

This item was submitted to [Loughborough's Research Repository](#) by the author.
Items in Figshare are protected by copyright, with all rights reserved, unless otherwise indicated.

Position statement part two: maintaining immune health

PLEASE CITE THE PUBLISHED VERSION

<http://www.isei.dk/>

PUBLISHER

© Association for the Advancement of Sports Medicine

VERSION

VoR (Version of Record)

LICENCE

CC BY-NC-ND 4.0

REPOSITORY RECORD

Walsh, Neil P., Michael Gleeson, David B. Pyne, David C. Nieman, Firdaus S. Dhabhar, Roy J. Shephard, Samuel J. Oliver, Stephane Bermon, and Alma Kajeniene. 2019. "Position Statement Part Two: Maintaining Immune Health". figshare. <https://hdl.handle.net/2134/10586>.

This item was submitted to Loughborough's Institutional Repository (<https://dspace.lboro.ac.uk/>) by the author and is made available under the following Creative Commons Licence conditions.



CC creative commons
COMMONS DEED

Attribution-NonCommercial-NoDerivs 2.5

You are free:

- to copy, distribute, display, and perform the work

Under the following conditions:

BY: **Attribution.** You must attribute the work in the manner specified by the author or licensor.

Noncommercial. You may not use this work for commercial purposes.

No Derivative Works. You may not alter, transform, or build upon this work.

- For any reuse or distribution, you must make clear to others the license terms of this work.
- Any of these conditions can be waived if you get permission from the copyright holder.

Your fair use and other rights are in no way affected by the above.

This is a human-readable summary of the [Legal Code \(the full license\)](#).

[Disclaimer](#) 

For the full text of this licence, please go to:
<http://creativecommons.org/licenses/by-nc-nd/2.5/>

Position Statement

Part two: Maintaining immune health

Neil P. Walsh¹, Michael Gleeson², David B. Pyne³, David C. Nieman⁴, Firdaus S. Dhabhar⁵, Roy J. Shephard⁶, Samuel J. Oliver¹, Stéphane Bermon⁷, Alma Kajeniene⁸

¹ School of Sport, Health and Exercise Sciences, Bangor University, UK.

² School of Sport, Exercise and Health Sciences, Loughborough University, UK.

³ Department of Physiology, Australian Institute of Sport, Australia.

⁴ Human Performance Labs, North Carolina Research Campus and Appalachian State University, USA.

⁵ Department of Psychiatry and Behavioural Sciences and Stanford Institute for Immunity, Transplantation, and Infection, Stanford University, USA.

⁶ Faculty of Physical Education and Health, University of Toronto, Canada.

⁷ Monaco Institute of Sports Medicine and Surgery (IM₂S), Monaco.

⁸ Kaunas Sports Medicine Center and Kaunas University of Medicine, Lithuania.

CONSENSUS STATEMENT

The physical training undertaken by athletes is one of a set of lifestyle or behavioural factors that can influence immune function, health and ultimately exercise performance. Others factors including potential exposure to pathogens, health status, lifestyle behaviours, sleep and recovery, nutrition and psychosocial issues, need to be considered alongside the physical demands of an athlete's training programme.

The general consensus on managing training to maintain immune health is to start with a programme of low to moderate volume and intensity; employ a gradual and periodised increase in training volumes and loads; add variety to limit training monotony and stress; avoid excessively heavy training loads that could lead to exhaustion, illness or injury; include non-specific cross-training to offset staleness; ensure sufficient rest and recovery; and instigate a testing programme for identifying signs of performance deterioration and manifestations of physical stress. Inter-individual variability in immunocompetence, recovery, exercise capacity, non-training stress factors, and stress tolerance likely explains the different vulnerability of athletes to illness. Most athletes should be able to train with high loads provided their programme includes strategies devised to control the overall strain and stress. Athletes, coaches and medical personnel should be alert to periods of increased risk of illness (e.g. intensive training weeks, the taper period prior to competition, and during competition) and pay particular attention to recovery and nutritional strategies.

Correspondence:

Neil Walsh; email: n.walsh@bangor.ac.uk; telephone: +44 1248 383480

Although exercising in environmental extremes (heat, cold, altitude) may increase the stress response to acute exercise and elevate the extent of leukocyte trafficking it does not appear to have marked effects on immune function other than a depression of cell-mediated immunity when training at altitude. The available evidence does not support the contention that athletes training and competing in cold (or hot) conditions experience a greater reduction in immune function compared with thermoneutral conditions. Nevertheless, it remains unknown if athletes who regularly train and compete in cold conditions report more frequent, severe or longer-lasting infections. Research should identify whether the airway inflammation associated with breathing large volumes of cold dry air or polluted air impairs airway defences and whether athletes (and their physicians) wrongly interpret the sore throat symptoms that accompany exercising in cold or polluted air as an infection.

Elite athletes can benefit from immunonutritional support to bolster immunity during periods of physiological stress. Ensuring adequate energy, carbohydrate and protein intake and avoiding deficiencies of micronutrients are key to maintaining immune health. Evidence is accumulating that some nutritional supplements including flavonoids such as quercetin and *Lactobacillus* probiotics can augment some aspects of immune function and reduce illness rates in exercise-stressed athletes. Limited data are non-supportive or mixed for use of N-3 polyunsaturated fatty acids, β -glucans, bovine colostrums, ginseng, echinacea or megadoses of vitamin C by athletes.

Relatively short periods of total sleep deprivation in humans (up to 3 consecutive nights without sleep) do not influence the risk of infection, and the reported increase in natural killer cell activity with this duration of total sleep deprivation would seem to rule out the possibility of an “open-window” for respiratory infections. Very little is known about the effects of more prolonged sleep disruption and repeated sleep disturbances on immune function and infection incidence, although recent studies have highlighted the importance of sleep quantity (total duration of sleep per night) and quality (number of awakenings per night) to protect against the common cold in healthy adults.

Short- or long-term exercise can activate different components of a physiological stress response. Prolonged intense exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress. Psychological stress is likely additive to the effects of physical stress and whereas short exposures to both physical or psychological stress can have a beneficial effect on immune function, chronic exposure to stress exerts detrimental effects on immune function and health. However, regular moderate exercise could be an important factor in ameliorating the negative health effects of chronic stress via the optimization and maintenance of the survival-promoting physiological changes induced by the short-term or acute stress response. Further research on mechanisms mediating the salubrious effects of exercise, and on the relationship between exercise and the psychosocial stress-status of an individual, is likely to be helpful for more fully and widely harnessing the health benefits of exercise.

It is agreed by everyone that prevention of infection is always superior to treatment and this is particularly true in athletes residing in countries with limited medical facilities. Although there is no single method that completely eliminates the risk of contracting an infection, there are several effective ways of reducing the number of infectious episodes incurred over a given period. These means of reducing infection risk include appropriate management of training loads, use of appropriate recovery strategies, good personal hygiene, avoiding contact with large crowds, young children and sick people, good nutrition, getting adequate good quality sleep and limiting other life stresses to a minimum. Part two of the position statement includes sections on: training considerations (David Pyne); nutritional countermeasures to exercise-induced immune perturbations (David Nieman); effects of stress on immune function (Firdaus Dhabhar); sleep disruption and immune function (Roy Shephard); environmental extremes and the immune response to exercise (Neil Walsh and Samuel Oliver) and finally, prevention and treatment of common infections (Stéphane Bermon and Alma Kajeniene).

Key Words: exercise; sport; immune; leukocyte; pathogen; infection; training; overtraining; overreaching; adaptation; diet; supplement; stress; in vivo; sleep; environment; treatment; prevention

TRAINING CONSIDERATIONS

Background

There is considerable incentive for athletes, coaches, and teams to implement practical strategies that limit the risk of training-related perturbations in immune function. The physical training undertaken by athletes is one of a set of lifestyle or behavioural factors that can influence immune function, health and ultimately exercise performance. Other factors including health status, lifestyle behaviours, pathogen transmission, nutrition and psychosocial issues, need to be considered alongside the physical demands of an athlete's training programme. Guidelines on prescribing training to keep athletes healthy are sought-after in the sporting community.

The challenge of preparing guidelines for prescribing training in the absence of specific experimental studies has been acknowledged (8, 134). There are only a few training studies that have directly examined the relationship between training loads and patterns of illness in highly trained athletes, and the effectiveness of various training and lifestyle interventions – see reviews (85, 171) and the respiratory infections and exercise section in part one of this position statement. It is difficult to study elite athletes in their regular training environment especially during preparations for major competition. Experimental control of training, lifestyle and dietary practices, and other confounders such as time missed with injury can be problematic. Investigators have generally used moderately active individuals, often volunteers in graduate research programmes, as participants in exercise immunology studies. The predominance of short cross-sectional studies of the acute effects of exercise rather than long-term prospective studies of athletes in training over weeks, months or years is another issue (85). The limited number of experimental studies makes it difficult to develop definitive practical guidelines for athletes, coaches, clinicians and team officials.

To overcome the shortage of studies, clinicians and scientists working with athletes need to translate and apply selected findings of studies in related fields. Research areas including clinical immunology, nutritional immunology, sports medicine, exercise physiology, psychoneuroimmunology and sports psychology should yield useful insights. Moderate physical activity may enhance immune function and reduce infection incidence mainly in less fit subjects, and pre-event fitness status can also influence the risk of illness (185). However, results from studies involving sedentary or only moderately active individuals may not easily translate to highly trained athletes. Guidelines for maintaining good health (as discussed later in this part of the position statement) and training will also depend on the experience, skills and knowledge of coaches, athletes, clinicians and scientists.

In most sports it is accepted that there exists a dose-response relationship between training and performance (7). Athletes in endurance sports generally require high training volumes to develop the background necessary for success in high-level competition. Sudden increases in either training volume or intensity, or in combination, may place additional pressure on immune function. Post-exercise immune function dysfunction is most pronounced when the exercise is continuous, prolonged (>1.5 h), of moderate to high intensity (55–75% maximal O₂ uptake), and performed with minimal nutritional support (85) (as discussed in the following section). The risk of developing symptoms of non-functional overreaching (short-term decrements in performance capacity where the athlete is unable to recover fully after sufficient rest) or overtraining (long-term decrements that may take several weeks or months to resolve) (131) can be increased by monotonous training without alternating hard and easy training days, a lack of a complete rest day once per week, increasing loads when the total load is already high, and too many competitions (171). In terms of planning and monitoring, integrated indices of training loads in a multivariate model are likely to be more highly correlated with illness than individual factors such as training load, volume or intensity (72). An imbalance between training loads and recovery is also a major contributor to the onset of fatigue, overtraining and illness (141). A well planned recovery programme is essential if athletes are to stay healthy and be ready to perform at their best.

Consensus

The general consensus on managing training to maintain immune health is to start with a programme of low to moderate volume and intensity; employ a gradual and periodised increase in training volumes and loads; add variety to limit training monotony and stress; avoid excessive training distances that could lead to exhaustion, illness or injury (75); include non-specific cross training to offset staleness; ensure sufficient rest and recovery; and instigate a testing programme for identifying signs of performance deterioration and manifestations of physical stress (85, 171). Inter-individual variability in recovery, exercise capacity, non-training stress factors, and stress tolerance likely explains the differential vulnerability of athletes to illness (172). Most athletes should be able to train with high loads provided their programme includes strategies devised to control the overall strain and stress (Table 1). Athletes should be encouraged to undertake intensive training in

the knowledge that variations in performance and fatigue are symptoms to be expected and respected, and not necessarily problems to overcome (206). Athletes, coaches and medical personnel should be alert to these periods of increased risk of illness (e.g. intensive training weeks, the taper period prior to competition, and during competition) and pay particular attention to recovery and nutritional strategies (151).

Table 1. Suggested strategies for modifying training and recovery activities to limit the risk of training-induced impairments in immune health.

Training Descriptor	Comment
Frequency	Increase the frequency of shorter training sessions rather than enduring fewer but longer sessions.
Volume	Reduce the overall weekly training volume and/or volume of individual training sessions.
Intensity	Avoid prolonged intensive training sessions or activities. Employ shorter sharper (spike) sessions mixed with lower-intensity work.
Load (volume x intensity)	Systematically manipulate the training volume and/or intensity to manage the degree of training load.
Load increments	Reduce the size of increments in frequency, volume, intensity and load of training e.g. increases of 5-10% per week rather than 15-30%.
Load sequencing – weekly microcycle	Undertake two or three easy-moderate training sessions after each high intensity session rather than the traditional pattern of simply alternating hard – easy sessions.
Load sequencing – multi-week macrocycle	Plan an easier recovery or adaptation week every 2 nd or 3 rd week rather than using longer 3 – 6 week cycles with increasing loads.
Recovery – session/week	Implement recovery activities immediately after the most intensive or exhaustive training sessions.
Recovery - season	Permit athletes at heightened risk of illness a longer period of passive and active recovery (several weeks) after completion of a season or major competition.

Controversies

Studies are often limited by: using participants with moderate fitness rather than highly trained athletes; poor description or omission of training details; absence of a suitable control group; and, a modest sample size that reduces statistical power. Changes in immune function after exercise are often transient and small in magnitude (106). Although a substantial amount of research has been conduct-

ed, several important questions remain unanswered. Are different guidelines needed for (previously) sedentary individuals, moderately active and highly-trained athletes? How much exercise or training is too much? Should guidelines be general or sports-specific? Which are the best clinical signs and symptoms of overtraining or impending illness (37)? Which diagnostic tests are useful in monitoring immune status (3)? A section in part one of this position statement highlights the strengths and weaknesses of various methods used to assess immune status and the challenges associated with interpreting the clinical significance of results from these tests. What is the relative effectiveness of other tactics such as nutritional countermeasures (see section that follows), sleep (see sleep disruption section in this part of the position statement) and recovery interventions (111, 181)? Given limitations in time, money and resources, coaches are often unable to implement every strategy and a process of prioritising training, recovery and behavioural interventions is necessary.

Future directions

A systematic programme of clinical and experimentally controlled research is needed to formulate evidence-based training guidelines or recommendations to maintain immune health in athletes. Studies are needed with both recreational and elite athletes. Modelling studies of responses to physical training (16) should shed light on the relative influence of training volume, intensity and loads on the immune system. Molecular biology is already yielding some insights for identifying athletes more at risk of illness (36) and should further our understanding of how the immune system responds to various types of training. For a more detailed account of a role for “omics” in exercise immunology, readers are directed to the “omics” section in part one of this position statement. Studies should also address how individual variations in the risk of illness relate to training (172). A combination of field-based diagnostic technology, experimental research, insightful analytical approaches (99), and the clinical/practical experience of physicians and athletes/coaches is likely to be the most effective approach for managing the training and immunity of athletes.

NUTRITIONAL COUNTERMEASURES TO EXERCISE-INDUCED IMMUNE PERTURBATIONS

Background

Nutrition, exercise, mental stress, and other lifestyle factors influence immune function and the risk of certain types of infection such as upper respiratory tract infections (URTI). In contrast to moderate physical activity, prolonged and intensive exertion by athletes causes numerous changes in immunity in multiple body compartments and an increased risk of URTI (150). Elite athletes must train intensively to compete at the highest levels and they can benefit from immunonutritional support to bolster immunity during periods of physiological stress (151). Non-athletes engaging in moderate physical activity programmes do not require nutritional supplements, and can obtain all needed nutrients from a healthy and balanced diet.

Each acute bout of heavy exertion leads to physiological stress and transient but clinically significant changes in immunity and host pathogen defence, with elevations in stress hormones, pro- and anti-inflammatory cytokines, and reactive oxygen species (85, 148). Natural killer cell activity, various measures of T and B cell function, upper airway neutrophil function, salivary IgA concentration, granulocyte oxidative burst activity, skin delayed-type hypersensitivity response, and major histocompatibility complex (MHC) II expression in macrophages are suppressed for at least several hours during recovery from prolonged, intense endurance exercise (as discussed in detail in part one of this position statement). These immune changes occur in several compartments of the immune system and body (e.g., the skin, upper respiratory tract mucosal tissue, lung, blood, muscle, and peritoneal cavity).

During the “open window” of impaired immunity (which may last between three and 72 hours, depending on the immune measure), pathogen resistance is lowered, increasing the risk of subclinical and clinical infection (150). Epidemiological studies indicate that athletes engaging in marathon and ultramarathon race events and/or very heavy training are at increased risk of URTI (150) (as described in the section on respiratory infections and exercise in part one of this position statement). Together, these epidemiological and exercise immunology studies support the viewpoint that heavy exercise workloads increase URTI risk through altered immune function.

Consensus

Various nutritional agents have been tested for their capacity to attenuate immune changes and inflammation following intensive exercise, thus lowering the magnitude of physiologic stress and URTI risk. This strategy is similar to the immunonutritional support provided to patients recovering from trauma and surgery, and to the frail elderly (151). Some question the value of using immunonutritional support for athletes because blocking the transient immune changes, oxidative stress, and inflammation following heavy exertion interferes with important signaling mechanisms for training adaptations (88, 182). Another viewpoint is that efficacious nutritional supplements only partially block exercise-induced immune dysfunction, inflammation, and oxidative stress, analogous to the beneficial use of ice packs to reduce swelling following mild injuries (209, 225). This debate will hopefully spur additional research on the overall value of immunonutritional support for athletes.

Table 2 summarizes published findings on a variety of supplements, with a focus on those investigated by several different research groups on human athletes. Results for most nutritional supplements tested as countermeasures to exercise-induced inflammation, oxidative stress, and immune dysfunction following heavy exertion have been disappointing. Early studies focused on large dose vitamin and/or mineral supplements, and no consistent countermeasure benefit has been observed (41, 42, 87, 157, 158). A series of studies dating back to the mid-1990s have shown that carbohydrate supplement ingestion before and/or during prolonged exercise attenuates increases in blood neutrophil and monocyte counts, stress hormones, and anti-inflammatory cytokines such as interleukin (IL)-6, IL-10, and IL-1ra, but has little effect on decrements in salivary IgA output and T cell

and natural killer cell function (26, 41, 85, 149, 153). Thus, carbohydrate ingestion during heavy exercise has emerged as an effective but partial countermeasure to immune dysfunction, with favourable effects on measures related to stress hormones and inflammation, but with limited effects on markers of innate or adaptive immunity. Glutamine and amino acid supplements are not recommended because the best studies show no benefits when compared to placebo, perhaps due to abundant storage pools within the body that cannot be sufficiently depleted by exercise (85, 86, 113).

Controversies and future directions

The growing realization that extra vitamins, minerals, and amino acids do not provide countermeasure benefits for healthy and well-fed athletes during heavy train-

Table 2. Summary of rationale and findings for selected immunonutritional supplements.

Immunonutritional Supplement	Proposed Rationale	Recommendation Based On Current Evidence
Vitamin E	Quenches exercise-induced reactive oxygen species (ROS) and augments immunity	Not recommended; may be pro-oxidative with heavy exertion
Vitamin C	Quenches ROS and augments immunity	Not recommended; not consistently different from placebo
Multiple vitamins and minerals	Work together to quench ROS and reduce inflammation	Not recommended; not different from placebo; balanced diet is sufficient
Glutamine	Important immune cell energy substrate that is lowered with prolonged exercise	Not recommended; body stores exceed exercise-lowering effects
Branched chain amino acids (BCAAs)	BCAAs (valine, isoleucine, and leucine) are the major nitrogen source for glutamine synthesis in muscle	Not recommended; data inconclusive, and rationale based on glutamine is faulty
Carbohydrate	Maintains blood glucose during exercise, lowers stress hormones, and thus counters immune dysfunction	Recommended; up to 60 g per hour of heavy exertion helps dampen immune inflammatory responses, but not immune dysfunction
Bovine colostrums	Mix of immune, growth, and hormonal factors improve immune function and the neuroendocrine system, and lower illness risk	Jury still out, with mixed results
Probiotics	Improve intestinal microbial flora, and thereby enhance gut and systemic immune function	Jury still out, with mixed results
N-3 PUFAs (fish oil)	Exerts anti-inflammatory effects post-exercise	Not recommended; no different from placebo
β -glucan	Receptors found on immune cells, and animal data show supplementation improves innate immunity and reduces infection rates	Not recommended; human study with athletes showed no benefits
Herbal supplements (e.g., Ginseng, Echinacea)	Contain bioactive molecules that augment immunity and counter infection	Not recommended; humans studies do not show consistent support within an athletic context
Quercetin	<i>In vitro</i> studies show strong anti-inflammatory, anti-oxidative, and anti-pathogenic effects. Animal data indicate increase in mitochondrial biogenesis and endurance performance, reduction in illness	Recommended, especially when mixed with other flavonoids and nutrients; human studies show strong reduction in illness rates during heavy training and mild stimulation of mitochondrial biogenesis and endurance performance in untrained subjects; anti-inflammatory and anti-oxidative effects when mixed with green tea extract and fish oil

ing has shifted the focus to other types of nutritional components. *In vitro*/cell culture, animal, and epidemiological research indicate that advanced supplements such as probiotics, bovine colostrum, β -glucan, flavonoids and polyphenols such as quercetin, resveratrol, curcumin, and epigallocatechin-3-gallate (EGCG), N-3 polyunsaturated fatty acids (N-3 PUFAs or fish oil), herbal supplements, and unique plant extracts (e.g., green tea extract, blackcurrant extract, tomato extract with lycopene, anthocyanin-rich extract from bilberry, polyphenol-rich pomegranate fruit extract), warrant well-conducted studies with athletes to determine if they are effective countermeasures to exercise-induced immune dysfunction and risk of URTI (6, 124, 144, 152, 155). Limited data are non-supportive or mixed for use of N-3 PUFAs (156), probiotics (221), bovine colostrums (202), ginseng (196), or Echinacea (196) by athletes.

An evolving hypothesis is that the immune system is so diverse that a mixture of these advanced supplements, perhaps within a carbohydrate beverage, will probably perform better than one supplement by itself (6, 156). The “pharma” approach of using large doses of a single molecule is not as effective as a “cocktail” strategy for nutritional supplements.

A secondary hypothesis is that the primary immune target of nutrient supplements should be the nonspecific, innate arm of the immune system to enhance immunosurveillance against a wide variety of pathogens in athletes. If the nutritional supplement improves natural killer cell, macrophage, and granulocyte function before and/or after heavy exertion, then risk of infection is more effectively countered than when the target is the slower moving adaptive immune components (154, 155, 159).

Some nutritional supplements exert impressive effects *in vitro* and in animal-based models, but then fail when studied under double-blinded, placebo-controlled conditions in human athletes. A prime example is β -glucan, a polysaccharide found in the bran of oat and barley cereal grains, the cell wall of baker's yeast, certain types of fungi, and many kinds of mushrooms. Rodent studies indicate that oat β -glucan supplements offset the increased risk of infection associated with exercise stress through augmentation of macrophage and neutrophil function, but these results were not upheld in a study of human cyclists (144, 159).

The physiologic effects of dietary polyphenols such as quercetin, EGCG, curcumin, lycopene, resveratrol, luteolin, and tiliroside are of great current interest to exercise immunologists due to their antioxidative, anti-inflammatory, anti-pathogenic, cardioprotective, anticarcinogenic, and mitochondrial stimulatory activities (151, 152). Several recent quercetin supplementation studies in human athletes have focused on potential influences as a countermeasure to post-exercise inflammation, oxidative stress, and immune dysfunction, in improving endurance performance, and in reducing illness rates following periods of physiologic stress (162). When quercetin supplementation is combined with other polyphenols and food components such as green tea extract, isoquercetin, and fish oil, a substantial reduction in exercise-induced inflammation and oxidative stress occurs in athletes, with chronic augmentation of innate immune function (155). Quercetin

supplementation (1,000 mg/day for two to three weeks) also reduces illness rates in exercise-stressed athletes (154). Animal studies support a role for quercetin as an exercise mimetic for mitochondrial biogenesis, and recent data in untrained human subjects indicate modest enhancement in skeletal muscle mitochondrial density and endurance performance (162). Quercetin has multiple bioactive effects that support athletic endeavour, and research continues to define optimal dosing regimens and adjuvants that amplify these influences (152, 162).

Summary remarks

Endurance athletes must train hard for competition and are interested in strategies to keep their immune systems robust and to avoid illness despite the physiological stress they experience. The ultimate goal is to provide athletes with a sports drink or supplement bar containing carbohydrate and a cocktail of advanced supplements that will lower infection risk, exert significant and measurable influences on their innate immune systems, and attenuate exercise-induced oxidative stress and inflammation. The athlete can combine this strategy with other approaches that help maintain immunity and health.

EFFECTS OF STRESS ON IMMUNE FUNCTION – IMPLICATIONS FOR THE EFFECTS OF EXERCISE ON HEALTH

Understanding the psychological, biological, and health effects of exercise in the context of stress and stress physiology is important for several reasons: **First**, the process of exercising induces a physiological stress response and increases circulating concentrations of noradrenaline (norepinephrine), adrenaline (epinephrine), cortisol, and other stress-related factors including cytokines (93, 166). An acute or short-term stress response can have beneficial effects. However, intense prolonged exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress (85). **Secondly**, exercise, when performed under the appropriate conditions, could be a factor in ameliorating the deleterious health effects of chronic stress and increased allostatic load (viz. the physiological cost that results from ongoing adaptive efforts to maintain homeostasis in response to stressors) (128, 223). A novel and important mechanism mediating the salubrious effects of exercise could be through its optimization of the beneficial, survival-promoting effects of the short-term or acute stress response (44). **Thirdly**, the psychosocial stress status of an individual may be important for determining whether a given exercise regimen is salubrious or harmful.

Although the word “stress” generally has negative connotations, stress is a familiar and ubiquitous aspect of life, being a stimulant for some, and a burden for many. Numerous definitions have been proposed for stress, each focusing on aspects of an internal or external challenge/stimulus, on stimulus perception, or on a physiological response to the stimulus (190). An integrated definition proposes that *stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physio-*

logical fight or flight systems in the body (stress response) (46). The stress response induces the release of the principal stress hormones (noradrenaline, adrenaline, and cortisol/corticosterone) as well as a myriad of neurotransmitters, hormones, peptides, cytokines and other factors. Since virtually every cell in the body expresses receptors for one or more of these factors, all cells and tissues can receive biological signals that alert them regarding the presence of a stressor. The only way that a stressor can affect brain, body, and health is by inducing biological changes through a physiological stress response.

Although stress can be harmful when it is chronic or long lasting (43, 82, 128), a short-term fight-or-flight stress response has salubrious adaptive effects (44, 45, 50). Therefore, the duration of stress is an important factor in determining its effects on immune function and health. *Acute stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months (46). Dysregulation of the circadian cortisol rhythm is one marker that is related to the deleterious effects of chronic stress (46, 192). It is important to note that there are significant individual differences in stress perception, processing, and coping that mediate differences in the intensity and duration of a physiological response to a given stressor (32, 49, 50, 92). It is known that chronic or long-term stressors can have adverse effects on health, many of which may be mediated through immune mechanisms. However, it is important to recognize that a psycho-physiological stress response is one of nature's fundamental survival mechanisms (44). Without a fight-or-flight stress response, a lion has no chance of catching a gazelle, just as the gazelle has no chance of escape. During such short-term stress responses observed in nature, physiological systems act in synchrony to enable survival. Therefore, it was hypothesized that just as the stress response prepares the cardiovascular, musculoskeletal and neuroendocrine systems for fight or flight, under certain conditions, stress may also prepare the immune system for challenges (e.g. wounding or infection) that may be imposed by a stressor (e.g. predator or surgical procedure) (48, 50). Short duration stressors induce a redistribution of immune cells within the body and immune function is significantly enhanced in organs like the skin to which leukocytes traffic during acute stress. Studies have also identified mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function through which acute stressors may enhance innate as well as adaptive immunity.

Effects of acute versus chronic stress on immune cell distribution

Effective immunoprotection requires rapid redistribution and recruitment of leukocytes into sites of surgery, wounding, infection, or vaccination. Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood (9, 48, 52, 69, 194). An acute stress-induced redistribution of leukocytes within different body compartments is perhaps one of the most under-appreciated effects of stress (51). Acute stress induces an initial increase followed by a decrease in blood mononuclear leukocyte numbers (48, 187). Stress conditions that result in activation of the sympathetic nervous system induce an increase in circulating leukocyte numbers (both mononuclear and polymorphonuclear cells). These conditions

may occur during the beginning of a stress response, very short duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the hypothalamic-pituitary-adrenal axis induce a decrease in circulating mononuclear cell (viz. lymphocyte and monocyte) numbers. These conditions often occur during the later stages of a stress response, exposure to long duration acute stressors (order of hours), or during severe stress or prolonged and/or intense exercise. An elegant example comes from Schedlowski et al. who measured changes in blood T cell and natural killer (NK) cell numbers as well as plasma catecholamine and cortisol levels in parachutists 2 hours before, immediately after, and 1 hour after a jump (193). Results showed a significant increase in T cell and NK cell numbers immediately (minutes) after the jump that was followed by a significant decrease an hour later. An early increase in plasma catecholamines preceded early increases in lymphocyte numbers, whereas the more delayed rise in plasma cortisol preceded the later decrease in lymphocyte numbers (193). Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in blood NK cell numbers, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte “functional activity.” A similar profile of changes in lymphocyte and monocyte numbers has been characterized in patients experiencing surgery stress and has been related to successful postsurgical recovery (187).

Thus, an acute stress response induces biphasic changes in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress, or exercise, the body’s “soldiers” (leukocytes), exit their “barracks” (spleen, lung, marginated pool and other organs) and enter the “boulevards” (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, the effect being most prominent for NK cells and polymorphonuclear granulocytes. As the stress response continues, leukocytes exit the blood and take position at potential “battle stations” (such as the skin, lung, gastro-intestinal and urinary-genital tracts, mucosal surfaces, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor (45, 48, 50). Such a redistribution of leukocytes results in a decrease in blood mononuclear leukocyte numbers. Thus, acute stress induces a redistribution of several leukocyte subsets from the barracks, through the boulevards, and to potential battle stations within the body. It is important to note that in addition to leukocyte redistribution, acute stressors also enhance immune function through additional mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function (215).

In contrast to acute stress, chronic stress induces deleterious changes in leukocyte numbers. First, exposure to chronic stress results in lower resting-state immune cell numbers that would imply a diminished capacity to mount immune responses (46). Secondly, exposure to chronic stress decreases the magnitude of acute stress-induced immune cell redistribution (46). In effect, chronic stress reduces the number of “soldiers” in the body’s army, and reduces the capacity of the remaining leukocytes to mobilize from “boulevards to battle stations” during a fight-or-flight response.

Acute stress psychophysiology as an endogenous adjuvant

It has been proposed that a psycho-physiological stress response is nature's fundamental survival mechanism that could be harnessed therapeutically to augment immune function during vaccination, wound healing or infection (54). These adjuvant-like immuno-enhancing effects of acute stress may have evolved because many stressful situations (aggression, accident) result in immune activation (wounding, infection) and vice versa. Interestingly, in modern times, many medical procedures involving immune activation (vaccination, surgery) also induce a stress response. In keeping with the above hypothesis, studies have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the acute stress of surgery, also show significantly enhanced recovery (187). Similarly, an elegant series of adjuvant effects of acute mental stress or exercise can enhance vaccine-induced humoral and cell-mediated immunity in human subjects (60, 62) (for review see: (61)). Although acute stress- (or exercise-) induced immunoenhancement may serve to increase immunoprotection during vaccination, infection, or wounding, it may also exacerbate immunopathology if the enhanced immune response is directed against innocuous or self-antigens, or becomes dysregulated following prolonged activation as seen during chronic stress.

Numerous studies have been conducted to elucidate mechanisms mediating acute stress-induced enhancement of immune function. Viswanathan and Dhabhar (216) used a subcutaneously implanted surgical sponge model to elucidate the effects of stress on the kinetics, magnitude, subpopulation, and chemoattractant specificity of leukocyte trafficking to a site of immune activation or surgery. Results showed that an acute stress-induced increase in leukocyte trafficking coupled with specific chemokines and cytokines released during the initiation cascades of inflammation can alter the course of different (innate versus adaptive, early versus late, acute versus chronic) protective or pathological immune responses (216). Since the skin is one target organ to which leukocytes traffic during stress, studies were conducted to examine whether skin immunity is enhanced when immune activation/antigen exposure occurs following a stressful experience. Studies showed that acute stress experienced at the time of novel or primary antigen exposure results in a significant enhancement of the ensuing skin immune response (54). Compared to controls, mice restrained for 2.5 hours before primary immunization with keyhole limpet haemocyanin (KLH) showed a significantly enhanced immune response when re-exposed to KLH nine months later. This immunoenhancement was mediated by an increase in numbers of memory and effector helper T cells in sentinel lymph nodes at the time of primary immunization. Further analyses showed that the early stress-induced increase in T cell memory was followed by a robust increase in infiltrating lymphocyte and macrophage numbers months later at a novel site of antigen re-exposure. Enhanced leukocyte infiltration was driven by increased levels of the Type-1 cytokines, interleukin (IL)-2, interferon- γ (IFN- γ) and tumour necrosis factor- α observed at the site of antigen re-exposure. Other investigators have similarly reported stress-induced enhancement of Type-1 cytokine driven cell-mediated immunity (13, 189, 222) and Type-2 cytokine driven humoral immunity (Type-2 cytokines include for example IL-4 and IL-10) (30, 222). Viswanathan et al. (215)

further showed that important interactive components of innate (dendritic cells and macrophages) and adaptive (surveillance T cells) immunity are mediators of the stress-induced enhancement of a primary immune response. Although much work remains to be done, to identify further molecular, cellular, and physiological mechanisms, studies have also identified endocrine and immune mediators of these effects showing that corticosterone and adrenaline are important systemic mediators and IFN- γ is an important local mediator of immunoenhancement induced by acute stress (47, 53).

Effects of chronic stress on immune function

The immuno-suppressive and dysregulatory effects of chronic stress have been reviewed extensively (2, 33, 64, 82, 101). Chronic stress is known to dysregulate immune responses (82) by altering the cytokine balance from Type-1 to Type-2 cytokine-driven responses (83) and accelerating immunosenescence (65), and to suppress immunity by decreasing numbers (46), trafficking (46), and function of protective immune cells while increasing regulatory/suppressor T cells (192). Through these effects, chronic stressors are thought to exacerbate pro-inflammatory diseases and increase susceptibility to infections and cancer (44). Exercise and cancer is discussed in detail in part one of the position statement.

Importance of relationship between stress and exercise

Understanding the psychological, physiological, and health effects of exercise in the context of stress and stress physiology is critical for several important reasons: First, the process of exercising invariably induces a physiological stress response and results in higher circulating concentrations of noradrenaline, adrenaline, cortisol, other stress-related factors, and even cytokines (93, 166). Exercise-induced pain, exhaustion, or injury could also induce psychological stress. Moreover, intense prolonged exercise (85) or exercising under extreme environmental conditions (218), may lead to chronic exposure to stress hormones which may make the individual susceptible to the deleterious health effects of chronic stress. Thus, short- or long-term exercise can activate different components of a physiological stress response. The relative concentrations of exercise-induced stress-related hormones, cytokines and other factors induced in the body are likely to depend on a host of factors including the genetic makeup, psycho-physiological health, and fitness of the individual, as well as the type, intensity, duration, and chronicity of exercise. Since immune cells and organs have receptors for, and respond to, the myriad of stress-related physiological factors that are released during exercise, many effects of exercise on the immune system are likely to be mediated by these factors. Secondly, when performed under appropriate conditions, exercise could be a significant factor in ameliorating the deleterious health effects of chronic stress (169, 223). The type, intensity, duration and frequency of exercise and the conditions under which it should be performed in order to effectively reduce the stress burden of different individuals need to be understood and defined clearly. It is likely that one would need different strokes for different folks, i.e., running could serve as a “de-stressor” for some while others would benefit from aerobics, swimming, dancing or yoga. The most desirable results are likely to arise when the physical as well as psychosocial aspects of the exercise are matched with factors such as the fitness, capability, temperament, personality, etc., of the exercis-

ing individual. **Thirdly**, the psychosocial stress status of an individual may affect the relationship between exercise and health positively or negatively. For example, a chronically stressed individual may react differently to the effects of exercise, and may have lower thresholds for exercise-induced wear and tear compared to someone who is not chronically stressed. This is an area of research that is ripe for investigation and is relevant for the well-being of recreational and elite athletes, as well as armed forces and other professions for whom exercise is a critical aspect of training and job-performance.

Conclusion

Exercise and stress are intricately linked. Exercise induces a physiological stress response. Intense and/or prolonged exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress. However, moderate exercise could be an important factor in ameliorating the negative health effects of chronic stress. Moreover, the stress status of an individual could in turn affect the degree and extent of the salubrious effects of exercise. One important mechanism mediating the salubrious effects of exercise could be the optimization and maintenance of the survival-promoting physiological changes induced by the short-term or acute stress response. Further research into the effects of exercise and stress on immune function and health, on mechanisms mediating the salubrious effects of exercise, and on the relationship between exercise and the psychosocial stress-status of an individual, is likely to be helpful for harnessing the health benefits of exercise more fully and widely.

SLEEP DISRUPTION AND IMMUNE FUNCTION

Background

There seems quite a close interaction between immune function and sleep. In laboratory animals the intracerebral infusion of interleukin (IL)-1, interferon- γ (IFN- γ) or tumour necrosis factor- α (TNF- α) tends to induce sleep (112, 164), and studies of circulating cytokine levels in patients with excessive daytime sleepiness suggest that these same factors influence human sleep patterns (91, 214). Associations have also been observed between abnormalities of immune function and various forms of sleep disruption of interest to the exercise scientist. Issues include sleep deprivation, shift work, and disturbances of the circadian rhythm associated with global travel. However, it has been difficult to determine whether the observed changes in immune responses reflect a disturbance of sleep per se, disturbances of the circadian periodicity of hormone secretions (114, 145, 213), a general stress response, or a cognitive reaction to loss of sleep.

The following is a brief review of the impact of various types of sleep disturbance upon immune responses, noting the practical significance for the physically active individual.

Sleep deprivation

Sleep deprivation may be acute (for example, because of the anxiety associated with international competition, or the demands of extended military combat (20)), or chronic (due to pain, or the obstructed breathing associated with severe obesity or airway congestion due to respiratory infection). Although abnormalities of immune function have been described in these various situations, they reflect in part such factors as overall anxiety, very prolonged exercise, and a shortage or excess of food rather than a direct influence of sleep deprivation upon the immune system.

Animal studies have failed to demonstrate consistent immunological responses, perhaps because of problems in enforcing wakefulness in rats and mice. In laboratory studies of humans, some authors have noted alterations of immune function after 4-5 hours of sleep disturbance, but others have not seen changes unless participants remained awake for several days. One study found that keeping healthy volunteers awake between 22:00 and 03:00 led to decreases in both total natural killer (NK) cell activity and activity per NK cell, total lymphokine activated killer cell activity and activity per precursor cell (CD16+56+ cells and CD25+ cells), together with a decrease in concanavalin-stimulated IL-2 production (100). After a night of recovery sleep, NK cell activity was restored, but IL-2 levels remained depressed. By using actigraphy to monitor sleep, a recent study showed decreased NK cell mobilization in response to a cognitive stress test in healthy women who had experienced disrupted sleep (224). Indeed, wrist-mounted actigraph movement monitors may present a simple and inexpensive method to monitor sleep quantity and quality in athletes and soldiers. Sleep deprivation from 23:00 to 03:00 has also been shown to induce markers of inflammation, particularly in women; this is thought to be secondary to an activation of nuclear factor-kappa B, and an up-regulation of pro-inflammatory genes (103). In consequence, increases in lipopolysaccharide-stimulated production of IL-6 and TNF- α have been observed (102), together with increased levels of C-reactive protein (132). CD4+, CD16+, CD56+ and CD57+ lymphocyte counts were decreased after one night without sleep (57), in a manner reminiscent of exposure to other forms of stress (166). More prolonged sleep deprivation leads to increases in leukocyte, granulocyte and monocyte counts and the proportion of lymphocytes in the S phase of the cell cycle (57), with enhanced NK cell activity, interferon production and IL-1 and IL-2 like activity, and increased levels of C-reactive protein (57, 132, 165). However, some authors have found that the increase of NK cell activity is a relatively late phenomenon, seen after 64 h (57) but not 40 h of sleep deprivation (138). Recovery of the various immune parameters follows a similar pattern to the restoration of neuro-behavioural function, suggesting a relationship between immunological change and biological pressures to sleep.

Laboratory studies have also shown small decrements in parameters such as maximal oxygen intake (39) and endurance exercise performance (163) following one or more nights without sleep. One practical consequence is that an individual who attempts to maintain a given submaximal exercise intensity must use a larger fraction of maximal aerobic power, thereby potentially exaggerating normal immune responses to vigorous exercise.

Shift work

Shift work is of two main types- an 8-h rotating shift (which requires repeated displacements of the individual's circadian rhythm), and prolonged periods of night work (which increase a person's total exposure to light, often with disruptions of normal social life). Adverse effects seem linked mainly to prolonged periods of night work (40). Such employment is associated with an increased risk of breast, prostate and colon cancers (34, 40). Plainly, the socio-economic, demographic, dietary and lifestyle characteristics of shift workers could contribute to this risk. Exposure to light during the night hours decreases body concentrations of melatonin, thus stimulating the hypothalamic-pituitary-gonadal axis, and causing an increased production of testosterone and/or oestrogen (95, 207). Other investigators have postulated that prolonged night work alters the balance of cytokines that regulate tumour growth. In their view, a chronic decrease in NK cells and cytotoxic, tumour-infiltrating lymphocytes leads to a decreased production of tumour inhibiting cytokines (IL-1, IL-2, IFN- γ and TNF- α) and an increased production of tumour stimulating cytokines such as IL-10 (12, 24, 56, 123).

Disturbances of circadian rhythm

Athletes need to adjust their circadian rhythms as a consequence of latitudinal travel. The normal, free-running cycle has a length of 25-27 h. Disturbances are thus greater for an eastward displacement of 6 h (where the circadian clock must be adjusted by moving 18 h forward) than for a corresponding westward journey (where the circadian balance is restored by a 6-h shift). Various determinants of physical performance show a circadian fluctuation (198), and such characteristics may be less than optimal during the daytime until adjustment is complete. However, for many athletes the temporary disturbance of cognitive function is more important than any deterioration of physical performance. Current attempts to speed circadian adjustments are based on pre-travel exposure to bright light at the new hour of waking, immediate adoption of the new schedule of meals and exercise on arrival, and (for some physicians) the ingestion of melatonin (73). Given the known interactions between cytokines and sleepiness, there seems scope for future studies that attempt to speed circadian adaptations by manipulating cytokine levels.

The normal circadian variation of immune responses reflects parallel changes in hormone secretion (213). Total circulating lymphocytes present essentially a mirror image of plasma cortisol concentrations, peaking around 20:00-21:00 when cortisol is at its nadir. Most authors also agree that circulating counts for individual leukocyte subsets are highest during sleep, although the timing of peak concentrations is disputed. Haus et al. (96) and Ritchie et al. (183) reported increased eosinophil, monocyte, lymphocyte, T and B cell counts between 24:00 and 02:00. Others also found the largest numbers of B and NK cells in the early morning (70, 80). On the other hand, Abo et al. (1) and Bertouch et al. (10) found the acrophase for B cells in the evening, with the T cell and the CD4+/CD8+ ratios conforming to a similar pattern (70, 71, 109). Plasma IL-6 concentrations rise with the onset of sleep (176). Plasma IL-1 concentrations peak around midnight, followed by a peaking of IL-2 and a decline of NK cell activity, these various changes apparent-

ly being linked to the onset of slow-wave sleep. Responsiveness to pokeweed mitogen but not phytohaemagglutinin is increased during the sleeping hours (136, 137, 139). The maximum stimulation of cytolytic activity by IFN- γ is seen in the early morning, but the inhibitory effect of cortisol peaks at night; moreover, oral melatonin given around 18:00 augments the response to IFN- γ (79). There are also circadian variations in serum immunoglobulin concentrations (178) and the *in vitro* production of cytokines in whole blood (98, 168).

Clinical significance and future directions

Stimulation of inflammatory processes in those experiencing chronic sleep disruption may increase the risk of chronic disorders such as atherosclerosis, diabetes mellitus, Crohn's disease, and rheumatoid arthritis (208). Suggestions that immune disturbances increase the risk of cancer in shift workers also merit further exploration.

Sleep deprivation appears to reduce the antibody response to viruses in experimental animals and very prolonged periods of total sleep deprivation (typically about 20 consecutive days without sleep) result in lethal bloodstream infection and mortality in animals (21, 67, 211). However, much shorter periods of total sleep deprivation in humans (e.g. 3 consecutive nights without sleep) do not seem to influence the risk of infection, and the reported increase in NK cell activity with this duration of total sleep deprivation (57) would seem to rule out the possibility of an "open-window" for respiratory infections (147).

There is a pressing need to study whether disturbances to sleep quantity (total duration of sleep per night) or quality (number of awakenings per night) may have an adverse effect on immune health of the athlete or soldier. One recent study showed little effect of one night of total sleep deprivation on selected immune indices at rest and after exercise (181). However, very little is known about the effects of more prolonged sleep disruption or repeated sleep disturbances on immune function and infection incidence. One recent landmark study, albeit in healthy adults, showed that those who self-reported poor sleep quantity and/or quality exhibited increased symptoms of the common cold after intra-nasal inoculation with rhinovirus (31). Adults who slept for less than 7 h per night were almost 3-times more likely to develop symptoms of the common cold than those who slept more than 8 h per night. These findings highlight the importance of sleep quantity and quality in protecting humans against upper respiratory tract infections. Athlete and military support staff should consider monitoring sleep quantity and quality using a small, inexpensive and non-invasive movement sensor such as an actigraph. The utility of pharmacological and non-pharmacological interventions to improve sleep quantity and/or quality in those who frequently experience sleep disruption should be investigated alongside objective measures of immune status and infection incidence.

ENVIRONMENTAL EXTREMES AND THE IMMUNE RESPONSE TO EXERCISE

Background

Athletes, military personnel, mountaineers and those in physically demanding occupations are often required to reside in, or to perform vigorous physical activity in, adverse environmental conditions. Potential adverse conditions include extremes of heat and humidity, cold, high altitude and air pollutants. Lay people commonly believe that a hot bath or sauna can have therapeutic effects for all manner of ailments and that getting cold and wet increases the incidence of the common cold. Leading exercise immunologists have suggested that physical activity performed in stressful environments poses a greater than normal threat to immune function (199, 201), but this remains controversial (218).

This section summarises what we do and do not know about the immune response to exercise in environmental extremes, outlining some controversies and directions for future research. For a comprehensive review, readers are directed elsewhere (218).

Heat stress and immune function

Consensus

Exercising in hot conditions in which core temperature rises by $\geq 1^{\circ}\text{C}$ compared with thermoneutral conditions (where core temperature rise is $< 1^{\circ}\text{C}$) augments anticipated increases in circulating stress hormones including catecholamines and cytokines, with associated elevations in circulating leukocyte counts (38, 180). Controlled studies that have clamped the rise in core temperature by undertaking moderate intensity endurance exercise in cool water demonstrate a significant contribution of the rise in core temperature to the development of the leukocytosis and cytokinaemia of exercise (38, 180). However, with the exception of a reduction in stimulated lymphocyte responses after exercise in the heat (197), and in exertional heat illness (EHI) patients (core temperature $> 40^{\circ}\text{C}$) (59), laboratory studies show a limited effect of exercise in the heat on: neutrophil function, monocyte function, natural killer cell activity (NKCA) and mucosal immunity (116-118, 129, 135, 205). Therefore, most of the available evidence does not support the contention that exercising in the heat poses a greater threat to immune function compared with thermoneutral conditions. It is also worth mentioning that individuals exercising in the heat tend to fatigue sooner (compared with performing the same exercise in thermoneutral conditions), so that their exposure to exercise stress in the heat tends to be self-limiting (89).

Controversies and future directions

The findings from tightly restricted laboratory studies that have evoked only modest increases in core temperature (peak $< 39^{\circ}\text{C}$) become somewhat redundant when one considers that core temperature often exceeds 40°C in athletes and soldiers whilst exercising in the heat (59, 184). Although field studies provide the opportunity to investigate the effects of severe heat stress on immune function, these studies often lack adequate experimental control. Somewhat surprisingly, clinically significant outcomes such as *in vivo* immune responses and infection

incidence have not been compared between athletes and soldiers training in hot and humid conditions and those training in thermoneutral conditions. In this regard, the next best evidence we have comes from studies showing that whole-body heating with saunas reduces upper respiratory tract infection (URTI) incidence (66) and hot water immersion improves clinical outcomes for cancer patients (105).

Without doubt the most exciting ongoing controversy in this sub-discipline of exercise-immunology centres on whether the immune system is involved in the aetiology of exertional heat stroke (EHS). Unlike the more mild EHI, EHS is a life threatening acute heat illness characterised by hyperthermia (core temperature $>40^{\circ}\text{C}$) and neurological abnormalities that can develop after exposure to high ambient temperature and humidity (142). The putative involvement of immune dysregulation in the aetiology of EHS was first described in the exercise immunology literature by Shephard and Shek (201) and more recently refined by Lim and Mackinnon (120). During exercise-heat stress, gastrointestinal ischaemia can result in damage to the intestinal mucosa and leakage of lipopolysaccharide (LPS) into the portal circulation. The LPS is typically neutralized firstly by the liver and secondly by monocytes and macrophages. However, these defences may become overwhelmed, resulting in increased LPS in the peripheral circulation; the increase in circulating LPS may be exacerbated if immune function is impaired during heavy training (e.g. via decreased anti-LPS antibodies) (15). In turn, a sequence of events ensues involving LPS binding to its binding protein, the transfer of LPS to its receptor complex, toll-like receptor-4, with subsequent nuclear factor-kappa B activation and translation and production of inflammatory mediators including interleukin (IL)- 1β , tumour necrosis factor alpha (TNF- α), IL-6 and inducible nitric oxide synthase (195). These events can lead to the systemic inflammatory response syndrome (SIRS), intravascular coagulation and eventually to multi-organ failure. This is an attractive model, particularly for cases of EHS that are otherwise difficult to explain, because the pyrogenic cytokines (e.g. IL- 1β , and TNF- α) can alter thermoregulation (IL-1 induces fever) and cause cardiovascular instability resulting in collapse of the athlete or soldier (Figure 1).

Authors often cite support for an involvement of immune dysregulation in the aetiology of EHS from studies showing the following: circulating LPS levels in ultramarathon runners similar to florid sepsis (15); improved heat tolerance in heat-stressed animals treated with corticosteroids and antibiotics to prevent increases in circulating LPS (77, 78); cytokinaemia in EHS patients (17); symptoms of heat stroke in animals receiving IL-1 or TNF- α (122); enhanced survival in heat-stressed animals receiving IL-1 receptor antagonist (27) and important roles for heat shock proteins (e.g. HSP72) in cellular acquired thermal tolerance (126). In addition, recent work in rats shows that experimentally induced inflammation (via intramuscular injection of turpentine) compromises heat tolerance, further supporting a role for immune dysregulation in heat stroke (121).

However attractive an immune model of heat illness appears, there are many inconsistencies and gaps in knowledge that require elucidation. For example,

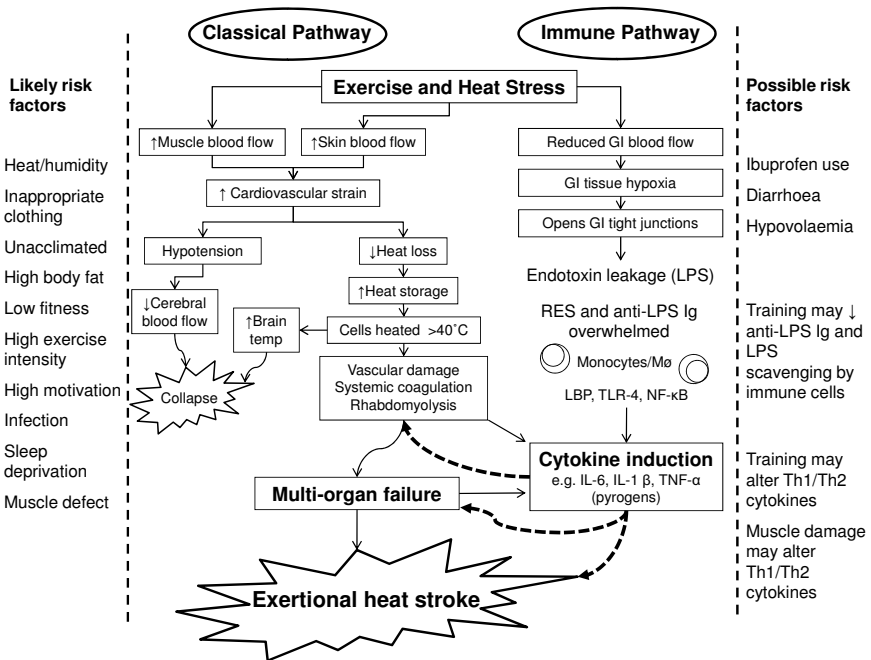


Figure 1. Classical and immune pathways of exertional heat stroke (EHS). GI = gastrointestinal; LPS = lipopolysaccharide; RES = reticuloendothelial system; Ig = immunoglobulin; Mφ = macrophage; LBP = lipopolysaccharide binding protein; TLR-4 = toll-like receptor-4; NF-κB = nuclear factor-kappa B. Solid arrows indicate likely links in pathway; broken arrows indicate unsubstantiated in EHS aetiology.

there exists great variability in circulating LPS and cytokine levels in heat stroke and EHS casualties (15, 17, 23, 218). There is no consensus about the level of circulating LPS associated with clinical manifestations of EHS, although Moore et al. (140) have suggested a threshold of 60 pg.ml⁻¹. In light of this, it seems unreasonable that one widely cited paper presents pre-exercise circulating LPS in ultra-distance triathletes of 81 pg.ml⁻¹; it would be reasonable to assume that triathletes attend a race without initial clinical manifestations of heat illness (15). Similarly, studies reporting cytokinaemia in heat stroke and EHS patients show large variability in responses between patients and levels that are more often than not below the magnitude seen during SIRS and sepsis (17). Lack of experimental control in field studies and delay in admitting patients to hospital for blood collection add to the confusing picture regarding cytokines and heat stroke pathology. It is quite conceivable that the cytokinaemia of EHS is instrumental in the recovery from EHS, but this idea needs substantiating (119). On a more critical note, studies reporting raised circulating LPS and cytokines in end-stage heat stroke tell us very little about a putative involvement of the immune system in the aetiology of heat stroke. Prospective studies in humans are required to examine the extent of any immune dysregulation prior to collapse (218). An important yet unanswered question is whether the time course of LPS leakage from the gut, the resulting

cytokinaemia, altered thermoregulation and cardiovascular instability during exercise-heat stress coincide with the development of EHS. Human studies have shed some light on this, albeit using an experimental model of endotoxaemia that did not involve exercise-heat stress (133, 212). Infusing 2 ng.kg^{-1} *Escherichia coli* endotoxin evoked maximal circulating TNF concentration 60-90 min after infusion and maximal body temperature 180 min after infusion (212). A decrease in blood pressure, which would be expected to contribute to the collapse in an EHS casualty, was not observed until 120 min after endotoxin infusion. Given the time course of these responses, an involvement of immune dysregulation in EHS during relatively short duration exercise (e.g. <60 min) appears less likely. A significant proportion of EHI cases, particularly in military personnel, occur in exercise bouts lasting <60 min (59, 175). The more traditional predisposing factors for EHS (Figure 1) such as high heat load, effort unmatched to fitness and underlying illness (175) alongside a recently proposed muscle defect causing excessive endogenous heat production likely play a prominent role in EHS aetiology (174).

Cold stress and immune function

Consensus

The term 'colds' may come from the popular belief that cold exposure causes URTI (25, 200). To date, there is no conclusive evidence to support a direct effect of prolonged cold exposure on URTI incidence. Reports from a number of Antarctic studies have shown little evidence of URTI among personnel except immediately after the visit of supply ships, when new strains of virus are imported into the community (76, 200), although the extent of cold exposure among study participants may have been relatively small.

Current consensus is that a continuum exists for the effects of passive body cooling on immune function. Very mild decreases in core temperature ($\sim 0.5^\circ\text{C}$) have little or even stimulatory effects on immune function (19, 115) but modest ($\sim 1^\circ\text{C}$) (35) and severe ($\sim 4^\circ\text{C}$) (220) decreases in core temperature have depressive effects on immune function. Compared with exercise in thermoneutral conditions, exercise in cold air conditions is associated with similar, or slightly lower, core temperature and neuro-endocrine activation (217) and similar immune modulation (179, 217, 218).

Controversies and future directions

Although lay people believe that getting cold and wet causes the common cold, this remains controversial because evidence from studies where participants were inoculated intra-nasally with cold viruses after cold exposure does not support such a belief (58). Nevertheless, more recent, novel work indicates that cooling body parts such as the feet increases self-reporting of cold symptoms (104). The authors claim this is due to reflex vasoconstriction in the upper airways and an associated reduction in respiratory defence. To settle this controversy, more experimental work is required that overcomes the limitations of existing studies. For example, published investigations have not mimicked the typical exposure to the common cold (58), have been limited by a small number of participants (58) or did not involve appropriate virology to quantify common cold incidence objectively after cold exposure (104).

To summarise, the limited evidence does not support the contention that athletes training and competing in cold conditions experience a greater reduction in immune function vs. those exercising under thermoneutral conditions. Nevertheless, it remains unknown if athletes who regularly train and compete in cold conditions report more frequent, severe or longer-lasting infections. Research should identify whether the airway inflammation associated with breathing large volumes of cold dry air (81) or polluted air (55) impairs airway defences (both ciliary function and immune responses) and whether athletes wrongly interpret as an URTI the symptoms of sore throat or exercise-induced bronchospasm that accompany exercising in cold or polluted air. As soldiers are often required to spend prolonged periods of activity interspersed with inactivity in cold and wet conditions they are particularly susceptible to hypothermia (core temperature $\leq 35^{\circ}\text{C}$) and associated reductions in immune function. The influence of hypothermia on *in vivo* immune function, wound healing and infection risk warrants further enquiry.

Altitude stress and immune function

Consensus

Athletes often train, and sometimes compete, at modest altitude (up to 2500 m) whereas mountaineers and occupational groups (e.g. high altitude miners and soldiers) often perform at high altitude (4000 m or higher). Upper respiratory and gastrointestinal tract symptoms are common in lowlanders who travel to high altitude (108, 143, 191, 203) and there are some reports that elite athletes experience increased URTI symptoms during and immediately after training camps at modest altitude (5, 90). Anecdotal reports of impaired wound healing in mountaineers at high altitude (170) are supported by laboratory studies in animals showing that breathing hypoxic air (12% $\text{O}_2 \approx 4000 \text{ m}$) impairs wound healing after intradermal injection with *Escherichia coli* (110). The small number of investigations that have examined immune function in humans working and training at altitude (Table 3) indicate that NKCA and humoral immunity are either unaffected or enhanced (11, 28, 29, 68, 108, 130, 173). In contrast, cell mediated immunity is consistently reported to be impaired at altitude, with studies indicating decreases in CD4+:CD8+ T-lymphocyte ratio (68, 226) and T-lymphocyte proliferation (68, 173). Increased sympathetic nervous activity and hypothalamic–pituitary–adrenal axis activity are thought to play a prominent role in immune modulation at altitude (188).

Controversies and future directions

Although a small body of evidence supports the commonly held belief that high altitude exposure increases URTI (191, 203) this remains controversial because there exists some overlap in the symptoms of acute mountain sickness and URTI. Given the acknowledged immune alterations with exercise performed at sea level (85) and the additional stress responses to exercise with increasing altitude (127) an appealing hypothesis is that a continuum of responses exists whereby exercise with increasing altitude is associated with a greater degree of immune depression (127, 218). Unfortunately, only limited information from well controlled laboratory and field studies is available in this regard. Relatively little is known about the influence of altitude on innate immune function (Table 3) and the studies to date typically have not employed adequate experimental control (97). It is quite conceivable that other stressors experienced by athletes and mountaineers at alti-

Table 3. Immune function and infection symptoms during sojourns and athletic training in hypoxia. M = male; F = female; SL = sea level; TR = temporary altitude resident; Ig = immunoglobulin; NKCA = natural killer cell activity; URT = upper respiratory tract; LHTL = live high train low; IHT = intermittent hypoxia training, CRP = C-reactive protein. ND = no difference.

Reference	Participants	Hypoxic exposure and activity/training	Immune function and infection symptoms
Chohan et al.(29)	10 altitude natives (M), 8 TR (M) and 31 SL (M).	Natives and TR at 3692m. TR resided at 3692m for 2 years. Activity unknown.	↑ Serum Ig response to inoculation with T-cell dependent vaccine in natives and TR vs. SL.
Chohan and Singh (28)	24 altitude natives (M), 45 TR (M) and 66 SL (M).	Natives and TR at 3692m. TR resided at 3692m for 2 years. Activity unknown.	↑ T-lymphocyte function in natives and TR vs. SL residents.
Meehan et al.(130)	7 (M). No controls.	28 days of progressive decompression to 7620m in a chamber. Minimal activity.	ND in nasal IgA: protein, nasal lysosome: protein, CD4+:CD8+ ratio, lymphocyte function or NKCA.
Biselli et al.(11)	18 TR (M) and 18 SL controls (M).	20 days at 4930m. Activity level unknown.	ND serum Ig [G, A, M] and B-cell response to vaccine (T-cell independent) vs. control.
Bailey et al.(5)	10 elite runners TR and 19 SL controls (12M: 7F).	28 days at 1640m. Training at same relative exercise intensity in both groups.	↑ URT and gastrointestinal symptoms in runners at altitude vs. SL controls.
Pyne et al.(173)	10 elite swimmers TR (5M: 5F) and 8 staff controls (M).	21 days at 2102m. 3 sessions per day for swimmers (~5.5 h/day). Staff <4 h/week.	ND in infections or lymphocyte proliferation between groups. ↓ T-lymphocyte proliferation and ↑ B-cell proliferation vs. pre in both groups.
Hitomi et al.(97)	7 M. No controls.	7 days. IHT 2 h/day at 4500m. Activity unknown.	↑ neutrophil function vs. pre following IHT.
Tiollier et al.(210)	6 LHTL elite cross country (3M: 3F) and 5 elite controls (2M: 3F).	18 days. LHTL 11 h/day for 6 days each at 2500, 3000 and 3500m. Both groups trained at 1200m with matched load (~3h/day). 5 control athletes at 1200m.	ND in saliva [IgA] between groups. ↓saliva [IgA] in LHTL group at 2500 and 3500m vs. pre.
Facco et al.(68)	13 F. No controls.	21 days at 5050m. 1.5 h exercise 3-5 days/week.	ND in NKCA, ↓CD4+:CD8+ ratio and lymphocyte proliferation vs. pre.
Kleessen et al.(108)	7 Mountaineers (5M: 2F). No controls.	47 day altitude expedition where 29 days >5000m.	ND in serum Ig [G, A, M] and total faecal bacteria. ↑ CRP and gram-negative faecal bacteria vs. pre. ↓ Bifidobacteria (anti-microbial capacity) vs. pre.
Zhang et al.(226)	8 LHTL university soccer players (M) and 8 SL controls	28 days. LHTL 10h/day at equivalent of 3000m. Both groups trained at SL.	↑ URT symptoms in LHTL vs. control (2 LHTL with symptoms vs. 0 in control). ↓CD4+:CD8+

tude contribute to the observed alterations in infection incidence and immune function (e.g. raised physical and psychological stress, cold exposure and nutritional restriction).

In summary, although high altitude exposure has limited effects on humoral immunity, a number of studies have shown decreased cell-mediated immunity at high altitude. There is a need for tightly controlled laboratory and field studies employing exercising normoxia controls, resting hypoxia controls and clinically relevant *in vivo* immune methods to elucidate further the effects of altitude on immune health.

PREVENTION AND TREATMENT OF COMMON INFECTIONS

Background

Several studies (84, 160, 161, 167) have suggested that athletes are at increased risk of respiratory tract infections (URTI). For a more detailed account, readers are directed to the section on respiratory infections and exercise in part one of this

position statement. Exercise-induced suppression of some immune functions after intense and/or prolonged exercise and during strenuous training periods may explain the so-called “open window theory” and J-shaped curve paradigm, respectively. Regular sharing of the same training and living facilities within a team may also contribute to this increased frequency or duration of URTI (84). Moreover, the increased exposure to foreign (or new) pathogens while travelling put the athlete at a higher risk of gastrointestinal infections (GI) (14). Thus, acute URTI is the most common reason for presenting to a sports medicine clinic (74, 146), and it is the most common medical condition affecting athletes at both the summer and winter Olympic Games (94, 177).

Consensus

It is agreed by everyone that prevention is always superior to treatment and this is particularly true in athletes residing in countries with limited medical facilities. However, there is no single intervention that completely eliminates the risk of contracting an infection, but there are several effective ways of reducing the number, duration and severity of infectious episodes incurred over a period. Most of the following practical guidelines, driven by common sense, can be understood by everyone who keeps in mind the contagious nature of viruses, bacteria and fungi.

Practical guidelines for prevention of infections among athletes

- Check that your athletes are updated on all vaccines needed at home and for foreign countries should they travel abroad for training and competition.
- Minimize contacts with infected/sick people, young children, animals and potentially contaminated objects.
- Keep at distance from people who are coughing, sneezing or have a “runny nose”, and when appropriate wear or ask them to wear a disposable mask.
- Wash hands regularly, before meals, and after direct contact with potentially contagious people, animals, blood, secretions, public places and bathrooms. Carry alcohol-based gel with you where lavatories are not available or not clean enough.
- Use disposable paper towels and limit hand to mouth/nose contact when suffering from URTI or GI symptoms.
- Do not share drinking bottles, cups, towels, etc.
- While competing or training abroad, prefer cold beverage from sealed bottles, avoid crude vegetables, and meat. Wash and peel fruits before eating.
- Quickly isolate a team member with infection symptoms and move out his/her roommate.
- Protect airways from being directly exposed to very cold and dry air during strenuous exercise, by using a face mask.
- Ensure adequate level of carbohydrate intake before and during strenuous or prolonged exercise in order to limit the extent and severity of the exercise-induced immunodepression phase (see nutritional countermeasures section in this part of the position statement).
- Wear proper out-door clothing and avoid getting cold and wet after exercise.
- Get at least 7 hours sleep per night (31) (see sleep disruption section in this part of the position statement).
- Avoid crash dieting and rapid weight loss.

- Wear flip-flop or thongs when going to the showers, swimming pool and locker rooms in order to avoid dermatological diseases.
- Keep other life stresses to a minimum.

Should infection occur, the athlete and his or her entourage must use some basic guidelines for exercise during infectious episodes (186) before being referred to a physician.

Guidelines for exercise during episodes of URTI or GI in athletes

• *First day of illness:*

No strenuous exercise or competitions when experiencing URTI symptoms like sore throat, coughing, runny or congested nose. No exercise when experiencing symptoms like muscle/joint pain and headache, fever and generalized feeling of malaise, diarrhoea or vomiting. Drink plenty of fluids, keep from getting wet and cold, and minimize life-stress.

Consider use of topical therapy with nasal drainage, decongestants and analgesics if feverish. Report illness to a team physician or health care personnel and keep away from other athletes if you are part of a team training or travelling together.

• *Second day:*

If body temperature $>37.5-38^{\circ}\text{C}$, or increased coughing, diarrhoea or vomiting: no training. If no fever or malaise and no worsening of “above the neck” symptoms: light exercise (pulse <120 bpm) for 30-45 min, indoors during winter and by yourself.

• *Third day:*

If fever and URTI or GI symptoms are still present: consult your physician. In GI cases, antibiotics should be taken if unformed stools occur more than four times a day or for fever, blood, pus, or mucus in stools. Quinolones should be avoided whenever possible because of an increased risk of tendinopathy. If no fever or malaise and no worsening of initial symptoms: moderate exercise (pulse <150 bpm) for 45-60 min, preferably indoors and by yourself.

• *Fourth day:*

If no symptom relief: do not try to exercise but make an office visit to your doctor. Stool cultures or examination for ova and parasites should generally be reserved for cases that last beyond 10 to 14 days. If first day of improved condition, follow the guidelines below (186):

Guidelines for return to exercise after infections

- Wait one day without fever and with improvement of URTI or GI symptoms before returning to exercise.
- Stop physical exercise and consult your physician if a new episode with fever or worsening of initial symptoms or persistent coughing and exercise-induced breathing problems occur.
- Use the same number of days to step up to normal training as spent off regular training because of illness.
- Observe closely your tolerance to increased exercise intensity and take an extra day off if recovery is incomplete.

- Use proper outdoor clothing and specific cold air protection for airways when exercising in temperatures below -10°C the first week after URTI.

Controversies

The first one is infectious mononucleosis (IM). Indeed, strenuous physical training performed during the initial or convalescence phase of Epstein Barr virus infection can be associated with increased morbidity, relapse, delayed recovery, and splenic rupture. This last occurrence is rare (0.1% of IM) on the athletic field and rarely fatal now (22). Most splenic ruptures occur between 4 days and 4 weeks after onset and very few occur beyond week 5 (63). Four recent reviews (4, 107, 125, 219) suggested that all spleens that rupture are enlarged, but it is important to note that splenomegaly is found in 50% of IM and that physical examination is quite insensitive to detect an enlarged at-risk spleen reliably. Although return to sport after IM is still a topic of debate, we recommend First, a week without febrile episodes or systemic symptoms and a substantial decrease in serum viral antibody titres and liver enzymes before starting light exercise; Secondly, exclude the possibility of hepatosplenomegaly in an athlete returning to contact sports, by performing abdominal ultrasound or CT scan; Thirdly, observe the tolerance of each training session and its recovery and discontinue the exercise if relapse or worsening while waiting for a consultation with the physician.

The second is about the diagnosis of viral myocarditis, which is the reason for sudden cardiac death in 5-22% of athletes under 35 years of age (see review (18)). For the purpose of prevention it is thus recommended to stop elite sport for 4 weeks after an unspecific infection. As some athletes experience up to six colds or viral (and probably unspecific) infections per year, one can understand why this recommendation is rarely implemented. Thus, it is important to take subtle discomforts seriously and initiate further evaluation when viral infection is strongly suspected particularly in spring and summer (Parvovirus B19, Herpes virus 6, Echovirus, Coxsackie, Poliovirus). Electrocardiogram, laboratory parameters, serologic markers, and echocardiography are helpful in diagnosis of myocarditis, but are not specific. Magnetic resonance imaging of the heart has become an important tool, but is not affordable by all. The cost-benefit ratio of myocarditis diagnosis in athletes remains a matter of controversy.

Future directions

As a high proportion of episodes of respiratory symptoms in athletes have not been associated with identification of a respiratory pathogen (37, 204), other potentially treatable causes of upper respiratory symptoms should be considered, particularly in athletes with recurrent symptoms. A better understanding of this phenomenon could lead to significant changes in the prevention and management of common infections in athletes.

REFERENCES

1. Abo T, Kawate T, Itoh K and Kumagai K. Studies on the bioperiodicity of the immune response. I. Circadian rhythms of human T, B, and K cell traffic in the peripheral blood. *J Immunol* 126: 1360-1363, 1981.
2. Ader R. *Psychoneuroimmunology IV*. San Diego: Academic Press, 2006.
3. Albers R, Antoine JM, Bourdet-Sicard R, Calder PC, Gleeson M, Lesourd B, Samartin S, Sanderson IR, Van Loo J, Vas Dias FW and Watzl B. Markers to measure immunomodulation in human nutrition intervention studies. *Br J Nutr* 94: 452-481, 2005.
4. Auwaerter PG. Infectious mononucleosis: return to play. *Clin Sports Med* 23: 485-97, xi, 2004.
5. Bailey DM, Davies B, Romer L, Castell L, Newsholme E and Gandy G. Implications of moderate altitude training for sea-level endurance in elite distance runners. *Eur J Appl Physiol Occup Physiol* 78: 360-368, 1998.
6. Bakker GC, van Erk MJ, Pellis L, Wopereis S, Rubingh CM, Cnubben NH, Kooistra T, van Ommen B and Hendriks HF. An antiinflammatory dietary mix modulates inflammation and oxidative and metabolic stress in overweight men: a nutrigenomics approach. *Am J Clin Nutr* 91: 1044-1059, 2010.
7. Banister EW, Morton RH and Clarke JR. Clinical dose-response effects of exercise. In: *The physiology and pathophysiology of exercise tolerance*, edited by Steinacker JM and Wand SA. New York: Plenum, 1997, p. 297-290.
8. Barnett A, Cerin E, Reaburn P and Hooper S. The effects of training on performance and performance-related states in individual elite athletes: a dynamic approach. *J Sports Sci* 28: 1117-1126, 2010.
9. Benschop RJ, Rodriguez-Feuerhahn M and Schedlowski M. Catecholamine-induced leukocytosis: early observations, current research, and future directions. *Brain Behav Immun* 10: 77-91, 1996.
10. Bertouch JV, Roberts-Thomson PJ and Bradley J. Diurnal variation of lymphocyte subsets identified by monoclonal antibodies. *Br Med J (Clin Res Ed)* 286: 1171-1172, 1983.
11. Biselli R, Le Moli S, Matricardi PM, Farrace S, Fattorossi A, Nisini R and D'Amelio R. The effects of hypobaric hypoxia on specific B cell responses following immunization in mice and humans. *Aviat Space Environ Med* 62: 870-874, 1991.
12. Blask DE. Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev* 13: 257-264, 2009.
13. Blecha F, Barry RA and Kelley KW. Stress-induced alterations in delayed-type hypersensitivity to SRBC and contact sensitivity to DNFB in mice. *Proc Soc Exp Biol Med* 169: 239-246, 1982.
14. Boggess BR. Gastrointestinal infections in the traveling athlete. *Curr Sports Med Rep* 6: 125-129, 2007.
15. Bosenberg AT, Brock-Utne JG, Gaffin SL, Wells MT and Blake GT. Strenuous exercise causes systemic endotoxemia. *J Appl Physiol* 65: 106-108, 1988.
16. Bosquet L, Montpetit J, Arvisais D and Mujika I. Effects of tapering on performance: a meta-analysis. *Med Sci Sports Exerc* 39: 1358-1365, 2007.
17. Bouchama A, Parhar RS, el Yazigi A, Sheth K and al Sedairy S. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *J Appl Physiol* 70: 2640-2644, 1991.

18. Brennan FH, Stenzler B and Oriscello R. Diagnosis and management of myocarditis in athletes. *Curr Sports Med Rep* 2: 65-71, 2003.
19. Brenner IK, Castellani JW, Gabaree C, Young AJ, Zamecnik J, Shephard RJ and Shek PN. Immune changes in humans during cold exposure: effects of prior heating and exercise. *J Appl Physiol* 87: 699-710, 1999.
20. Brenner IK, Severs YD, Rhind SG, Shephard RJ and Shek PN. Immune function and incidence of infection during basic infantry training. *Mil Med* 165: 878-883, 2000.
21. Brown H and Dougherty T. The diurnal variation of blood leucocytes in normal and adrenalectomized mice. *Endocrinology* 58: 365-375, 1956.
22. Burroughs KE. Athletes resuming activity after infectious mononucleosis. *Arch Fam Med* 9: 1122-1123, 2000.
23. Camus G, Poortmans J, Nys M, Deby-Dupont G, Duchateau J, Deby C and Lamy M. Mild endotoxaemia and the inflammatory response induced by a marathon race. *Clin Sci (Lond)* 92: 415-422, 1997.
24. Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernandez-Montesinos R, Guerrero JM and Pozo D. The modulatory role of melatonin on immune responsiveness. *Curr Opin Investig Drugs* 7: 423-431, 2006.
25. Castellani JW, IK MB and Rhind SG. Cold exposure: human immune responses and intracellular cytokine expression. *Med Sci Sports Exerc* 34: 2013-2020, 2002.
26. Chen YJ, Wong SH, Wong CK, Lam CW, Huang YJ and Siu PM. The effect of a pre-exercise carbohydrate meal on immune responses to an endurance performance run. *Br J Nutr* 100: 1260-1268, 2008.
27. Chiu WT, Kao TY and Lin MT. Increased survival in experimental rat heatstroke by continuous perfusion of interleukin-1 receptor antagonist. *Neurosci Res* 24: 159-163, 1996.
28. Chohan IS and Singh I. Cell mediated immunity at high altitude. *Int J Biometeorol* 23: 21-30, 1979.
29. Chohan IS, Singh I, Balakrishnan K and Talwar GP. Immune response in human subjects at high altitude. *Int J Biometeorol* 19: 137-143, 1975.
30. Cocke R, Moynihan JA, Cohen N, Grota LJ and Ader R. Exposure to conspecific alarm chemosignals alters immune responses in BALB/c mice. *Brain Behav Immun* 7: 36-46, 1993.
31. Cohen S, Doyle WJ, Alper CM, Janicki-Deverts D and Turner RB. Sleep habits and susceptibility to the common cold. *Arch Intern Med* 169: 62-67, 2009.
32. Cohen S and Hamrick N. Stable individual differences in physiological response to stressors: implications for stress-elicited changes in immune related health. *Brain Behav Immun* 17: 407-414, 2003.
33. Cohen S, Miller GE and Rabin BS. Psychological stress and antibody response to immunization: a critical review of the human literature. *Psychosom Med* 63: 7-18, 2001.
34. Costa G, Haus E and Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health* 36: 163-179, 2010.
35. Costa RJ, Smith AH, Oliver SJ, Walters R, Maassen N, Bilzon JL and Walsh NP. The effects of two nights of sleep deprivation with or without energy restriction on immune indices at rest and in response to cold exposure. *Eur J Appl Physiol* 109: 417-428, 2010.
36. Cox AJ, Gleeson M, Pyne DB, Callister R, Fricker PA and Scott RJ. Cytokine gene polymorphisms and risk for upper respiratory symptoms in highly-trained athletes. *Exerc Immunol Rev* 16: 8-21, 2010.

37. Cox AJ, Gleeson M, Pyne DB, Callister R, Hopkins WG and Fricker PA. Clinical and laboratory evaluation of upper respiratory symptoms in elite athletes. *Clin J Sport Med* 18: 438-445, 2008.
38. Cross MC, Radomski MW, VanHelder WP, Rhind SG and Shephard RJ. Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocyte subsets. *J Appl Physiol* 81: 822-829, 1996.
39. Davis GM, Pyley MJ, Gottesman ST, Shephard RJ and Goode RC. Variations in cardiorespiratory and strength parameters during moderate exercise and sleep deprivation. *Can J Appl Spts Sci* 7: 236-237, 1982.
40. Davis S and Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control* 17: 539-545, 2006.
41. Davison G and Gleeson M. Influence of acute vitamin C and/or carbohydrate ingestion on hormonal, cytokine, and immune responses to prolonged exercise. *Int J Sport Nutr Exerc Metab* 15: 465-479, 2005.
42. Davison G and Gleeson M. The effect of 2 weeks vitamin C supplementation on immunoendocrine responses to 2.5 h cycling exercise in man. *Eur J Appl Physiol* 97: 454-461, 2006.
43. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection versus immunopathology. *Allergy Asthma Clin Immunol* 4: 2-11, 2008.
44. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *Neuroimmunomodulation* 16: 300-317, 2009.
45. Dhabhar FS and McEwen BS. Stress-induced enhancement of antigen-specific cell-mediated immunity. *J Immunol* 156: 2608-2615, 1996.
46. Dhabhar FS and McEwen BS. Acute stress enhances while chronic stress suppresses cell-mediated immunity in vivo: a potential role for leukocyte trafficking. *Brain Behav Immun* 11: 286-306, 1997.
47. Dhabhar FS and McEwen BS. Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc Natl Acad Sci U S A* 96: 1059-1064, 1999.
48. Dhabhar FS and McEwen BS. Bidirectional effects of stress & glucocorticoid hormones on immune function: Possible explanations for paradoxical observations. In: *Psychoneuroimmunology*, edited by Ader R, Felten DL and Cohen N. San Diego: Academic Press, 2001, p. 301-338.
49. Dhabhar FS, McEwen BS and Spencer RL. Adaptation to prolonged or repeated stress--comparison between rat strains showing intrinsic differences in reactivity to acute stress. *Neuroendocrinology* 65: 360-368, 1997.
50. Dhabhar FS, Miller AH, McEwen BS and Spencer RL. Differential activation of adrenal steroid receptors in neural and immune tissues of Sprague Dawley, Fischer 344, and Lewis rats. *J Neuroimmunol* 56: 77-90, 1995.
51. Dhabhar FS, Miller AH, McEwen BS and Spencer RL. Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. *J Immunol* 154: 5511-5527, 1995.
52. Dhabhar FS, Miller AH, McEwen BS and Spencer RL. Stress-induced changes in blood leukocyte distribution. Role of adrenal steroid hormones. *J Immunol* 157: 1638-1644, 1996.

53. Dhabhar FS, Satoskar AR, Bluethmann H, David JR and McEwen BS. Stress-induced enhancement of skin immune function: A role for gamma interferon. *Proc Natl Acad Sci U S A* 97: 2846-2851, 2000.
54. Dhabhar FS and Viswanathan K. Short-term stress experienced at time of immunization induces a long-lasting increase in immunologic memory. *Am J Physiol Regul Integr Comp Physiol* 289: R738-R744, 2005.
55. Diamond G, Legarda D and Ryan LK. The innate immune response of the respiratory epithelium. *Immunol Rev* 173: 27-38, 2000.
56. Dimitrov S, Lange T, Tiekens S, Fehm HL and Born J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain Behav Immun* 18: 341-348, 2004.
57. Dinges DF, Douglas SD, Zaugg L, Campbell DE, McMann JM, Whitehouse WG, Orne EC, Kapoor SC, Icaza E and Orne MT. Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. *J Clin Invest* 93: 1930-1939, 1994.
58. Douglas RC, Jr., Couch RB and Lindgren KM. Cold doesn't affect the "common cold" in study of rhinovirus infections. *JAMA* 199: 29-30, 1967.
59. DuBose DA, Wenger CB, Flinn SD, Judy TA, Dubovtsev AI and Morehouse DH. Distribution and mitogen response of peripheral blood lymphocytes after exertional heat injury. *J Appl Physiol* 95: 2381-2389, 2003.
60. Edwards KM, Burns VE, Adkins AE, Carroll D, Drayson M and Ring C. Meningococcal A vaccination response is enhanced by acute stress in men. *Psychosom Med* 70: 147-151, 2008.
61. Edwards KM, Burns VE, Carroll D, Drayson M and Ring C. The acute stress-induced immunoenhancement hypothesis. *Exerc Sport Sci Rev* 35: 150-155, 2007.
62. Edwards KM, Burns VE, Reynolds T, Carroll D, Drayson M and Ring C. Acute stress exposure prior to influenza vaccination enhances antibody response in women. *Brain Behav Immun* 20: 159-168, 2006.
63. Eichner ER. Sports medicine pearls and pitfalls--defending the spleen: return to play after infectious mononucleosis. *Curr Sports Med Rep* 6: 68-69, 2007.
64. Epel ES. Psychological and metabolic stress: a recipe for accelerated cellular aging? *Hormones (Athens)* 8: 7-22, 2009.
65. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD and Cawthon RM. Accelerated telomere shortening in response to life stress. *Proc Natl Acad Sci U S A* 101: 17312-17315, 2004.
66. Ernst E, Pecho E, Wirz P and Saradeth T. Regular sauna bathing and the incidence of common colds. *Ann Med* 22: 225-227, 1990.
67. Everson CA. Sustained sleep deprivation impairs host defense. *Am J Physiol* 265: R1148-R1154, 1993.
68. Facco M, Zilli C, Siviero M, Ermolao A, Travain G, Baesso I, Bonamico S, Cabrelle A, Zaccaria M and Agostini C. Modulation of immune response by the acute and chronic exposure to high altitude. *Med Sci Sports Exerc* 37: 768-774, 2005.
69. Fauci AS and Dale DC. The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. *J Clin Invest* 53: 240-246, 1974.
70. Fernandes G. Chronobiology of immune functions: cellular and humoral aspects. In: *Biological rhythms in clinical and laboratory medicine*, edited by Touitou Y and Haus E. Heidelberg: Springer Verlag, 1994, p. 493-503.

71. Fernandes G, Carandente F, Halberg E, Halberg F and Good RA. Circadian rhythm in activity of lympholytic natural killer cells from spleens of Fischer rats. *J Immunol* 123: 622-625, 1979.
72. Foster C. Monitoring training in athletes with reference to overtraining syndrome. *Med Sci Sports Exerc* 30: 1164-1168, 1998.
73. French J. Circadian rhythms, jet lag and the athlete. In: *Current Therapy in Sports Medicine*, edited by Torg J and Shephard RJ. St. Louis: Mosby, 1995, p. 596-600.
74. Fricker PA. Infectious problems in athletes: an overview. In: *Medical Problems in Athletes*, edited by Fields KB and Fricker PA. Malden: Blackwell Science, 1997, p. 3-5.
75. Fry RW, Morton AR and Keast D. Periodisation of training stress--a review. *Can J Sport Sci* 17: 234-240, 1992.
76. Gard S. Respiratory virus infections other than influenza. *Arch Environ Health* 17: 543-546, 1968.
77. Gathiram P, Wells MT, Brock-Utne JG and Gaffin SL. Prophylactic corticosteroid increases survival in experimental heat stroke in primates. *Aviat Space Environ Med* 59: 352-355, 1988.
78. Gathiram P, Wells MT, Brock-Utne JG, Wessels BC and Gaffin SL. Prevention of endotoxaemia by non-absorbable antibiotics in heat stress. *J Clin Pathol* 40: 1364-1368, 1987.
79. Gatti G, Carignola R, Masera R, Satori ML, Salvadori A, Magro E and Angeli A. Circadian-stage specified effects of melatonin on human natural killer (NK) cell activity: in vivo and in vitro studies. *Ann Rev Chronopharmacol* 5: 25-28, 1989.
80. Gatti G, Carvalho R, Delponte D, Masera R, Carignola R, Caradente F and Angeli A. Circadian changes of human natural killer cells and their in vitro susceptibility to cortisol inhibition. *Ann Rev Chronopharmacol* 3: 75-78, 1987.
81. Giesbrecht GG. The respiratory system in a cold environment. *Aviat Space Environ Med* 66: 890-902, 1995.
82. Glaser R and Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 5: 243-251, 2005.
83. Glaser R, MacCallum RC, Laskowski BF, Malarkey WB, Sheridan JF and Kiecolt-Glaser JK. Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. *J Gerontol A Biol Sci Med Sci* 56: M477-M482, 2001.
84. Gleeson M. The scientific basis of practical strategies to maintain immunocompetence in elite athletes. *Exerc Immunol Rev* 6: 75-101, 2000.
85. Gleeson M. Immune function in sport and exercise. *J Appl Physiol* 103: 693-699, 2007.
86. Gleeson M. Dosing and efficacy of glutamine supplementation in human exercise and sport training. *J Nutr* 138: 2045S-2049S, 2008.
87. Gleeson M, Nieman DC and Pedersen BK. Exercise, nutrition and immune function. *J Sports Sci* 22: 115-125, 2004.
88. Gomez-Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borrás C, Pallardo FV, Sastre J and Vina J. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *Am J Clin Nutr* 87: 142-149, 2008.
89. Gonzalez-Alonso J, Teller C, Andersen SL, Jensen FB, Hyldig T and Nielsen B. Influence of body temperature on the development of fatigue during prolonged exercise in the heat. *J Appl Physiol* 86: 1032-1039, 1999.

90. Gore CJ, Hahn A, Rice A, Bourdon P, Lawrence S, Walsh C, Stanef T, Barnes P, Parisotto R, Martin D and Pyne D. Altitude training at 2690m does not increase total haemoglobin mass or sea level VO₂max in world champion track cyclists. *J Sci Med Sport* 1: 156-170, 1998.
91. Gozal D, Serpero LD, Kheirandish-Gozal L, Capdevila OS, Khalyfa A and Tauman R. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing. *Sleep* 33: 319-325, 2010.
92. Gunnar M and Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol* 58: 145-173, 2007.
93. Hackney AC. Exercise as a stressor to the human neuroendocrine system. *Medicina (Kaunas)* 42: 788-797, 2006.
94. Hanley DF. Medical care of the US Olympic Team. *JAMA* 236: 147-148, 1976.
95. Hansen J. Risk of breast cancer after night- and shift work: current evidence and ongoing studies in Denmark. *Cancer Causes Control* 17: 531-537, 2006.
96. Haus E, Lakatua DJ, Swoyer J and Sackett-Lundeen L. Chronobiology in hematology and immunology. *Am J Anat* 168: 467-517, 1983.
97. Hitomi Y, Miyamura M, Mori S, Suzuki K, Kizaki T, Itoh C, Murakami K, Haga S and Ohno H. Intermittent hypobaric hypoxia increases the ability of neutrophils to generate superoxide anion in humans. *Clin Exp Pharmacol Physiol* 30: 659-664, 2003.
98. Hohagen F, Timmer J, Weyerbrock A, Fritsch-Montero R, Ganter U, Krieger S, Berger M and Bauer J. Cytokine production during sleep and wakefulness and its relationship to cortisol in healthy humans. *Neuropsychobiology* 28: 9-16, 1993.
99. Hopkins WG, Marshall SW, Batterham AM and Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sports Exerc* 41: 3-13, 2009.
100. Irwin M, McClintick J, Costlow C, Fortner M, White J and Gillin JC. Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *FASEB J* 10: 643-653, 1996.
101. Irwin MR. Human psychoneuroimmunology: 20 years of discovery. *Brain Behav Immun* 22: 129-139, 2008.
102. Irwin MR, Carrillo C and Olmstead R. Sleep loss activates cellular markers of inflammation: sex differences. *Brain Behav Immun* 24: 54-57, 2010.
103. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O and Cole S. Sleep loss activates cellular inflammatory signaling. *Biol Psychiatry* 64: 538-540, 2008.
104. Johnson C and Eccles R. Acute cooling of the feet and the onset of common cold symptoms. *Fam Pract* 22: 608-613, 2005.
105. Katschinski DM, Wiedemann GJ, Longo W, d'Oleire FR, Spriggs D and Robins HI. Whole body hyperthermia cytokine induction: a review, and unifying hypothesis for myeloprotection in the setting of cytotoxic therapy. *Cytokine Growth Factor Rev* 10: 93-97, 1999.
106. Kendall A, Hoffman-Goetz L, Houston M, MacNeil B and Arumugam Y. Exercise and blood lymphocyte subset responses: intensity, duration, and subject fitness effects. *J Appl Physiol* 69: 251-260, 1990.
107. Kinderknecht JJ. Infectious mononucleosis and the spleen. *Curr Sports Med Rep* 1: 116-120, 2002.

108. Kleessen B, Schroedl W, Stueck M, Richter A, Rieck O and Krueger M. Microbial and immunological responses relative to high-altitude exposure in mountaineers. *Med Sci Sports Exerc* 37: 1313-1318, 2005.
109. Knapp MS and Pownall R. Lymphocytes are rhythmic: is this important? *Br Med J (Clin Res Ed)* 289: 1328-1330, 1984.
110. Knighton DR, Halliday B and Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. *Arch Surg* 119: 199-204, 1984.
111. Koenig D, Grathwohl D, Weinstock C, Northoff H and Berg A. Upper respiratory tract infection in athletes: influence of lifestyle, type of sport, training effort, and immunostimulant intake. *Exerc Immunol Rev* 6: 102-120, 2000.
112. Krueger JM and Majde JA. Sleep as a host defense: its regulation by microbial products and cytokines. *Clin Immunol Immunopathol* 57: 188-199, 1990.
113. Krzywkowski K, Petersen EW, Ostrowski K, Kristensen JH, Boza J and Pedersen BK. Effect of glutamine supplementation on exercise-induced changes in lymphocyte function. *Am J Physiol Cell Physiol* 281: C1259-C1265, 2001.
114. Kusaka Y, Kondou H and Morimoto K. Healthy lifestyles are associated with higher natural killer cell activity. *Prev Med* 21: 602-615, 1992.
115. Lackovic V, Borecky L, Vigas M and Rovinsky J. Activation of NK cells in subjects exposed to mild hyper- or hypothermic load. *J Interferon Res* 8: 393-402, 1988.
116. Laing SJ, Blackwell J, Gwynne D, Walters R and Walsh NP. Neutrophil degranulation response to 2 hours of exercise in a 30 degrees C environment. *Aviat Space Environ Med* 76: 1068-1073, 2005.
117. Laing SJ, Gwynne D, Blackwell J, Williams M, Walters R and Walsh NP. Salivary IgA response to prolonged exercise in a hot environment in trained cyclists. *Eur J Appl Physiol* 93: 665-671, 2005.
118. Laing SJ, Jackson AR, Walters R, Lloyd-Jones E, Whitham M, Maassen N and Walsh NP. Human blood neutrophil responses to prolonged exercise with and without a thermal clamp. *J Appl Physiol* 104: 20-26, 2008.
119. Leon LR, Blaha MD and DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. *J Appl Physiol* 100: 1400-1409, 2006.
120. Lim CL and Mackinnon LT. The roles of exercise-induced immune system disturbances in the pathology of heat stroke: the dual pathway model of heat stroke. *Sports Med* 36: 39-64, 2006.
121. Lim CL, Wilson G, Brown L, Coombes JS and Mackinnon LT. Pre-existing inflammatory state compromises heat tolerance in rats exposed to heat stress. *Am J Physiol Regul Integr Comp Physiol* 292: R186-R194, 2007.
122. Lin MT, Liu HH and Yang YL. Involvement of interleukin-1 receptor mechanisms in development of arterial hypotension in rat heatstroke. *Am J Physiol* 273: H2072-H2077, 1997.
123. Lucey DR, Clerici M and Shearer GM. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. *Clin Microbiol Rev* 9: 532-562, 1996.
124. Lyall KA, Hurst SM, Cooney J, Jensen D, Lo K, Hurst RD and Stevenson LM. Short-term blackcurrant extract consumption modulates exercise-induced oxidative stress and lipopolysaccharide-stimulated inflammatory responses. *Am J Physiol Regul Integr Comp Physiol* 297: R70-R81, 2009.

125. Macknight JM. Infectious mononucleosis: ensuring a safe return to sport. *Phys Sportsmed* 30: 27-41, 2002.
126. Maloyan A, Palmon A and Horowitz M. Heat acclimation increases the basal HSP72 level and alters its production dynamics during heat stress. *Am J Physiol* 276: R1506-R1515, 1999.
127. Mazzeo RS. Altitude, exercise and immune function. *Exerc Immunol Rev* 11: 6-16, 2005.
128. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 338: 171-179, 1998.
129. McFarlin BK and Mitchell JB. Exercise in hot and cold environments: differential effects on leukocyte number and NK cell activity. *Aviat Space Environ Med* 74: 1231-1236, 2003.
130. Meehan R, Duncan U, Neale L, Taylor G, Muchmore H, Scott N, Ramsey K, Smith E, Rock P and Goldblum R. Operation Everest II: alterations in the immune system at high altitudes. *J Clin Immunol* 8: 397-406, 1988.
131. Meeusen R, Duclos M, Gleeson M, Rietjems J, Steinacker JM and Urhausen A. Prevention, diagnosis and treatment of the Overtraining Syndrome. *Eur J Sport Sci* 6: 1-14, 2006.
132. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, Dinges DF and Mullington JM. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* 43: 678-683, 2004.
133. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Cerami A, Wolff SM and Wilmore DW. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 318: 1481-1486, 1988.
134. Midgley AW, McNaughton LR and Jones AM. Training to enhance the physiological determinants of long-distance running performance: can valid recommendations be given to runners and coaches based on current scientific knowledge? *Sports Med* 37: 857-880, 2007.
135. Mitchell JB, Dugas JP, McFarlin BK and Nelson MJ. Effect of exercise, heat stress, and hydration on immune cell number and function. *Med Sci Sports Exerc* 34: 1941-1950, 2002.
136. Moldofsky H. Central nervous system and peripheral immune functions and the sleep-wake system. *J Psychiatry Neurosci* 19: 368-374, 1994.
137. Moldofsky H. Sleep and the immune system. *Int J Immunopharmacol* 17: 649-654, 1995.
138. Moldofsky H, Lue FA, Davidson JR and Gorczynski R. Effects of sleep deprivation on human immune functions. *FASEB J* 3: 1972-1977, 1989.
139. Moldofsky H, Lue FA, Eisen J, Keystone E and Gorczynski RM. The relationship of interleukin-1 and immune functions to sleep in humans. *Psychosom Med* 48: 309-318, 1986.
140. Moore GE, Holbein ME and Knochel JP. Exercise-associated collapse in cyclists is unrelated to endotoxemia. *Med Sci Sports Exerc* 27: 1238-1242, 1995.
141. Mujika I. The influence of training characteristics and tapering on the adaptation in highly trained individuals: a review. *Int J Sports Med* 19: 439-446, 1998.
142. Muldoon S, Deuster P, Brandom B and Bungler R. Is there a link between malignant hyperthermia and exertional heat illness? *Exerc Sport Sci Rev* 32: 174-179, 2004.
143. Murdoch DR. Symptoms of infection and altitude illness among hikers in the Mount Everest region of Nepal. *Aviat Space Environ Med* 66: 148-151, 1995.

144. Murphy EA, Davis JM, Carmichael MD, Mayer EP and Ghaffar A. Benefits of oat beta-glucan and sucrose feedings on infection and macrophage antiviral resistance following exercise stress. *Am J Physiol Regul Integr Comp Physiol* 297: R1188-R1194, 2009.
145. Nakachi K and Imai K. Environmental and physiological influences on human natural killer cell activity in relation to good health practices. *Jpn J Cancer Res* 83: 798-805, 1992.
146. Nieman DC. Exercise, upper respiratory tract infection, and the immune system. *Med Sci Sports Exerc* 26: 128-139, 1994.
147. Nieman DC. Upper respiratory tract infections and exercise. *Thorax* 50: 1229-1231, 1995.
148. Nieman DC. Immune response to heavy exertion. *J Appl Physiol* 82: 1385-1394, 1997.
149. Nieman DC. Influence of carbohydrate on the immune response to intensive, prolonged exercise. *Exerc Immunol Rev* 4: 64-76, 1998.
150. Nieman DC. Is infection risk linked to exercise workload? *Med Sci Sports Exerc* 32: S406-S411, 2000.
151. Nieman DC. Immunonutrition support for athletes. *Nutr Rev* 66: 310-320, 2008.
152. Nieman DC. Quercetin's bioactive effects in human athletes. *Curr Topic Nutraceut Res* 8: 33-44, 2010.
153. Nieman DC, Henson DA, Gojanovich G, Davis JM, Murphy EA, Mayer EP, Pearce S, Dumke CL, Utter AC, McAnulty SR and McAnulty LS. Influence of carbohydrate on immune function following 2 h cycling. *Res Sports Med* 14: 225-237, 2006.
154. Nieman DC, Henson DA, Gross SJ, Jenkins DP, Davis JM, Murphy EA, Carmichael MD, Dumke CL, Utter AC, McAnulty SR, McAnulty LS and Mayer EP. Quercetin reduces illness but not immune perturbations after intensive exercise. *Med Sci Sports Exerc* 39: 1561-1569, 2007.
155. Nieman DC, Henson DA, Maxwell KR, Williams AS, McAnulty SR, Jin F, Shanely RA and Lines TC. Effects of quercetin and EGCG on mitochondrial biogenesis and immunity. *Med Sci Sports Exerc* 41: 1467-1475, 2009.
156. Nieman DC, Henson DA, McAnulty SR, Jin F and Maxwell KR. n-3 polyunsaturated fatty acids do not alter immune and inflammation measures in endurance athletes. *Int J Sport Nutr Exerc Metab* 19: 536-546, 2009.
157. Nieman DC, Henson DA, McAnulty SR, McAnulty L, Swick NS, Utter AC, Vinci DM, Opiela SJ and Morrow JD. Influence of vitamin C supplementation on oxidative and immune changes after an ultramarathon. *J Appl Physiol* 92: 1970-1977, 2002.
158. Nieman DC, Henson DA, McAnulty SR, McAnulty LS, Morrow JD, Ahmed A and Heward CB. Vitamin E and immunity after the Kona Triathlon World Championship. *Med Sci Sports Exerc* 36: 1328-1335, 2004.
159. Nieman DC, Henson DA, McMahan M, Wrieden JL, Davis JM, Murphy EA, Gross SJ, McAnulty LS and Dumke CL. Beta-glucan, immune function, and upper respiratory tract infections in athletes. *Med Sci Sports Exerc* 40: 1463-1471, 2008.
160. Nieman DC, Johanssen LM and Lee JW. Infectious episodes in runners before and after a roadrace. *J Sports Med Phys Fitness* 29: 289-296, 1989.
161. Nieman DC, Johanssen LM, Lee JW and Arabatzis K. Infectious episodes in runners before and after the Los Angeles Marathon. *J Sports Med Phys Fitness* 30: 316-328, 1990.

162. Nieman DC, Williams AS, Shanely RA, Jin F, McAnulty SR, Triplett NT, Austin MD and Henson DA. Quercetin's influence on exercise performance and muscle mitochondrial biogenesis. *Med Sci Sports Exerc* 42: 338-345, 2010.
163. Oliver SJ, Costa RJ, Laing SJ, Bilzon JL and Walsh NP. One night of sleep deprivation decreases treadmill endurance performance. *Eur J Appl Physiol* 107: 155-161, 2009.
164. Opp MR, Kapas L and Toth LA. Cytokine involvement in the regulation of sleep. *Proc Soc Exp Biol Med* 201: 16-27, 1992.
165. Palmblad J, Cantell K, Strander H, Froberg J, Karlsson CG, Levi L, Granstrom M and Unger P. Stressor exposure and immunological response in man: interferon-producing capacity and phagocytosis. *J Psychosom Res* 20: 193-199, 1976.
166. Pedersen BK and Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 80: 1055-1081, 2000.
167. Peters EM. Exercise, immunology and upper respiratory tract infections. *Int J Sports Med* 18 Suppl 1: S69-S77, 1997.
168. Petrovsky N, McNair P and Harrison LC. Circadian rhythmicity of interferon-gamma production in antigen-stimulated whole blood. *Chronobiologia* 21: 293-300, 1994.
169. Phillips AC, Burns VE and Lord JM. Stress and exercise: Getting the balance right for aging immunity. *Exerc Sport Sci Rev* 35: 35-39, 2007.
170. Pugh L and Ward M. Some effects of high altitude on man. *Lancet* 271: 1115-1121, 1956.
171. Pyne DB, Gleeson M, McDonald WA, Clancy RL, Perry C, Jr. and Fricker PA. Training strategies to maintain immunocompetence in athletes. *Int J Sports Med* 21 Suppl 1: S51-S60, 2000.
172. Pyne DB, Hopkins WG, Batterham AM, Gleeson M and Fricker PA. Characterising the individual performance responses to mild illness in international swimmers. *Br J Sports Med* 39: 752-756, 2005.
173. Pyne DB, McDonald WA, Morton DS, Swigget JP, Foster M, Sonnenfeld G and Smith JA. Inhibition of interferon, cytokine, and lymphocyte proliferative responses in elite swimmers with altitude exposure. *J Interferon Cytokine Res* 20: 411-418, 2000.
174. Rae DE, Knobel GJ, Mann T, Swart J, Tucker R and Noakes TD. Heatstroke during endurance exercise: is there evidence for excessive endothermy? *Med Sci Sports Exerc* 40: 1193-1204, 2008.
175. Rav-Acha M, Hadad E, Epstein Y, Heled Y and Moran DS. Fatal exertional heat stroke: a case series. *Am J Med Sci* 328: 84-87, 2004.
176. Redwine L, Hauger RL, Gillin JC and Irwin M. Effects of sleep and sleep deprivation on interleukin-6, growth hormone, cortisol, and melatonin levels in humans. *J Clin Endocrinol Metab* 85: 3597-3603, 2000.
177. Reeser JC, Willick S and Elstad M. Medical services provided at the Olympic Village polyclinic during the 2002 Salt Lake City Winter Games. *Wisc Med J* 102: 20-25, 2003.
178. Reinberg A, Schuller E, Clench J and Smolensky MH. Circadian and circannual rhythms of leukocytes, proteins and immunoglobulins. In: *Recent advances in the chronobiology of allergy and immunology*, edited by Smolensky MH, Reinberg A and McGovern JP. Oxford: Pergamon Press, 1980, p. 251-259.

179. Rhind SG, Gannon GA, Shek PN, Brenner IK, Severs Y, Zamecnik J, Buguet A, Natale VM, Shephard RJ and Radomski MW. Contribution of exertional hyperthermia to sympathoadrenal-mediated lymphocyte subset redistribution. *J Appl Physiol* 87: 1178-1185, 1999.
180. Rhind SG, Gannon GA, Shephard RJ, Buguet A, Shek PN and Radomski MW. Cytokine induction during exertional hyperthermia is abolished by core temperature clamping: neuroendocrine regulatory mechanisms. *Int J Hyperthermia* 20: 503-516, 2004.
181. Ricardo JS, Cartner L, Oliver SJ, Laing SJ, Walters R, Bilzon JL and Walsh NP. No effect of a 30-h period of sleep deprivation on leukocyte trafficking, neutrophil degranulation and saliva IgA responses to exercise. *Eur J Appl Physiol* 105: 499-504, 2009.
182. Ristow M, Zarse K, Oberbach A, Kloting N, Birringer M, Kiehnkopf M, Stumvoll M, Kahn CR and Bluher M. Antioxidants prevent health-promoting effects of physical exercise in humans. *Proc Natl Acad Sci U S A* 106: 8665-8670, 2009.
183. Ritchie AW, Oswald I, Micklem HS, Boyd JE, Elton RA, Jazwinska E and James K. Circadian variation of lymphocyte subpopulations: a study with monoclonal antibodies. *Br Med J (Clin Res Ed)* 286: 1773-1775, 1983.
184. Roberts WO. Exercise-associated collapse in endurance events: A classification system. *Phys Sportsmed* 17: 49-55, 1989.
185. Romeo J, Warnberg J, Pozo T and Marcos A. Physical activity, immunity and infection. *Proc Nutr Soc* 69: 390-399, 2010.
186. Ronsen O. Prevention and management of respiratory tract infections in athletes. *New Stud Athlet* 20: 49-56, 2005.
187. Rosenberger PH, Ickovics JR, Epel E, Nadler E, Jokl P, Fulkerson JP, Tillie JM and Dhabhar FS. Surgical stress-induced immune cell redistribution profiles predict short-term and long-term postsurgical recovery. A prospective study. *J Bone Joint Surg Am* 91: 2783-2794, 2009.
188. Rostrup M. Catecholamines, hypoxia and high altitude. *Acta Physiol Scand* 162: 389-399, 1998.
189. Saint-Mezard P, Chavagnac C, Bosset S, Ionescu M, Peyron E, Kaiserlian D, Nicolas JF and Berard F. Psychological stress exerts an adjuvant effect on skin dendritic cell functions in vivo. *J Immunol* 171: 4073-4080, 2003.
190. Sapolsky RM. The influence of social hierarchy on primate health. *Science* 308: 648-652, 2005.
191. Sarnquist FH. Physicians on Mount Everest. A clinical account of the 1981 American Medical Research Expedition to Everest. *West J Med* 139: 480-485, 1983.
192. Saul AN, Oberyszyn TM, Daugherty C, Kusewitt D, Jones S, Jewell S, Malarkey WB, Lehman A, Lemeshow S and Dhabhar FS. Chronic stress and susceptibility to skin cancer. *J Natl Cancer Inst* 97: 1760-1767, 2005.
193. Schedlowski M, Jacobs R, Stratmann G, Richter S, Hadicke A, Tewes U, Wagner TO and Schmidt RE. Changes of natural killer cells during acute psychological stress. *J Clin Immunol* 13: 119-126, 1993.
194. Schwab CL, Fan R, Zheng Q, Myers LP, Hebert P and Pruett SB. Modeling and predicting stress-induced immunosuppression in mice using blood parameters. *Toxicol Sci* 83: 101-113, 2005.
195. Selkirk GA, McLellan TM, Wright HE and Rhind SG. Mild endotoxemia, NF-kappaB translocation, and cytokine increase during exertional heat stress in trained and untrained individuals. *Am J Physiol Regul Integr Comp Physiol* 295: R611-R623, 2008.

196. Senchina DS, Shah NB, Doty DM, Sanderson CR and Hallam JE. Herbal supplements and athlete immune function--what's proven, disproven, and unproven? *Exerc Immunol Rev* 15: 66-106, 2009.
197. Severs Y, Brenner I, Shek PN and Shephard RJ. Effects of heat and intermittent exercise on leukocyte and sub-population cell counts. *Eur J Appl Physiol Occup Physiol* 74: 234-245, 1996.
198. Shephard RJ. Sleep, biorhythms and human performance. *Sports Med* 1: 11-17, 1984.
199. Shephard RJ. Immune changes induced by exercise in an adverse environment. *Can J Physiol Pharmacol* 76: 539-546, 1998.
200. Shephard RJ and Shek PN. Cold exposure and immune function. *Can J Physiol Pharmacol* 76: 828-836, 1998.
201. Shephard RJ and Shek PN. Immune dysfunction as a factor in heat illness. *Crit Rev Immunol* 19: 285-302, 1999.
202. Shing CM, Hunter DC and Stevenson LM. Bovine colostrum supplementation and exercise performance: potential mechanisms. *Sports Med* 39: 1033-1054, 2009.
203. Singh I, Chohan IS, Lal M, Khanna PK, Srivastava MC, Nanda RB, Lamba JS and Malhotra MS. Effects of high altitude stay on the incidence of common diseases in man. *Int J Biometeorol* 21: 93-122, 1977.
204. Spence L, Brown WJ, Pyne DB, Nissen MD, Sloots TP, McCormack JG, Locke AS and Fricker PA. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. *Med Sci Sports Exerc* 39: 577-586, 2007.
205. Starkie RL, Hargreaves M, Rolland J and Febbraio MA. Heat stress, cytokines, and the immune response to exercise. *Brain Behav Immun* 19: 404-412, 2005.
206. Steinacker JM, Lormes W, Lehmann M and Altenburg D. Training of rowers before world championships. *Med Sci Sports Exerc* 30: 1158-1163, 1998.
207. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol* 38: 963-970, 2009.
208. Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: evidence for gender disparity. *Brain Behav Immun* 22: 960-968, 2008.
209. Sureda A, Tauler P, Aguilo A, Cases N, Llompert I, Tur JA and Pons A. Influence of an antioxidant vitamin-enriched drink on pre- and post-exercise lymphocyte antioxidant system. *Ann Nutr Metab* 52: 233-240, 2008.
210. Tiollier E, Schmitt L, Burnat P, Fouillot JP, Robach P, Filaire E, Guezennec C and Richalet JP. Living high-training low altitude training: effects on mucosal immunity. *Eur J Appl Physiol* 94: 298-304, 2005.
211. Toth LA, Tolley EA and Krueger JM. Sleep as a prognostic indicator during infectious disease in rabbits. *Proc Soc Exp Biol Med* 203: 179-192, 1993.
212. van Deventer SJ, Buller HR, ten Cate JW, Aarden LA, Hack CE and Sturk A. Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic, and complement pathways. *Blood* 76: 2520-2526, 1990.
213. Veldhuis JD, Johnson ML, Iranmanesh A and Lizarralde G. Rhythmic and non-rhythmic modes of anterior pituitary hormone release in man. In: *Biological rhythms in clinical and laboratory medicine*, edited by Touitou Y and Haus E. Heidelberg: Springer Verlag, 1994, p. 277-291.

214. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K and Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 82: 1313-1316, 1997.
215. Viswanathan K, Daugherty C and Dhabhar FS. Stress as an endogenous adjuvant: augmentation of the immunization phase of cell-mediated immunity. *Int Immunol* 17: 1059-1069, 2005.
216. Viswanathan K and Dhabhar FS. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. *Proc Natl Acad Sci U S A* 102: 5808-5813, 2005.
217. Walsh NP, Bishop NC, Blackwell J, Wierzbicki SG and Montague JC. Salivary IgA response to prolonged exercise in a cold environment in trained cyclists. *Med Sci Sports Exerc* 34: 1632-1637, 2002.
218. Walsh NP and Whitham M. Exercising in environmental extremes: a greater threat to immune function? *Sports Med* 36: 941-976, 2006.
219. Waninger KN and Harcke HT. Determination of safe return to play for athletes recovering from infectious mononucleosis: a review of the literature. *Clin J Sport Med* 15: 410-416, 2005.
220. Wenisch C, Narzt E, Sessler DI, Parschalk B, Lenhardt R, Kurz A and Graninger W. Mild intraoperative hypothermia reduces production of reactive oxygen intermediates by polymorphonuclear leukocytes. *Anesth Analg* 82: 810-816, 1996.
221. West NP, Pyne DB, Peake JM and Cripps AW. Probiotics, immunity and exercise: a review. *Exerc Immunol Rev* 15: 107-126, 2009.
222. Wood PG, Karol MH, Kusnecov AW and Rabin BS. Enhancement of antigen-specific humoral and cell-mediated immunity by electric footshock stress in rats. *Brain Behav Immun* 7: 121-134, 1993.
223. Woods JA, Vieira VJ and Keylock KT. Exercise, inflammation, and innate immunity. *Immunol Allergy Clin North Am* 29: 381-393, 2009.
224. Wright CE, Erbllich J, Valdimarsdottir HB and Bovbjerg DH. Poor sleep the night before an experimental stressor predicts reduced NK cell mobilization and slowed recovery in healthy women. *Brain Behav Immun* 21: 358-363, 2007.
225. Yfanti C, Akerstrom T, Nielsen S, Nielsen AR, Mounier R, Mortensen OH, Lykkesfeldt J, Rose AJ, Fischer CP and Pedersen BK. Antioxidant supplementation does not alter endurance training adaptation. *Med Sci Sports Exerc* 42: 1388-1395, 2010.
226. Zhang Y, Hu Y and Wang F. Effects of a 28-day "living high--training low" on T-lymphocyte subsets in soccer players. *Int J Sports Med* 28: 354-358, 2007.