There is limited existing evidence to support the common assumption that strenuous endurance exercise bouts impair immune competency

John P. Campbell*† and James E. Turner*‡

*Joint corresponding authors

Department for Health, University of Bath, Bath, United Kingdom.

†Email: j.campbell@bath.ac.uk Telephone 01225 38 5495

‡Email: j.e.turner@bath.ac.uk Telephone 01225 38 3566

Key words: Exercise, Physical activity, Endurance sports, Over-training, Upper respiratory tract infections, Open window hypothesis, Infection susceptibility, Immune competency, Immuno-suppression, Immuno-depression

Introduction

Research from the 1980s and 1990s led to three principles of exercise immunology being formed which imply that an acute bout of moderate-to-vigorous intensity endurance exercise can induce a short-term period of immuno-suppression. This prevailing dogma has been challenged recently [1]. Following acute bouts of exercise, particularly endurance activities, such as running for several hours, it has generally been accepted that; (i) infection risk is increased; (ii) salivary IgA temporarily declines; and (iii) transient decreases in the number and function of immune cells in blood represents immuno-suppression. These observations led to the 'open-window hypothesis' which purports that the immune system can be transiently compromised after some forms of acute exercise. In this editorial, we briefly summarise key messages from a recent narrative review that challenges these conclusions [1]. Our focus herein is on the immunological effects of moderate-to-vigorous intensity endurance exercise bouts. Other forms of exercise, such as strengthening or resistance exercise, are beyond the scope of this editorial. Overall, we state that there is limited robust evidence to support an immuno-

suppressive effect of any exercise form. We highlight that further research is required to fully understand the immunological effects of endurance exercise training that is particularly prolonged (i.e. at least several hours) regular (i.e. once or twice a day) demanding (i.e. moderate-to-vigorous intensity) and chronic (i.e. performed over weeks or months). In summary, the belief that forms of exercise can be immuno-suppressive is counterproductive for encouraging exercise as a preventative and therapeutic strategy for chronic disease. Indeed, we advocate research that examines the *benefits* of exercise for immune competency, and briefly highlight areas that could be prioritised.

Exercise and infections

Well known studies from the 1980s and 1990s reported that infectious episodes are increased after taking part in mass participation endurance sport events. For example, one third of participants in the 1982 Two Oceans 56 km ultra-marathon in Cape Town South Africa, self-reported symptoms of upper respiratory tract infections within two weeks of the race [2]. The age-matched control group, who shared a home with another of the race competitors, reported half the symptoms in the same period [2]. It should be considered however, that attending any mass participation event – whether exercising or not – is likely to increase the risk of encountering pathogens due to crowds of people. For example, a study has shown that around one third of people attending a mass-participation religious gathering reported infections, and symptom reporting was most common among individuals with the greatest exposure to crowds [3]. Similarly, it is often claimed that athlete populations exhibit a high frequency of illness symptoms. However, evidence shows that athletes exhibit a similar number of illness episodes as the general population annually, but their symptoms often cluster around winter months, sometimes during concentrated periods of training or when attending competition events [1].

A limitation of most studies interpreting self-reported illness symptoms is that potential infections were not confirmed by laboratory analysis. Indeed, a study of athletes reporting illness symptoms over five-months, used nasopharyngeal and throat swabs to show that only one third of self-diagnoses represented genuine infections [4]. Thus, most symptoms reported by athletes are likely to be caused by allergy, asthma or non-specific mucosal inflammation rather than pathogens and exercise-induced immuno-suppression [5]. Among the few genuine infections, if there is an immunological component of risk, then non-exercise factors most likely contribute. These can include long-haul air travel crossing multiple time-zones, exposure

to hypobaric hypoxia, radiation, temperature changes, sleep disruption, altered diet, dehydration and psychological stress [5, 6].

Exercise and salivary IgA

Studies are often cited showing that salivary IgA, measured as absolute concentration (mg/mL) or as secretion rate (IgA protein concentration multiplied by saliva flow rate; mg/mL/min) can decline by 20-25% following exercise bouts [1]. Yet, other studies, which are cited less, have shown the opposite effect [7]. Although resting levels of salivary IgA have been linked to self-reported illness symptoms, transient fluctuations and inter-individual differences could be driven by factors such as circadian rhythm, psychological stress, dehydration, diet, ethnicity, medications, biological sex, and phase of the menstrual cycle. Perhaps most importantly, given that periodontal disease is common among athletes [8], oral health status results in profound between-person salivary IgA variation [9] but is rarely considered. Measuring salivary IgA in isolation provides an incomplete and potentially confusing assessment of immune competency.

Recent studies have expanded salivary analyses to include several other anti-microbial proteins or peptides (e.g. alpha-amylase, human neutrophil peptides 1-3, human defensins 5-6, lactoferrin, LL-37, and lysozyme) characterising fluctuations in response to exercise [10]. However, many more proteins require exploration and validation as predictors of infection risk. For example, 151 differentially expressed proteins were identified when examining nasal mucosal washes from people infected with influenza compared to uninfected controls using a proteomic approach that quantified around 1000 proteins [11]. Many aspects of both cellular and humoral mucosal immunity have been examined as predictors of infections. Although salivary IgA has received most attention, it is likely that relationships between illness symptoms and most measurements of mucosal immunity are influenced by other factors [12]. Between-person differences in infection susceptibility – aside from the influence of pathogen exposure, environmental and behavioural factors – are most likely explained by single nucleotide polymorphisms in key genes leading to individual idiosyncrasies in multiple aspects of immune function.

Exercise and changes to immune cell frequency and functional capacity

During exercise, immune cell frequency in blood is increased [13]. Some cells detach from the endothelium and recirculate due to changes in shear forces, blood pressure, and sympathetic nervous system activity, whereas other cells mobilise from tissues such as the spleen. Upon exercise cessation, and most prominently among lymphocytes, cell frequency falls below resting levels to a nadir 1 or 2 hours later, usually returning to baseline within 24 hours. These post-exercise changes are partly due to the functional properties of the mobilised cells but also due to hypothalamic-pituitary-adrenal axis activation. Coinciding with changes in cell frequency, parallel alterations to cell function have been reported (e.g. cytokine production, proliferation, migration capability, cytotoxicity) typically characterised by increases during exercise, and decreases after, leading to speculation that immune function is transiently compromised [14].

A more contemporary viewpoint is that these observations, particularly among lymphocytes, are part of a well-orchestrated immune-surveillance response. Exercise redeploys highly functional sub-populations of T cells, B cells and Natural Killer cells to peripheral tissues (e.g. mucosal surfaces) to identify and eradicate infected cells and damaged or malignant cells; termed the acute-stress/exercise immune-enhancement hypothesis [15]. Pivotal research by Kruger and colleagues, using fluorescent cell tracking in rodents, showed that T cells are redeployed to the gut, lungs, and bone marrow following exercise [16] reflecting heightened immune-surveillance at sites where pathogens are likely to be encountered (gut, lungs) and heightened immuno-regulatory activities (in bone marrow). In addition, 24 hours after exercise, a small number of apoptotic lymphocytes accumulate in bone marrow and blood coinciding with a mobilisation of haematopoietic stem cells [17]. Further, injecting apoptotic lymphocytes (or their supernatant) into the bloodstream stimulates haematopoietic stem cell mobilisation within 2 hours [17]. These observations support the proposal that exercise reverses T cell immunosenescence by "making immunological space" [18]. In this hypothesis, it is proposed that exercise mobilises senescent T cells into blood, which home to tissues where some undergo apoptosis. Naïve T cells refill the "immunological space" that has been created, due to exercise-induced thymopoiesis or extrathymic development, perhaps in response to IL-7 released from contracting skeletal muscle [18, 19].

Although cell frequency in blood is informative, cell function is arguably more clinically relevant, but is strongly influenced by the number and type of cells assessed. During exercise, blood is predominantly occupied by cells capable of responding strongly to *in vitro* stimuli,

and therefore many studies have reported "improved" function of cells close to an exercise stimulus. In the hours following exercise, due to redeployment of highly functional cells to tissues, blood has fewer cells capable of responding to *in vitro* stimuli, explaining the commonly reported "decrease" in cell function post-exercise. Lancaster and colleagues demonstrated these effects in 2005, reporting that interferon-gamma production by stimulated CD8+ T cells is reduced 2 hours after moderate-intensity cycling for 2.5 hours [20]. Importantly, the reduced capacity to produce interferon-gamma was due to fewer interferon-gamma positive CD8+ T cells in blood at the time of sampling [20]. Adequate resolution can only be achieved by examining cell function on a per-cell and per-phenotype basis while considering the kinetics of cell sub-populations and their proportions in the samples assessed. For example, it has been shown that the frequency of CD8+ T cells producing cytokines is dependent on the proportion of naïve and memory cell sub-populations within the T cell pool, differentiated by CD27 and CD45RA [21].

These principles, although less widely investigated, also likely apply to cells of the innate immune system. For example, changes to neutrophil function with exercise might represent a shift in the proportion of immature and mature cells, and the concomitant migratory or homing capability of cells might therefore explain differences in cell function especially if reported between different biological fluids and tissues [22]. There has been an over-generalisation that "impaired" function of adaptive immune cells following exercise – which, as explained above, is influenced by individual cell properties and their proportions present in samples assayed – also applies to cells of the innate immune system. Indeed, some reports are often overlooked, showing that innate immune cells, such as macrophages and neutrophils, exhibit *increased* cell functions (e.g. chemotaxis, phagocytosis and microbiocidal capacity) following exercise [23, 24]. Thus, results of studies examining exercise-induced changes to cell frequency and function must be interpreted carefully considering differential effects on innate or adaptive immune cells, their sub-populations, and the time-dependent changes in the cellular composition of blood.

Neuroendocrine regulation of immune cell function

The catecholamines adrenaline and noradrenaline – a focus for some mechanistic investigations of exercise and immune cell function – are often labelled as "immuno-suppressors", which is an oversimplification [23, 24]. Conclusions have predominantly been

made with unfractionated lymphocytes, or CD4+ T cells isolated at rest, manipulating catecholamine exposure during proliferative stimulation using mitogens such as phytohaemagglutinin (PHA). There are, however, important nuances when interpreting *in vitro* experiments and extrapolating findings to *in vivo* processes, even at rest. First, the anti-proliferative effects of noradrenaline reported at high concentrations do not always occur with lower levels of noradrenaline, especially in the presence of glucocorticoids [23]. Instead, reports show these conditions can *stimulate*, rather than suppress, lymphocyte proliferation and are perhaps more representative of *in vivo* settings [23]. Indeed, although glucocorticoids are considered immunosuppressive, the exercise-induced cortisol response stimulates innate and adaptive immune cells to migrate out of the circulation for tissue immune-surveillance [25, 26]. Second, the suppressive effect that catecholamines can have on lymphocyte proliferation do not generalise to all cells. For example, catecholamines can *stimulate* macrophage and neutrophil function [23, 24] and there is further complexity when examining cell sub-populations. Experiments assessing adrenergic stimulation of Natural Killer cells, CD4+ and CD8+ T cells, and antigen presenting cells support a suppressive effect [27] but more resolution is provided by separating CD8+ T cells into naïve and memory sub-populations [28]. These results show differential effects of noradrenaline, which *stimulates* inflammatory cytokine production and *tempers* activation-induced proliferation in memory cells, but exerts minimal effects in naïve cells [28]. The complexities of *in vitro* results are amplified with *in vivo* studies, especially in an exercise context, and further investigations are required. However, we emphasise it is an oversimplification to conclude that forms of exercise, which stimulate a neuroendocrine response, suppress immune cell function and impair overall immune competency.

Questions that remain unanswered: future research for examining exercise, immune function and infection susceptibility

Epidemiological associations between exercise volume and infection risk – usually assessed via self-reported illness symptoms – are often described as a 'J-shaped curve' [29]. This relationship infers that people accumulating large volumes of exercise exhibit a greater infection risk than those who do not exercise, and compared to individuals who exercise at moderate levels, which is protective, the risk of infections is even greater [29]. However, the immunological effects of undertaking exceptionally large volumes of long-duration endurance exercise training, particularly when accumulated over weeks and months, are not well

understood. Circadian secretion profiles and overall exposure to various biochemical and neuroendocrine factors may be altered, and these changes could in principle, affect aspects of immune function [30]. In addition, given the rapidly developing field of immuno-metabolism, we anticipate metabolic investigations of immune cell function in an exercise context, and a renewed search for factors that are depleted (or accumulate) following individual or accumulated bouts of exercise. Although some factors have previously been discounted (e.g. the amino acid glutamine; [31]), and, extreme metabolic disruption via starvation has relatively modest effects on immune function [32], improvements in technology and immuno-metabolic understanding may yield further insights, especially in studies that tease apart complex interactions between exercise, nutrition, and immune competency. However, as with assessments of immune cell function, it is critical that immuno-metabolic measurements are examined on a per-cell and per-phenotype basis, considering the time-dependent influence exercise has on the cellular composition of blood. Potential biomarkers of immune competency, or processes that appear to be affected by exercise, should subsequently be validated against infections that have been confirmed with laboratory diagnostics.

Exercise-induced leukocytosis is one of the most reproduced findings in exercise physiology, and we anticipate future studies will continue to replicate classical findings with emerging forms of popular exercise. A recent example is sprint-interval exercise, also referred to as High Intensity Interval Exercise (HIIE), which, as might be expected, stimulates T cell and Natural Killer cell trafficking, but responses are larger following a continuous and sustained exercise stimulus [33]. Other studies have shown that frequent HIIE (or High Intensity Interval Training; HIIT) does not compromise mucosal immunity [34] and that both HIIT and continuous training similarly improve innate immune cell function at rest [35]. Exploring the immunological effects of different exercise modes has merit for improving understanding of immune function, especially if the optimal mode of exercise is yet to be established for particular groups (e.g. patients with chronic disease).

Conclusion: exercise in general is beneficial for immune competency across the lifespan in health and disease

In summary, based on current evidence, it is misleading to state that *any* form of exercise is immuno-suppressive. This belief is counterproductive for encouraging exercise as a preventative and therapeutic strategy for chronic disease. Indeed, we encourage research that

examines exercise-induced *enhancement* of immune competency, which could be particularly beneficial for elderly people and patients with diseases that have an immunological aetiology. For example, the acute immune response to single exercise bouts, and chronic adaptation with regular endurance exercise training, both bolster immune responses to vaccination in younger and older people [36]. When forms of exercise are prescribed to reduce cancer risk or to facilitate cancer therapy, there are likely to be multiple mechanisms, and some are probably immunological. These mechanisms might elicit their effects via the transitory responses to acute exercise bouts, the cumulative effects of repeated transitory responses, or the long-term chronic adaptation with exercise training. However, in settings where tumour cells have developed – or are perhaps developing – a strong emphasis has been placed on the effects that individual bouts of exercise can have. For example, acute moderate-to-vigorous intensity endurance exercise stimulates Natural Killer cells to detect and eliminate tumours (or pre-cancer cells) [37]. In addition, serum collected immediately after acute endurance exercise bouts has been shown to impair breast cancer cell viability, but serum collected at rest after long-term endurance training had no effects [38]. Finally, being regularly active, partly by engaging in forms of exercise, might limit or delay ageing of the immune system, potentially reducing the chance of developing infections and cancer [39, 40].

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