

Can exercise affect immune function to increase susceptibility to infection?

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Abstract

Multiple studies in humans and animals have demonstrated the profound impact that exercise can have on the immune system. There is a general consensus that regular bouts of short-lasting (i.e. up to 45 minutes) moderate intensity exercise is beneficial for host immune defense, particularly in older adults and people with chronic diseases. In contrast, infection burden is reported to be high among high performance athletes and second only to injury for the number of training days lost during preparation for major sporting events. This has shaped the common view that arduous exercise (i.e. those activities practiced by high performance athletes/military personnel that greatly exceed recommended physical activity guidelines) can suppress immunity and increase infection risk. However, the idea that exercise per se can suppress immunity and increase infection risk independently of the many other factors (e.g. anxiety, sleep disruption, travel, exposure, nutritional deficits, environmental extremes, etc.) experienced by these populations has recently been challenged. The purpose of this debate article was to solicit

opposing arguments centered around this fundamental question in the exercise immunology field: can exercise affect immune function to increase susceptibility to infection. Issues that were contested between the debating groups include: (i) whether or not athletes are more susceptible to infection (mainly of the upper respiratory tract) than the general population; (ii) whether exercise per se is capable of altering immunity to increase infection risk independently of the multiple factors that activate shared immune pathways and are unique to the study populations involved; (iii) the usefulness of certain biomarkers and the interpretation of in vitro and in vivo data to monitor immune health in those who perform arduous exercise; and (iv) the quality of scientific evidence that has been used to substantiate claims for and against the potential negative effects of arduous exercise on immunity and infection risk. A key point of agreement between the groups is that infection susceptibility has a multifactorial underpinning. An issue that remains to be resolved is whether exercise per se is a causative factor of increased infection risk in athletes. This article should provide impetus for more empirical research to unravel the complex questions that surround this contentious issue in the field of exercise immunology.

Keywords: Exercise immunology, Athletes, Immuno-suppression, Upper respiratory tract infections, Open window of infection risk, stress, physical activity.

Introduction

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Exercise immunology as a discipline came of age in the latter part of the twentieth century (121). Since 1990, ~5,000 peer-reviewed original research and review papers have been published, cutting across multiple themes including acute/chronic changes in athletic and non-athletic populations, clinical and

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translational perspectives, nutritional interactions and immunosenescence (91, 124, 141). Both cross-sectional and longitudinal studies in humans have demonstrated the profound impact that exercise can have on the immune system. Physical fitness and moderate intensity exercise training have been shown to improve immune responses to vaccination, lower chronic low-grade inflammation, and improve various immune markers in several disease states including cancer, HIV, cardiovascular disease, diabetes, cognitive impairment and obesity (39, 56, 67, 130). Conversely, arduous bouts of exercise, typically those practiced by athletes and other high-performance personnel (e.g. the military), have been associated with suppressed mucosal and cellular immunity, increased symptoms of upper respiratory tract infections (URTI), latent viral reactivation, and impaired immune responses to vaccine and novel antigens (15, 64, 91, 98). This body of research has informed the view in the exercise immunology field that regular bouts of short-lasting (i.e. up to 45 minutes) moderate intensity exercise are ‘immunoenhancing’ whereas repeated bouts of long-lasting (>2hours) arduous intensity exercise can be ‘immunosuppressive’ (126, 141). The J-curve and open-window hypothesis have been staples of the exercise immunology discipline for almost three decades, providing a set of theoretical frameworks to explain why exercise can apparently exert both enhancing and suppressive effects on the immune system and alter susceptibility to illness (89, 100). While the plethora of beneficial effects provided by regular short-lasting moderate intensity exercise on the immune system of older adults and people with chronic disease are undisputed (91, 126), the empirical research supporting the basis of these frameworks and the idea that any form of exercise can be considered ‘immunosuppressive’ has recently been challenged (17, 18).

The purpose of this debate article was to revisit a fundamental question in the exercise immunology field – can exercise affect immune function to *increase* susceptibility to illness? Renowned experts in exercise immunology were asked to provide a brief narrative supporting their contention that exercise is/is not capable of affecting immune function to increase sus-

ceptibility to illness. Providing the argument for (The Yes Case) are Maree Gleeson (University of Newcastle, Australia), David C. Nieman (Appalachian State University, USA) and David B. Pyne (University of Canberra, Australia). The argument against (The No Case) is provided by John P. Campbell (University of Bath, UK) and James E. Turner (University of Bath, UK). Both groups of authors were also asked to provide a rebuttal to the original narratives. Finally, points of agreement and issues that remain to be resolved are presented by the editorial team to provide impetus for future empirical research studies in the area.

Can Exercise Affect Immune Function to increase Susceptibility to Infection? – The Yes Case

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Introduction

The impact of exercise on innate and acquired immune parameters (magnitude, direction of changes and recovery time) is dependent on the intensity of exercise, and in high-performance sports, the duration and load of training. Immune function can be compromised at the high-performance end of the spectrum of physical activity, and place an individual at increased risk of infection (Figure 1). These risks are co-dependent on factors that regulate immune function (genetic, nutritional status, psychological stress, interrupted circadian rhythm), environmental stressors (extreme temperatures, allergens, airway irritants), or underlying health conditions that promote inflammatory processes [see reviews (12, 140, 141)]. As upper respiratory illness (URI) is the most common (35-65%) non-injury related presentation in sports medicine (49), there is substantial clinical and laboratory evidence of

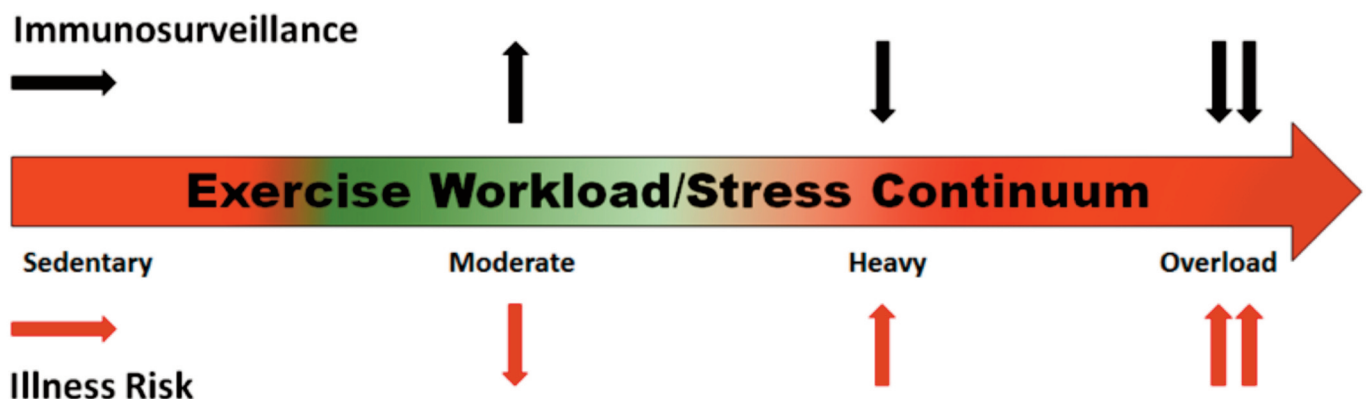


Figure 1:

Schematic model of the exercise workload/stress continuum and the relationship between immunosurveillance measures and risk of illness as the exercise workload is increased to moderate, heavy and overload.

exercise-related immune disturbance and increased susceptibility to URI in athletes undertaking strenuous exercise.

Animal and Cell Culture Data

Animal-based experiments assessing the linkage between muscular fatigue and pathogen resistance date back to the late 1800s. These early studies were reviewed by Baetjer (7) in 1932 who concluded that the data "appear to indicate that exhaustive exercise just preceding or immediately following infection, but more especially the latter, predisposes the animal to a more rapid and fatal attack of the infectious disease." Numerous studies since then have supported this observation and provided insights into how exercise fatigue impacts underlying immune intracellular processes (19, 21-23, 32, 47, 72, 79, 86, 87, 145). A representative murine study indicated higher mortality from herpes simplex type 1 virus (HSV-1) injected intranasally after prolonged strenuous (2.5-3.5 h to fatigue) compared to moderate (30 minutes) exercise (32). Antiviral resistance of lung macrophages from the exercise-fatigued group was suppressed, linking exercise-induced immune dysfunction with increased susceptibility to respiratory infection *in vivo*.

Immunometabolism is an emerging science that highlights connections between the metabolic state of immune cells and the nature of the immune response (44, 68, 76, 81, 90, 92, 102, 106, 120, 134). In response to an acute immunological challenge such as exercise stress, immune cells grow, proliferate, and generate molecules such as cytokines and cytotoxic granules. This immune activation requires metabolic reprogramming to generate sufficient energy to fuel these demands. This relationship between metabolic and immune systems is particularly apparent during recovery from physiologically demanding bouts of intensive exercise (11), and provides a new methodology for future research to better understand exercise-induced immune dysfunction (90).

URI in High Performance Athletes

While the majority of athletes have a similar incidence of URI to the general population, a small proportion (5-7%) experience recurrent episodes at significantly higher rates (48), often associated with persistent fatigue that interferes with training (111) and may affect competition performance (108). The incidence of URI in high-performance athletes can increase during periods of intense training, in association with increases in training load and competitions. Epidemiologic data collected during international competitions reveals that 7% of elite athletes (range 2-16%) experience an illness episode, with respiratory illness the major cause of presentation (30-64%) and infection the most common diagnosis (32-58%) by medical teams (4, 42, 84). Studies using self-reported URI rather than validated illness questionnaires (52, 105) may not be as accurate, but physician verification is common for elite athletes. Responsive, reliable and validated survey instruments for respiratory illness (8, 10) can be used confidently for research and clinical applications.

The aetiology of URI is rarely examined, with the few studies that included pathology indicating that ~30-40% of URI

episodes in athletes have an identified infective origin (28, 128). A single negative test point does not exclude the possibility of infection for other pathogens not included in the tested panels, or timing of the appearance of detectable levels of infections. Allergy is also a common clinical finding in high-performance athletes (28, 42, 84, 107), but regardless of the infectious and/or allergic stimulus (2, 70, 97) that induces an inflammatory cytokine cascade in the airways, a major concern for the athlete is the accompanying fatigue that can limit or prevent training (50, 57, 111) and impair performance (50, 108, 111).

Impact of Exercise on Immunity and URI Risk in High Performance Athletes

Intense exercise induces a well-characterised systemic and mucosal response in innate and acquired immune parameters (141). NK cell and neutrophil function, T- and B-lymphocyte function, salivary IgA output, skin delayed-type hypersensitivity response, major histocompatibility complex II expression in macrophages, and other biomarkers of immune function are altered for several hours to days during recovery from prolonged and intensive endurance exercise (119). Exercise has the potential to transiently alter immune protection, increase the risk of infection, or induce inflammatory processes in the airways (91). Suppression of immune parameters can occur in elite athletes over years of training (25, 111). This may result in temporary or sustained reactivation of viruses (61, 111), most likely due to an exercise-induced decline in cytotoxic T-cells (141).

Despite extensive laboratory studies of immune parameters in response to exercise, parallel examination of URI is often not included in the study design. Elite athletes prone to recurrent URI have altered/adverse cytokine responses to exercise in comparison with healthy athletes (29), and an underlying genetic predisposition to pro-inflammatory cytokine responses (27, 147). Differences in IFN- γ and IL-10 polymorphisms are known to affect illness severity, cytokine protein levels and duration/recovery time from various viral infections (136). A reversible defect in IFN- γ has been associated with illness-prone athletes experiencing fatigue (25). Viral reactivation of EBV is also a common finding (22-50%) in athletes experiencing recurrent URI (61, 111), and expression of EBV DNA in saliva is associated with a prior reduction in salivary IgA levels (61, 146), which is part of mucosal protection against viral infections (114).

Measurement of secretory IgA (SIgA) in saliva has shown consistent associations with URI in athletes. The consensus for studies of elite athletes is that low levels of salivary IgA and/or secretion rates (55, 58, 59), low pre-season salivary IgA levels (59), declining levels over a training period (57, 88), and failure to recover to pre-training resting levels (57), are associated with an increased risk of URI. Longitudinal studies have identified the impacts of intense training over both short (months) (50, 59) and long (years) (25, 111) periods on immune suppression and increased incidence of URI. Low levels of SIgA can occur prior to the symptoms (59, 61, 88). However, the best predictive use of salivary IgA is monitoring immune status in individual athletes with a history of URI (50, 57).

Concluding statement

A large body of evidence supports the proposition that elite athletes undertaking prolonged heavy intensive exercise can exhibit immune changes, in association with physiological, metabolic, and psychological stressors, and pathogen/allergen exposure, that increase the risk of infection and/or airway inflammation. Individual responses to different exercise workloads vary widely (46), and the changes in immune parameters reflect the magnitude of the stressors experienced by the athlete (Figure 1). A "survivor" effect exists for elite athletes whose immune system can be trained to adapt and attenuate responses to greater workloads than the general public. But athletes too have their limits, and their underlying genetic profile, in association with other stressors and environmental factors, will determine their risk profile for URI. We assert that multiple lines of laboratory-, field- and clinically-based evidence converge in support of the viewpoint that exercise at a high-performance level can affect immune function, increasing susceptibility to infection.

Can Exercise Affect Immune Function to increase Susceptibility to Infection? – The No Case

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Is there evidence that exercise impairs the normal functioning of the immune system?

A central dogma of exercise immunology has incontrovertibly persisted that strenuous exercise bouts, or periods of intensified training, impair aspects of cellular and humoral immunity, leading to an 'open window' of infection risk. Consistent and reliable evidence in support of this assertion is lacking (17, 18) (Figure 2).

Measurement of blood leukocyte frequency and functional competency in response to strenuous exercise is common in the literature (141). Exercise induces a bi-phasic response, whereby leukocyte frequency in blood increases, and then, upon exercise cessation, the frequency of some cells decreases below resting levels to a nadir one or two hours later (113) (Figure 2F). Coinciding with changes in cell number, parallel alterations to cell function are consistently reported (e.g., cytokine production, proliferation, migration capability, cytotoxicity), whereby increases are observed during exercise, followed by decreases shortly afterwards (77), leading to speculation that immune function is compromised. Evidence indicates that the fall in cell number after exercise does not reflect mass apoptosis. Instead, cells are redistributed out of the bloodstream to tissues and organs (Figure 2F). This phenomenon has been demonstrated in rodents with fluorescent cell tracking (74) and in humans by the proportional reduction of cells expressing homing receptors for tissue and organ sites (16, 75, 125). This redistribution effect is largely comprised of highly functional sub-populations of T cells and NK cells (16, 75, 125), and seems to confer host benefits, for example, by enhancing the identification and eradication of tumour cells in tissues (101). Following exercise, a small number of apoptotic lymphocytes accumulate in bone marrow and blood, coincid-

ing with mobilisation of haematopoietic stem cells (83). These observations support the proposal that exercise might reverse T cell immunosenescence (123), partly by selective apoptosis of senescent T cells, and by promoting the development and / or survival of naïve T cells, facilitated by myokine release from contracting skeletal muscle (39).

A mainstay of exercise immunology that is used to assess whether exercise impairs humoral immunity is the measurement of salivary IgA (Figure 2D). Some studies have reported a decline (e.g., 20-25%) in saliva IgA following exercise (132), yet, other studies do not show this effect (13). A reason for discordant findings is that IgA measured within-day and between-days is highly variable within a person. Such intra-individual differences – exacerbated at an inter-individual level – are likely orchestrated by multiple factors that include sleep and circadian rhythms, psychological stress, diet, and oral health (Figure 2D). Use of salivary IgA as a single measure of immune competency in the hours and days after exercise should be interpreted with caution. At a systemic level, it has never been demonstrated that exercise suppresses plasma cell immunoglobulin production. This could be due to the long half-life (1-3 weeks) and high concentration of immunoglobulins in blood, which together, may mask any subtle suppression of plasma cell immunoglobulin synthesis.

Is there evidence that exercise increases susceptibility to illness?

Observational studies have reported that symptoms of upper respiratory tract infections were more common in competitors of mass-participation endurance sporting events (103) (Figure 2A). However, a limitation of studies from this era was that infection symptoms were not confirmed by laboratory analysis. Subsequently, a study using molecular techniques showed that only one-third of illness symptoms reported by athletes over five-months represented genuine infections (128). Although more recent research showed three-quarters of illness symptoms reported by athletes were infectious (133), it is likely that a substantial number of perceived illnesses are caused by factors such as allergy, asthma or non-specific mucosal inflammation, and not infection due to exercise-induced immuno-suppression. Among the genuine infections, it seems speculative to isolate exercise as a sole factor as other non-exercise factors contribute, including: long-haul air travel, sleep disruption, altered diet, and psychological stress (54, 131) (Figure 2E). Importantly, attending any mass participation event – whether exercising or not – increases the risk of encountering pathogens due to crowds (Figure 2B-C). Indeed, it has been shown that one-third of people attending a mass-participation religious gathering reported infections (24). Thus, guidelines to reduce infection risk (e.g., hygiene practices) are relevant (138). Finally, we are not aware of robust evidence showing that endurance athletes develop more infections annually than the general population.

Will future research demonstrate that exercise is capable of impairing immune competency?

Research over four decades has examined whether strenuous exercise suppresses immunity. The lack of compelling evi-

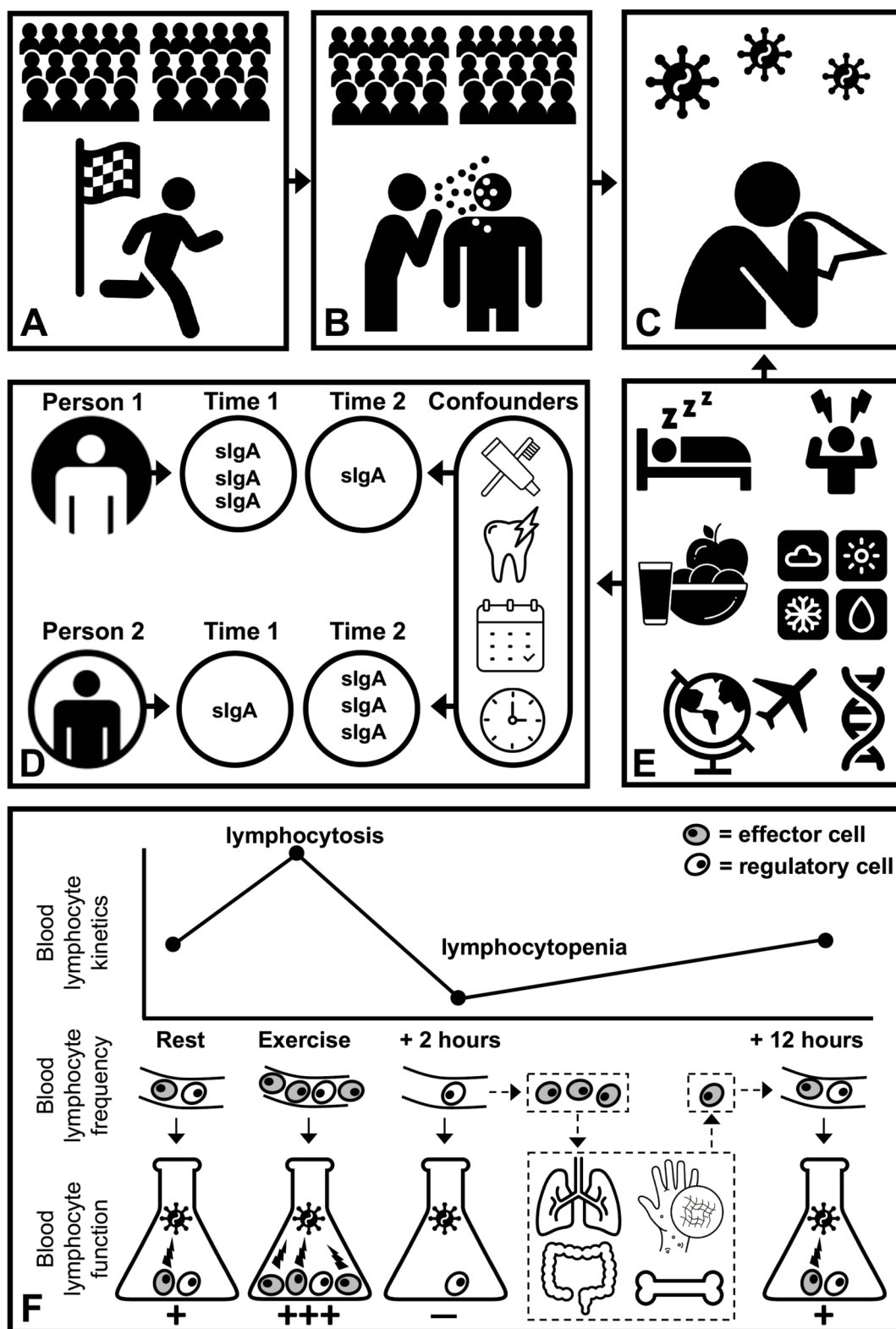


Figure 2:

A-C: Athletes competing in mass-participation events, and even spectators, are at an increased risk of infection due to heightened pathogen exposure from crowds because some people will be harboring infections. **D:** In saliva, secretory immunoglobulin-A (sIgA) concentration and secretion rate exhibit profound inter- and intra-individual variation, likely due to oral health, psychological stress or sleep, and diurnal or seasonal changes respectively. **E:** Non-exercise factors influence infection risk, including poor sleep quality and quantity, psychological stress, inadequate nutrition, extreme environmental conditions, air travel (particularly across multiple time zones) and single-nucleotide polymorphisms in critical immune defence genes. **F:** Acute bouts of exercise mobilise lymphocytes into peripheral blood, characterised by a selective mobilisation of effector T cells and NK cells. Following exercise, these effector cells extravasate to tissues such as the lungs, Peyer's patches, bone marrow or inflammatory sites (e.g. in skin) for immune-surveillance. The number of effector and regulatory cells in blood typically returns to pre-exercise values within 12 hours. Assessing the functional capacity of lymphocytes (or major sub-types such as T cells and NK cells) in blood samples collected at rest, during exercise, or afterwards, is confounded by the proportions of effector and regulatory cells, even when accounting for total cell number. Functional capacity (e.g. proliferation, cytokine production, cytotoxicity) is directly related to the number of effector cells in samples.

dence suggests that: (i) the detrimental effects of exercise on immunity are negligible, and / or (ii) research has not been designed optimally to assess immune competency. As we have discussed elsewhere (17, 18), it could be speculated that exercise is capable – in principle – of impairing aspects of cellular immune function due to the energy cost of exercise and metabolic perturbations that can occur in the absence of appropriate nutrition. However, to date, immuno-metabolic stress has not been investigated at a single cell level in the context of exercise. It could also be speculated that heightened steroid hormone production, or adrenaline exposure during exercise, may impair cell function. However, cell function can be regulated both positively and negatively by stress hormone exposure (93, 94) and different cell sub-types can respond differently to the same hormone (127). Thus, it is an over-simplification to denounce exercise as pan-immunosuppressive.

Given the aforementioned complexities, clinically relevant models of primary or secondary antigenic challenge should be used to examine the effects of exercise on immunity. Pertinently, previous research has examined the effects of a marathon on the response to vaccination (43). In this study, participants were vaccinated with tetanus toxoid approximately 30 minutes after exercise. This post-exercise time-point coincides with elevated cortisol levels, 'reduced' blood lymphocyte frequency, 'impaired' lymphocyte function and metabolic perturbations. Antibody titres were measured 15 days later and compared to those from a control group who did not compete in the marathon. Although the sample size included 4 runners and 59 controls, the results indicated that antibody titres were *higher* in those who received the vaccine following the marathon (43). Similar methodology was employed by administering diphtheria and tetanus toxoid and a pneumococcal polysaccharide vaccine to 22 athletes 30 minutes after a triathlon (15). After 14 days antibody titres from athletes were compared with those from 33 control participants who received the vaccine without prior exercise, and there were no differences between groups (15). If energy depletion or stress hormones were capable of hindering immunity following exercise, then one would expect impaired rather than *enhanced* or *unchanged* vaccine responses following exercise. These findings align with an emerging theorem in the field, that, on the balance of available evidence, exercise may in fact enhance immune competency and regulation.

Response to the No Case

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There is agreement between the debating groups that regular bouts of moderate-to-vigorous physical activity (MVPA) enhance the exchange of immune cells between the circulation and peripheral lymphoid tissues (1, 16, 36, 125, 126). The net effect is enhancement of immune surveillance,

improved health, and decreased risk of illness (91, 123, 126).

Despite the large number of studies describing changes in immune parameters, this debate centers on the effect of acute and chronic exercise on the immune system and risk of illness and infection. This issue was the focus of investigation by the early pioneers in exercise immunology, including Pedersen and Hoffman-Goetz, who in 1994 and again in 2000, reviewed the literature and reasoned that "exercise-immune interactions can be viewed as a subset of stress immunology" (66, 99). These investigators emphasized that "many clinical physical stressors (e.g. surgery, trauma, burn, and sepsis) induce a pattern of hormonal and immunological responses that have similarities to that of exercise" (66).

This interpretation has withstood the test of time, especially when evaluation of animal and human studies is made in the full context of the exercise workload - stress continuum (15, 22, 32, 43, 50, 61, 72, 86, 91, 98, 108, 121, 131, 140, 141, 145). Unfortunately, the argument by the opposing debate group that "consistent and reliable evidence in support of this assertion is lacking" was supported using many references that included MVPA workloads well within recommended levels for the general community (16, 39, 74, 75, 83, 100, 101). However, high-performance athletes and other personnel (e.g. elite military groups) undertake workloads well beyond the recommended upper levels over extended periods. Individuals in these cohorts can have an increased risk of respiratory infection (4, 42, 48, 52, 85, 96, 107, 111, 131) associated with altered immune biomarkers (25, 27, 50, 55, 57, 59, 61, 88). The consensus among investigators is that exercise-induced immune changes reflect the physiological and metabolic stress experienced by the individual (12, 34, 91, 121, 140, 141).

Several lines of evidence across animal and human studies support the paradigm that illness risk may be elevated during periods of unusually heavy exertion, especially when other stressors are present. These factors include mental depression or anxiety, international travel across several time zones, participation in competitive events, lack of sleep, temperature extremes, and low dietary energy intake and nutritional deficiencies (31, 34, 38, 54, 60, 65, 73, 84, 91, 111, 112, 131, 136, 144).

The opposing debate group disregarded these findings because of mistrust in self-reported acute respiratory illness (ARI) symptom data. However, Barrett and others (8, 10) have shown carefully that individuals are capable of reporting ARI symptoms that agree with physician-based diagnosis. There are no perfect tools or gold standard for assessing ARI episodes and symptoms. Studies show that etiological pathogens cannot reliably be detected using laboratory methods in 20-40% of people with classic ARI symptoms (9, 28, 128, 144). ARI episodes caused by viral infection can be asymptomatic at the time of testing in 25-35% of people (9, 28, 128), while symptoms can also be linked to a non-viral cause (28, 70, 84, 111). Defining ARI is part of the challenge, but epidemiological and clinical trial ARI data contributes to the discussion and should not be discarded.

Until recently, exercise-induced immune responses were measured using a few targeted biomarkers, but increasingly the focus has shifted to multi-omics approaches (91). Advances in measurement technologies and bioinformatics will improve our capacity to measure both the beneficial effects of moderate exercise on immunity, and the downturn in immunity that can occur during periods of heavy exercise training. In a representative study, an integrative omics approach was used to explore immunosuppression in female physique athletes undertaking prolonged periods of intense training coupled with low-energy availability (116). Several molecular pathways were elucidated and included dysregulated hematopoiesis, suppressed immune cell proliferation, and loss of immune cell function by reduced antibody and chemokine secretion. Most of these measures of dysregulated immune function were reversed during an 18-week weight regain period.

Data generated from multi-omics approaches will reshape our future understanding of how exercise influences immune function and the complex interactions with neuroendocrine systems in individuals to either enhance protection, or increase the risk of illness and infections in susceptible individuals.

Response to the Yes Case

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James E. Turner, University of Bath, Bath, UK

There is limited evidence supporting the proposition that exercise suppresses immunity. The Yes case claims ‘substantial evidence’ exists because ‘upper respiratory illness (URI) is the most common non-injury presentation in sports medicine’. URI is also the most common health problem in primary care (45) and is therefore not a problem unique to sport. Given the ubiquity of URI, the incidence among athletes is not in question. At the crux of this debate is whether exercise causatively suppresses immunity to a clinically meaningful degree, and in doing so, increases the risk of URI in a sub-group of athletes. We posit herein, that it is misleading to conclude from existing evidence, that exercise is the causative factor of URI among athletes.

Immune competency is strongly influenced by non-exercise factors

The Yes case states that, in the context of exercise, infection ‘risks are co-dependent on factors that regulate immune function (genetic, nutritional status, psychological stress, interrupted circadian rhythm)’. Crucially, this statement acknowledges that infection risk is ‘co-dependent’ on other factors. Our standpoint is that infection risk is fundamentally dependent on non-exercise factors given the evidence that polymorphisms in critical immune-defence genes, inadequate nutrition, psychological stress, poor sleep quality or quantity, and environmental conditions dysregulate immunity (54, 117, 131). Importantly, these ‘factors’ are rarely controlled in exercise studies. Thus, without measuring these non-exercise factors, and in the absence of mechanistic human evidence that exercise causatively suppresses immunity at a humoral, cellu-

lar and systems level, the *a priori* assumption that exercise is a *de facto* cause of immune suppression is unsubstantiated. Immunological idiosyncrasies, unrelated to exercise, most likely explain why, as highlighted in the Yes case, that ‘the majority of athletes have a similar incidence of URI to the general population’ (51).

The primary risk factor for infections is exposure

Evidence cited in the Yes case relating to infection incidence predominantly relies on studies surveying athletes around the time of competitions, which are often attended by large groups of athletes or spectators (4, 42). Other studies, assessing illness symptoms over longer periods, may not accurately capture time spent by athletes in settings where they are in close proximity to other people or crowds. Our standpoint is that public travel to, or attendance at, any mass-participation event is likely to increase exposure to pathogens (17, 24). Thus, anyone attending a sporting event, whether a competitor or spectator, is at a heightened risk of infection (Figure 2A-C). Indeed, this risk is likely to be exacerbated in subgroups of people – both athletes and non-athletes alike – due to aforementioned inter-individual differences in immune competency.

If exercise causatively suppresses immunity increasing infection risk, what is the mechanism?

Firstly, it is stated in the Yes case that ‘measurement of sIgA has shown consistent associations with URI in athletes’, however, numerous well-conducted studies have found no associations (5, 20, 53, 95, 104, 118, 135). It is stated that ‘low levels of sIgA can occur prior to the symptoms’ of infection, but it is just as likely that sIgA does not decline at this time because of the profound intra-individual variability of sIgA (109). Moreover, in studies linking sIgA to infections, confounding factors known to impact sIgA secretion, are rarely considered (14) (Figure 2D). Pertinently, many studies show that exercise does not alter sIgA levels, bringing into question the relevance of correlating sIgA with infections assumed to be brought about by exercise (3, 33, 71, 110, 115, 139).

Secondly, some evidence cited in the Yes case as supporting exercise-induced immune-suppression must be interpreted carefully. For example, conclusions drawn from a systematic review (119), do not account for temporal changes in the cellular composition of blood as explained previously (17) (Figure 2F). Separately, the observational studies which examined immunological features of ‘illness prone’ individuals lack important methodological controls (25, 111), and rather than signposting exercise-induced immune-suppression, the results highlight inter-individual differences in basal immune function. The most robust evidence shows that transient changes in cell numbers and function after exercise represent immune-surveillance (35) (Figure 2F), and evidence that exercise suppresses immunity at a systems level is lacking (17). Further, lifelong exercise (40) and physical fitness (129) might facilitate the deletion of senescent immune cells, theoretically maintaining global immune competency (123).

Thirdly, results from animal models are inconsistent due to methodological heterogeneity; some show exercise

improves responses to infectious (80, 122, 142) and neoplastic challenge (6). For example, a study cited in the Yes case, showed that rodents intranasally infected with HSV-1 after strenuous exercise exhibited 36% lower morbidity and 61% lower mortality than non-exercise controls (86). In addition, important confounders must be considered. For example, in one study cited by the Yes case, cold exposure, was the key factor – rather than exercise – driving morbidity and mortality (79). Other work has shown that forced exercise, compared to voluntary exercise, induces psychological stress which is the cause of immune dysregulation rather than exercise per se (26). Further, it must be considered whether experimental infections in animal studies provide a representative dose and route or method of pathogen entry. Conclusions must also be interpreted considering exercise timing: if already infected, some studies show exercise can be detrimental, but this does not represent *risk* of becoming infected.

Finally, the Yes case does not appraise the most robust evidence in humans showing that immunity is enhanced or at least unchanged with pathogenic challenge after exercise (15, 43, 78), supporting systematic reviews that exercise in general does not suppress immunity or increase risk of infections (62, 63).

Summary

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The purpose of this debate article was to solicit opposing arguments centered around the following question: can exercise affect immune function to increase susceptibility to infection. After reviewing the original narratives and responses from each camp, we asked the debating groups to highlight points of agreement and issues that remain to be resolved. These were then coalesced by the editorial team (Simpson, Kruger and Walsh) and summarised as follows:

Points of Agreement:

- Regular bouts of moderate to vigorous intensity exercise are beneficial for the normal functioning of the immune system and likely help lower the risk of respiratory infection/illness and some cancers. The frequent exchange of immune cells between the blood and the tissues with each bout of moderate to vigorous intensity exercise likely contributes to enhanced immune surveillance, improved health and a lower risk of illness.
- Infection susceptibility has a multifactorial underpinning. Both groups acknowledge that factors such as stress, sleep, nutrition, circadian misalignment and infection/vaccination history could directly impact or contribute to impaired immunity and infection risk, particularly in situations when pathogen exposure is more likely.

- There is a critical need for more research to help unravel the immune modulating effects of exercise, with multi-omics and immunometabolism-based studies being pivotal to further our understanding. The Yes camp suggest that further studies using these techniques will provide experimental support for the concept that reductions in immune competency reflects the physiological stress imposed from excessive exercise workloads. The No camp have called for more systems-level (e.g., immune response to vaccination) studies that control for confounding factors (e.g., nutrition, sleep, hygiene and prior exposure from infections and/or vaccinations) to determine if very large volumes of exercise (e.g., ultra-endurance activities and prolonged period of training) impair global immune competency.
- Both camps acknowledge that the field has moved on substantially from salivary IgA and total blood lymphocyte counts after acute exercise as measures of immune competency. While the lymphocytopenia observed after acute high-intensity/prolonged exercise was identified as a biomarker supporting the concept of an ‘open-window’ in the 1990’s, the contemporary interpretation is that this particular measure reflects a redistribution of lymphocytes from the blood to the tissues after exercise, albeit experimental data in humans is still currently lacking.

Issues to be resolved:

- Whether or not athletes are more susceptible to illness/infection than the general population continues to be debated between the Yes and No camps. The No camp identify the reliance on self-reported measures of upper respiratory illness symptoms as a limitation. They also contend that exposure to pathogens is the major cause of upper respiratory infection, is the most common health problem in primary care, and is therefore not unique to sport. The Yes camp counter that the questionnaires used for these studies have been extensively validated and agree with physician-based diagnoses. They also posit that there is no substantial evidence that post-race infectious episodes among athletes are linked to increased exposure from spectators at major sporting events. Moreover, the Yes camp asserted that most illnesses in humans are based on multiple risk factors, and to exclude arduous exercise as one of the important risk factors is highly selective.
- The Yes camp argue that several lines of evidence across animal and human studies support the paradigm that illness risk may be elevated during periods of heavy exertion that go beyond recommended physical activity guidelines, especially when other stressors are present. The No camp contend that, even if athletes are more susceptible to infection than the general population, it is difficult to discern exercise (regardless of volume) as the causative factor independently of the non-exercise factors that are potential confounders (e.g. nutrition, anxiety, travel, sleep disturbances, tem-

perature variations, genetic polymorphisms and prior exposure due to infection and/or vaccination).

- There continues to be disagreement on the use of salivary IgA as a biomarker to determine infection risk in athletes. The Yes camp point to the clinical evidence linking low salivary IgA levels as a biomarker of recurrent mucosal infections regardless of exercise status. They also highlighted that the most effective use of salivary IgA was monitoring individual athletes with a history of URI. The No camp argue that salivary IgA is profoundly influenced by an array of factors including diurnal variation, psychological stress and oral health and therefore has limited clinical use as a single marker of infection risk in athletes.
- Both camps challenged statements made by the other regarding the scientific evidence that is available to substantiate their claims. The No camp highlighted several experimental design features they feel should be taken into consideration when interpreting results from animal studies, suggesting that misleading conclusions could be drawn due to experimental heterogeneity (e.g. forced versus voluntary exercise, and the timing of exercise relative to infection/neoplastic challenge). The Yes camp argue that most of the evidence cited by the No camp to show immune enhancing effects of exercise are in response to bouts of moderate to vigorous intensity exercise and of relatively short duration (e.g. 30-45 minutes), are in special populations who likely have lowered immunity to begin with (e.g. older adults), and that these volumes/intensities of exercise are well within the recommended physical activity guidelines for the general population. The Yes camp contend that undertaking exercise workloads beyond these recommendations for extended periods of time is what can impair immune competency and increase infection risk.
- Finally, both camps point to markers of global immunity to measure immune competency (e.g. vaccination, latent viral reactivation) in people exposed to different volumes/intensities of exercise. The No camp argue that the most robust evidence in humans indicates that immunity is enhanced or at least unchanged with pathogenic challenge after even arduous exercise. This is countered by the Yes camp who cite evidence of latent viral reactivation among high performance athletes as a marker of reduced immune competency after periods of intense exercise.

Conclusion:

While the debating groups were able to find areas of agreement on this topic (e.g. that infection susceptibility has a multifactorial underpinning), the idea that exercise, be it arduous or otherwise, can affect immune function and increase susceptibility to infection remains a contentious issue. Although the question at hand was to focus on whether exercise can affect immunity to increase susceptibility to infection, the lack of laboratory-controlled studies resulted in both camps address-

ing the issue of whether participation in high-performance events (e.g. elite sport, military activities) and not exercise *per se* alters immunity and infection risk. On reflection, this might have been a more pertinent question to ask as it would take into consideration not only arduous exercise (i.e. exercise that far exceeds the recommended physical activity guidelines), but also the multi-factorial aspects that share pathways for the immune response to challenges including life events, exposure, personal hygiene, sleep, travel, anxiety, mental fatigue, rumination, nutrition, etc. Moreover, this debate process has perhaps exposed the field of being too focused on the exercise component, while the multitude of other factors that could directly affect and/or interact with exercise to alter immunity and infection susceptibility may have been overlooked (41, 138). While the assertion that changes in immune function measures following acute bouts of strenuous exercise or periods of heavy training account for URI symptoms in athletes remains open for debate, URI symptoms will nevertheless hinder athletic training and competition regardless of the aetiology (138). Taking a multifactorial approach may allow us to develop evidence-based recommendations and countermeasures to better prepare athletes and military personnel for the multiple challenges they will face to their immune health during training and competition/deployment (137, 138). Indeed, this multi-factorial approach is currently taken in space immunology research to help understand why astronauts experience increased episodes of latent viral reactivation and altered hypersensitivity reactions during missions, with microgravity, radiation exposure, isolation/confinement stress, altered nutrition, circadian misalignment, exertion and physical deconditioning (e.g. muscle and bone loss) all believed to play a role (30).

If exercise is directly capable of altering immunity to increase susceptibility to infection then the duration/volume of exercise will likely be a key factor. While natural infection rates are always difficult to incorporate as endpoints in highly controlled studies, there is a critical need for more controlled comparative studies centered around exercise duration (e.g. bouts lasting <45 minutes to bouts lasting >2h) as a key variable, particularly those using reliable *in vivo* endpoint measures of immune function. To this end, vaccine or experimental infection models in humans that elicit both primary and recall immune responses combined with multi-omics approaches would be highly informative for future studies. While experimental rhinovirus models have been used with exercise in humans previously (143), these early studies lacked the appropriate technology to document changes in reliable *in vivo* endpoints such as viral replication and immune responses to re-exposure. Thus, experimental pathogen/antigen challenge studies in humans could be revisited (37, 143), incorporating more cutting edge technology such as RT-PCR, RNA sequencing, proteomics and metabolomics to determine if exercise (with volume/duration as a key variable) can increase susceptibility to infection and alter immunological control of pathogens in the host. While *in vitro* assays can be useful to determine the impact of exercise on certain aspects of immune function, it is important that the limitations and potential confounding factors (e.g. cell trafficking) of these methods are adequately appraised to avoid potentially flawed interpretations.

To address the number of issues that remain to be resolved, we suggest that more robust longitudinal studies are needed to determine, firstly, if athletes or other high-performance personnel are at greater risk of laboratory-confirmed infections compared to the general population. Secondly, we should determine if arduous physical exercise *per se* is a direct cause and/or a co-factor responsible for any potential increases in infection susceptibility among athletes/military personnel. Thirdly, further work is required to clarify the underlying causes of respiratory illness and whether they are infectious in origin or initiated by other inflammatory stimuli such as allergy or epithelial trauma; and finally, what are the immunological components/pathways (including genetic predisposition, multi-omics and immunometabolism-based studies) involved if arduous exercise increases infection susceptibility directly. Studies focused on laboratory-confirmed infections as an endpoint should consider seasonal variations, as confirmed infectious URI's are more prevalent during the autumn and winter months (~70%) compared to spring and summer (~35%) (128, 133). It would also be useful to compare athletes of different sports (e.g. endurance versus strength/power activities) who, presumably would be exposed to similar confounding factors (e.g. travel, stress, exposure), but differ in the key variable of interest, which is prolonged 'heavy' exercise. It will also be important for future experimental studies to control for these confounding variables (e.g. sleep, nutrition, life stress, anxiety, etc) that could influence the selected endpoint measures, even in the laboratory setting. This will present some challenges, as even laboratory-controlled studies have to contend with a number of immune-modulating psychological variables that come into play more so during prolonged compared to shorter bouts of arduous exercise (41). Moreover, psychological traits such as emotional intelligence and mental toughness can affect the individual's ability to regulate mood and psychological strain during prolonged exercise (69, 82).

While this research continues to evolve, it is important in the interim to emphasise the context of the message that is projected to the public and scientific community. On the one hand, if performing frequent and arduous bouts of exercise that far exceed recommended physical activity guidelines is projected to have no negative impact on immunity or infection rates, then the immune health of athletes and other high-performance personnel could be unjustly ignored and regarded as insignificant. On the other hand, if exercise is portrayed as being 'immunosuppressive' then this might discourage patients and clinicians from participating in and recommending exercise, and could also project the wrong message to the vast majority of the population who would benefit from increasing their physical activity levels to improve, not only immune function, but also general health and wellness. We anticipate this debate article will provide impetus for more empirical research in the area to unravel the complex questions that surround this contentious issue in the field of exercise immunology.

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