of the response to stress. The reduced ability to produce the immune enhancing hormone dehydroepiandrosterone (DHEA) results in an over-representation of immunosuppressive glucocorticoids in the circulation, and may contribute to immunosenescence (3,6).

We would argue that these changes to both the immune system and the HPA axis result in increased vulnerability to stress in older adults, and factors that can modify the impact of the stress response upon immunity should be sought. One potential intervention is exercise. There is evidence that physically active older adults have fewer infections than their sedentary counterparts (17). Further, participation in regular activity may also be an effective treatment for psychological conditions such as depression in this population (2). Consequently, the role of exercise in ameliorating the deleterious effects of stress on the immune system in older adults will be discussed.

## **IMMUNITY AND STRESS HORMONES IN AGING**

The immune system can be considered as two distinct, but interconnected elements; the innate and the adaptive immune systems. The innate response is often referred to as the 'first line of defence' against infection as it comprises mechanisms that are the first to react to an infection. The adaptive immune system is slower to respond but has the advantage that it includes memory of each pathogen encountered and that its response is specific for each pathogen, thus conferring a tailored and long lasting protection against further infection by the same pathogen. Aging is known to have deleterious effects upon both the innate and adaptive immune responses, though the latter is much better characterised.

### **The innate immune response**

The innate immune system consists of soluble components, namely the complement system, and cellular elements, including neutrophils which deal with rapidly dividing bacteria, eosinophils which respond to parasitic infections and macrophages which secrete soluble factors (TNF $\alpha$ , IL-1, IL-6) to co-ordinate and amplify the immune response and also provide immunity to intracellular bacteria.

With aging, innate immune responses decline, though not universally. For example, complement activation appears to be unaffected, but neutrophil bactericidal and phagocytic function is dramatically reduced. The latter is explained, in part, by a reduction in the number of cell surface receptors (CD16) that bind to the antibody coating bacterial pathogens (4). Macrophage function is also modified, although the literature is rather contradictory, including reports of reduced phagocytosis and

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superoxide function as seen in neutrophils, but enhanced secretion of IL-6 and IL-8 in response to mitogens and LPS. Natural killer (NK) cells are also affected by aging; while their numbers do not change with age, their cytotoxic capacity is reduced. That these changes affect immunity can be established by longitudinal studies. For example, in a recent study by Ogata and colleagues (19), NK cell cytotoxic capacity was measured in 188 people aged over 65 and mortality recorded over a 5 year period. Low NK cell function was associated with reduced survival in people over 75 years of age, suggesting that age related changes to NK cell function do affect mortality.

### **The adaptive immune response**

Adaptive immunity is provided by T and B lymphocytes, which develop and mature in the thymus and bone marrow respectively. T cells can be further classified into CD4 expressing helper cells (which in turn can be split into Th1 and Th2 types), CD8 expressing cytotoxic cells and CD25 expressing T regulatory cells, which have immune suppressive function. When a naïve T cell encounters antigen (presented by specialised cells such as dendritic cells), it will proliferate and differentiate into an effector cell or a memory cell, so that if the pathogen is encountered a second time a more rapid response can be achieved.

With aging, the thymus atrophies and fewer naïve T cells are produced. As the size of the T cell pool is maintained at a constant level, the proportion of T cells that are memory cells increases. Consequently, as we age, we are less able to deal with new pathogens as our immune systems have been fashioned to deal with the threats that we encounter on a regular basis throughout life. In addition to changes in the ratio of naïve to memory T cells, there is a decrease in the number and proliferative

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capacity of Th1 cells and an increase in memory Th2 cells; the latter have enhanced production of IL-10 which further suppresses the function of the Th1 cells. The end result is reduced cell-mediated, Th1-type, immunity. Finally, B cells produce antibody to provide extended protection against infections. With aging, antibody production in response to antigen declines; for example, older people produce a lower antibody titre in response to vaccination than younger individuals and the antibodies produced are of lower affinity. This is thought to be largely the result of a decline in T cell help for B cells, and a reduced vaccination response has been shown to correlate with a low clonal expansion of CD4 T helper cells in older adults.

### **Stress hormones**

Stress, whether physical or psychological, is broadly sensed by two systems within the hypothalamus, the HPA axis and the sympathetic-adrenal-medullary system. Stress induces the release of catecholamines from the adrenal medulla, and both cortisol and DHEA from the adrenal cortex. Catecholamines and cortisol can both be immunosuppressive if chronically elevated. In contrast, DHEA is a precursor to sex hormones and is immune enhancing. Our own *in vitro* studies have shown that cortisol suppresses neutrophil function and this can be overcome by co-incubation with DHEA sulphate (5).

As adrenocortical hormones are generated in response to stress and modulate immune function in an opposite manner (Table 2), any differential change in their production could therefore affect immunity. In humans, the production of DHEA and its sulphated form, DHEAS, declines with age, a process termed the adrenopause (Figure 1). The synthesis of DHEA is maximal in humans at age 20-30 and declines

gradually thereafter, so that by the seventh decade levels of DHEA can be as low as 10% of that seen in young adulthood (20). Adrenopause occurs at similar rates in both males and females and is a physiological phenomenon unique to the higher primates. However, although DHEA/S levels fall with age the production of glucocorticoids such as cortisol is remarkably unaltered (20), resulting in a relative excess of cortisol over DHEA/S and an imbalance of immune suppression over immune enhancement.

DHEA is a C19 steroid synthesised from cholesterol in the zona reticularis of the adrenal cortex, a process which requires two enzymes – P450<sub>scc</sub> and P450<sub>c17</sub>. A significant proportion of DHEA is converted to DHEAS by the hydroxysteroid sulphotransferase SULT2A1 and DHEAS is the major form of this steroid in serum (Figure 2). As levels of both DHEA and DHEAS fall with age, but cortisol levels do not, a loss of P450<sub>c17</sub> function with age has been proposed, though levels of SULT2A1 activity may also decline. The reason for this loss is not well established, though numbers of zona reticularis cells containing P450<sub>c17</sub> are reduced with age.

## **VULNERABILITY TO STRESS OF THE SENESCENT IMMUNE SYSTEM**

The age-related immunological and endocrinological changes outlined above may have implications for resilience to stress in older adults. We hypothesise that the combination of adrenopause, leading to a relative preponderance of cortisol, and an already reduced immune defence against infection, may leave this population particularly vulnerable to the negative effects of stress on immunity.

Psychosocial stress has been associated with immune system changes in older populations (10). For example, relative to age-matched controls, older adults exposed to the chronic stress of being the primary caregiver for a partner with dementia have



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shown a variety of immunological decrements. These include changes in immune cell counts, such as a decreased percentage of T-lymphocytes and helper T-lymphocytes; higher antibody titres to the Epstein-Barr virus, indicating poorer latent virus control; and poorer *in vitro* NK cell cytotoxicity, indicating a weakened ability to kill virus-infected cells.

More recently, *in vivo* assessments of immune function, such as healing rates of experimentally administered wounds and antibody response to vaccination, have been used to provide more clinically relevant outcome measures in psychosocial research. These studies have supported the previous work suggesting that stress is associated with reduced immune functioning in this population. For example, older adults have shown delayed wound healing in the mouth in comparison to younger adults. Further, experimentally induced punch biopsy wounds took significantly longer to heal in chronically stressed elderly caregivers than in matched controls, and immune cells from the caregivers produced significantly less of the cytokine IL-1 $\beta$  in response to stimulation *in vitro* than the cells of women who were not caregivers (13).

Elderly spousal care-givers also exhibit lower antibody titres following both influenza and pneumococcal vaccinations than matched control participants. These findings were not attributable to the physical strain of care-giving, as former caregivers also exhibited poorer antibody titres relative to non-carer controls. More recently, the stress of care-giving has been studied in the context of stress management interventions where, following an eight week intervention, more elderly caregivers mounted a four-fold increase in antibody titre to the influenza vaccine than non-intervention care-givers, although their response was still poorer than non caregiver controls (23). Although the mechanisms of the immune enhancement

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observed for caregivers are, as yet, not fully understood, these data support the clinical utility of attempts to identify interventions to reduce stress in the elderly.

Fewer studies have concentrated on the more mundane stress experienced by older populations, as opposed to the specific chronic stress of care-giving. Further, the studies that are published in this area failed to examine the increase in antibody titre from baseline, making it difficult to determine the influence of stress on the actual vaccination response. Our recent research in the UK focussed on a sample of community-based older adults who were attending their General Practice for the National Health Service annual influenza vaccination. Data showed that individuals who reported bereavement in the year prior to the vaccination mounted a poorer antibody response to two of the vaccine strains (21).

Physical bodily trauma, such as hip fracture, can also be considered as a chronic stressor, and is associated with decrements in immune function. For example, the experience of hip fracture in previously healthy adults aged over 65 years was associated with diminished neutrophil function (generation of superoxide) and a significant incidence (43%) of bacterial infection (5). Interestingly, this effect of trauma on neutrophil function and infection rates was not observed in a younger fracture group, suggesting that this immune impact of stress is worsened by the presence of immunosenescence. Such relative resilience of the younger immune system has been observed in non-elderly caregivers of multiple sclerosis patients who, unlike earlier observations in older adults, did not demonstrate reduced antibody responses to vaccination compared to controls (24).

Although this interaction model has not, to our knowledge, been directly tested in humans, the literature reveals a general consensus that such an investigation is

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likely to prove fruitful. For example, a meta-analysis revealed that older individuals are more likely to demonstrate negative immune responses to acute naturalistic stressors than younger individuals (22). Further, a recent review concludes that stress may act to exacerbate the effects of aging (10). A number of mechanistic possibilities underlying the increased immunological vulnerability to stress of older adults have been proposed in another review (11). These include evidence that older adults experience more serious and prolonged stressful exposures, have greater stress reactivity, and demonstrate poorer resilience to stress through factors such as reduced social support and poorer sleep patterns. Our hypothesis adds a further layer of complexity to this area of research by suggesting that the increased vulnerability to stress of older adults may be due, at least in part, to the observed age-related imbalance between cortisol and DHEA/S levels.

## **EXERCISE AS AN INTERVENTION TO REDUCE THE IMPACT OF STRESS ON IMMUNITY**

Whilst prolonged exhaustive exercise is associated with increased secretion of stress hormones and impaired immune responses, prolonged moderate exercise has direct and positive psychosocial and immunomodulatory effects (2,14). In support of our interactive model, there is evidence from animal research that regular moderate activity can buffer the negative impact of stress on immune responses. For example, antibody production has been shown to be reduced by stress in sedentary animals, but to a much lesser extent in animals that had regular exercise on a running wheel (8). However, the role of exercise in ameliorating the impact of stress on immunity in humans has received less attention. Two of the few studies to address this issue were

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conducted by Marion Kohut and colleagues, and examined the influence of exercise interventions on immunological and psychosocial parameters in older adults. The first study demonstrated that participation in a ten month aerobic fitness intervention was associated with better antibody and interferon gamma responses to influenza vaccination compared to control group. Importantly, there were also improvements in depression levels among the exercise group, and these partially mediated the interferon gamma, although not the antibody, benefits observed following intervention (15). A follow-up study, in which participants were randomly assigned to either an aerobic exercise treatment or a flexibility/strength exercise treatment, also demonstrated immunological improvements among the aerobic, but not the flexibility/strength exercise group. These included reduced serum CRP, IL-6, and IL-18. In contrast to the previous study, however, both groups experienced psychosocial benefits, including reduced depressive symptoms, which suggest that the effects of the aerobic exercise were not directly mediated by improvements in psychosocial scores (16). It is important to note, however, that these complex studies are relatively small in their sample size and, as such, may not have sufficient power to detect mediation. Further, we hypothesise that psychosocial mediation is more likely to be observed if an exercise intervention was administered to an elderly population identified as being exposed to a particular chronic stressor, such as caregiving, or with a specific psychological condition like depression.

More recently, a study of wound healing rates in healthy older adults has shown the benefit of a 3 month exercise program (7). This study of twenty eight volunteers showed accelerated wound healing after punch-biopsy in the exercise intervention group. Interestingly, the exercise group had a raised cortisol response during stress

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testing, but this did not prevent good wound healing. The study did not measure the DHEA/S response to exercise and, although it is well documented that DHEA/S levels increase in response to exercise and training in young adults, the literature regarding the effects of exercise on serum DHEA/S levels in older individuals (> 65 years) is lacking. However, studies of postmenopausal women did report increased DHEA and cortisol after exercise (12) and serum DHEA/S levels were positively associated with physical performance in elderly men (18). Exercise may therefore allow older adults to overcome the consequences of a heightened neuroendocrine response to stress and represent a positive intervention to improve immunity in older age, though more research into the effects of exercise on the HPA axis in the elderly is clearly required.

#### **CONCLUSIONS: STRESS MODULATION IN THE ELDERLY**

The immune response is negatively modified by both aging and chronic stress (Figure 3). The effects extend to both the innate and adaptive immune systems and have clinical significance in that they combine to result in reduced vaccination responses and an increased incidence and severity of infections and mortality in older adults. An altered stress reaction in the elderly, as a result of adrenopause, may be a significant component of immune suppression at times of chronic stress in the older adult. Several interventions have been proposed to improve immunity in older adults and we hypothesise that regular, moderate aerobic exercise may have real benefits for immunity in the elderly experiencing chronic emotional stress. At times of physical stress, such as after a hip-fracture or surgery, short term pharmacological intervention with DHEA to counteract elevated stress hormones is likely to be more appropriate.

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We conclude that maintaining a healthy balance of stress hormones in the elderly is essential to optimising immunity.

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Table 1.

<b>Disease</b>	<b>Incidence in elderly (&gt;65 years) versus non-elderly subjects</b>
Gram negative sepsis	50% increase in mortality
Bacterial dysentery	3-fold increase in incidence
Pneumonia	120-fold increase in incidence
GI-infections	400-fold increase in incidence
Influenza	160-fold increase in incidence

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Table 2

**Cortisol**

Decreased production of pro-inflammatory molecules (IL-1, TNF, GM-CSF, IL-2, IL-3, IL-4, IL-5, IL-8, prostaglandins, leukotrienes)

Reduced extravasation of inflammatory cells and inhibition of neutrophil function

Induction of apoptosis in lymphocytes and eosinophils

**DHEA/S**

Increased cytokine production (IL-2, IL-3, IFN-gamma)

Increased T cell function (CD8, DTH) and NK cell cytotoxicity

Decreased apoptosis of PBMC and enhanced neutrophil function



Figure 1

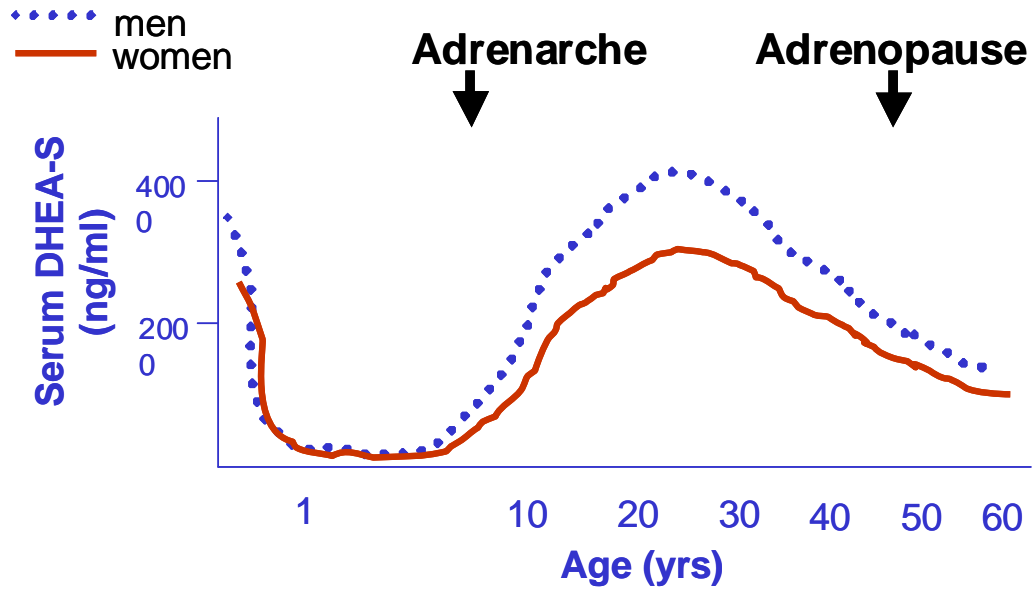


Figure 2

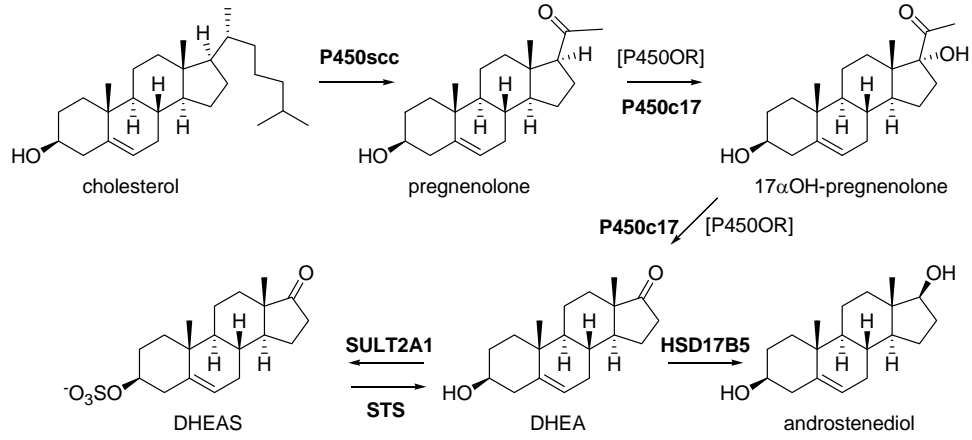
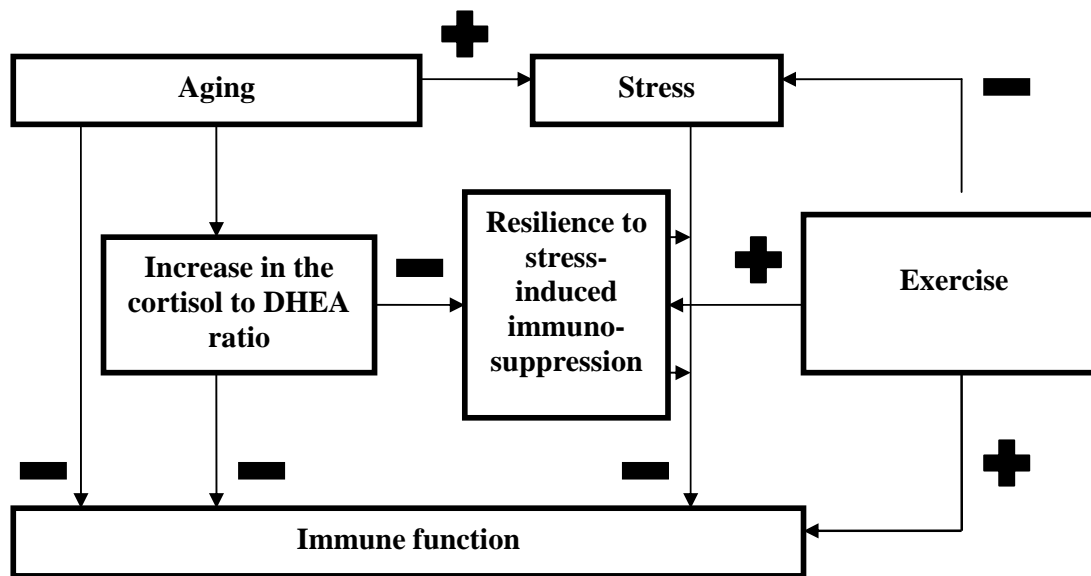


Figure 3



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#### Figure Legends

Table 1. Age related increases in infection incidence and infection-related mortality

Table 2: Effects of glucocorticoids (cortisol) and DHEA/S in immune responses

Figure 1: Changes to DHEAS levels with age

Figure 2: Synthesis of DHEA and downstream metabolites

Figure 3: The combined effects of Aging and Stress of the neuroendocrineimmune axis.

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