

# Upper respiratory tract infections and the immune system response. A review.

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## Systematic Review

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# Abstract

**Purpose:** the spreading of the COVID-19 epidemic raised a question on why very well trained, healthy, and young athletes have been infected. In this review, the emerging topic in the field of sport immunology has been studied with the aim to provide advice on how strengthening the immune system (IS) and how to help the recover after heavy effort and prevent upper respiratory tract infection (URTI) in athletes.

**Methods:** a literature search was performed on available public scientific databases. **Results:** URTI, a common illness among heavy trained athletes, happens in the time frame of temporary depression of the IS following heavy training or competition. T cells has been identified as the main factor in the immune response to counteract the cascade mediators of inflammation. Life habits, environmental and psycho-social factors such as sleep loss and life stressors are the major causes of IS depression, and it emerge that there is an optimal training load exposure which reinforce the IS, while too low or too much training being detrimental. **Conclusions:** immunodepression in heavy trained athletes can be counteracted with a proper distribution of training loads, nutritional interventions, correction of lifestyle habits such as sleep hygiene, thermotherapy, and recovery techniques. Psycho-social interventions also seem to have a positive effect on reducing the post exercise inflammation and in boosting the IS response. Novel bioinformatic approaches can help to understand the IS response in athletes and the management of critical situations.

## Introduction

A 29 years old male 3000 m dash runner (personal best 8.17.00) healed from Covid-19 after hospitalization for heavy respiratory symptoms, has triggered a discussion on the heavy exercise and the immune system in competitive athletes on Italian media [1].

Immune system response is a complex concept which refer to thousands of different factors, some orchestrating together and some working independently or in local networks, mediated by many mechanisms at transcriptional, molecular and systemic level.

An Immune Exposure has been defined as: “the process by which components of the immune system first encounter a potential trigger” [2]. To understand what really happens in the big picture of the immune response, recently some information theory approach was tried, modeling the process from the existing body of knowledge about the different phenomena which characterized this response, producing a complex modeling bioinformatics system, feeded by data originating in the existing knowledge of the immune response [2]. This approach produced a software environment where the human body organism of immune response can be mathematically simulated [2]. The immune response in athletes is, in some extent, different from that one happening in non-heavily trained organisms, due to the high demands of training. Further, different sports are different in the exposition to pathogens (e.g. water sports vs land sports), and in the environment where the sports take place (e.g. winter and mountain sport vs hot environments sports). Also, the organization and the contents of training in different sports, determine different responses of the athlete immune system, as well as sex, age, genetics factors and level of

qualification (e.g. amateur vs elite athletes). The interaction between these factors, are manifold, complex and mostly unknown. For example, a young athlete who compete in sport where physical appearance is important (e.g. artistic gymnastic) undergone severe diet restrictions, associate with heavy training regimes, while weight lifters have an high caloric intake, associate with intense loads of relatively short duration, and so on. The literature about immune system and sport is broad, but specifically there are few studies dealing with the respiratory tract infection and training and the existing theories are somewhat controversial.

## Methods

An online literature search was performed using PubMed from inception of the database to July 2020 with the following keywords used in different combinations: "upper respiratory tract infections and sport", "training and immune system" "endurance and immunity" "sleep and immunity" "exercise and inflammation" , "upper respiratory tract infections", "stress and training" , "training overload," "nutrition and recovery" "performance," "recovery," "fatigue," "stress". All titles and abstracts were carefully read, and relevant articles were retrieved for review. In addition, the reference lists from both original and review articles retrieved were also reviewed. Inclusion criteria were to deal with respiratory (upper and lower) tract infections in well trained athletes and in elite athletes, be the studies performed with humans (with the exception on one relevant study), be in English language, and be both experimental and theoretical studies. A total of 120 relevant papers were found from which 41 were selected for review.

### **Sport and upper respiratory tract infections.**

Existing literature about heavy exercise and the respiratory tract reports conflicting results about heavy training and its association with suppressed mucosal and cellular immunity and increasing symptoms of respiratory tract infections (URTI). During competition in the cold, the incidence of upper respiratory tract infection is obviously very high : 20 out of 44 (45%) athletes and 22 out of 68 (32%) staff members of Finnish team experienced symptoms of the common cold during a median stay of 21 days at Winter Olympic Games [3]. These results are of course influenced by the environmental conditions, but also in absence of cold weather has been shown that athletes participating in marathon in normal or hot environments [4], showed a 2- to 6-fold increased URTI risk during the 1-2-week post-race. In a large group of 2311 endurance runners, were found nearly 13.0% who reported illness in the week after the Los Angeles Marathon race compared with 2.2% of control runners<sup>3</sup>. This was confirmed by other epidemiological studies in triathletes and in marathon and ultramarathon race events and/or during and after very heavy training [5,6,7].

The decrease in exercise performance after a URTI can last 2-4 days, and runners who unwisely start an endurance race with systemic RTI symptoms are 2/3 times less likely to complete the race [8].

Nieman et al. observed that runners training >96 km/week doubled their odds for sickness (URTI) compared with those training <32 km/week [9]. Nieman also concluded that, following acute bouts of prolonged high-intensity endurance exercise, several components of the immune system are suppressed for several hours [10]. This has led to the concept of the 'open window' theory, which was described as the 1- to 9-hour period following prolonged endurance exercise when the host's defenses are decreased and the risk of URTI is increased. During this 'open window' period, athletes should be advised to remain isolated from all the possible sources of infection. The hypothesis of a J shape relationship between exercise dose and susceptibility to URTI has been proposed by Shepard, which identified in too low or to high exercise load a long term depressing effect on the immune system, with the heavier loads be a major factor to predispose to illness [11]. Another theoretical study [12] proposed instead a sinusoidal relationships (S shape) relationships between infection odd ratio and training load, being the infections high with low loads, lower with moderate exercise (protective role of moderate exercise) in moderate exercise, high in heavy trained but not elite athletes, and low again in elite athletes, having elite athletes an innate resistance to infections [12].

Psychological stress has been shown to influence the immune system increasing the susceptibility to respiratory infections. Too much life stress, has been experimental proven to be a major factor in decreasing body defenses [11]. Elite athletes prone to recurrent URTI have altered/adverse cytokine responses to exercise in comparison with healthy athletes [13]. The consensus for studies of elite athletes is that low levels of salivary IgA and/or secretion rates, low pre-season salivary IgA levels, declining levels over a training period, and failure to recover to pre-training resting levels, are associated with an increased risk of URTI [14]. Prolonged and strenuous aerobic exercise induces a marked decrease in plasma concentration of glucose and amino acids, which can lead to immunodepression. In this case, the maintenance of nutrient availability during and after vigorous exercise is essential for proper immune system control, which is coordinated by nutrient sensors (i.e., AMPK and mTOR) and metabolic pathways (i.e., glycolytic or oxidative phosphorylation) in immune cells [13]. Thymus, the site of production of T and B cells, is one of the main organs under stress for immune response. Thymic activity is reduced by strenuous exercise [14]. Since thymic production of T cells naturally decline with age, experimental results raised the concern that prolonging high intensity exercise into the 4th decade of life may have deleterious consequences for athletes' health [14, 15, 16]. Others available data suggest that the effects of conditioning could be mediated by a preferential effect on T cells [12, 16]. Prolonged and exhaustive exercise typically reduces peripheral blood type-1 T-cell number and their capacity to produce the pro-inflammatory cytokine, interferon- $\gamma$  [17]. Thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine, exhibits both pro-inflammatory and pro-homeostatic properties depending on the context and tissues in which it is expressed. It is well-known that TSLP can trigger the production of Th2 cytokines, such as IL-13 and IL-4 [18].

Moreover, heavy training loads are associated with elevated numbers of resting peripheral blood type-2 and regulatory T-cells, which characteristically produce the anti-inflammatory cytokines, interleukin-4 and interleukin-10, respectively. This appears to increase the risk of upper respiratory symptoms, potentially due to the cross-regulatory effect of interleukin-4 on interferon- $\gamma$  production and immunosuppressive

action of IL-10 [17]. Time course of the inflammatory response is a key factor in determine time windows who make the organism prone to infections. It is well known that WBC increases acutely after strenuous exercise. We observed an acute (after 1 hour cycling at exhaustion > 70% of  $VO_2$ max with 3 bursts of 10 minutes > 80%  $VO_2$ max), but not chronic (after 1 month training) of white blood cell count from  $6,27 \pm 2,34 \cdot 10^3 / \mu\text{l}$  to  $9,01 \pm 3,63 \cdot 10^3 / \mu\text{l}$  in trained cyclists [19].

Inflammatory response is a crucial biological response, which has been extensively studied in the context of skeletal muscle growth and repair, sarcopenia, and myopathies. Recruited and resident immune cells of injured muscle secrete pro-inflammatory cytokines such as IL-1, IL-8, IL-6, and TNF $\alpha$  triggering a cascade of downstream inflammatory signaling pathways where NF $\kappa$ B represents one of the most significant signaling molecule activated upon injury in skeletal muscle [20]. Environmental factors have a significant role in promoting respiratory tract infections. Air pollution has been shown to be a factor facilitating lung inflammation. Results from literature suggests that acute PM2.5 with different concentration can cause different degrees of adverse effects on lung, especially in high (> 500  $\mu\text{g}/\text{m}^3$ ) concentrations [21]. Some benefit has been observed from low intensity aerobic interval training in impeding the oxidative stress and inflammation caused by pollution exposure [21], helping in removing pollutants from the lungs. Some nutritional facts have been advocated to prevent RTI infection in athletes. Protective role of vitamin D has been invoked for normal population [22], albeit in athlete there was found any effect [23] of Vitamin D supplementation in preventing respiratory tract infections. Vitamin C and E has also been advocated [24], has as protective substances, thus fruit consumption [25]. Recently, intestine microbiota was indicated to have a potentiation role on the immune system [26]. Microbiota also stimulates T cells and neutrophils (Nf), inducing a pathogen spreading control, and B cells. Nutrition countermeasures to exercise stress, probiotics (a derived of dairy products, mainly lactobacillus) has been recently investigated and recommended to improve gut microbiota [27]. However, the link between gut microbiota, mucosal immunity and exercise stimulation has not yet fully explored, leading to several possibilities for further research in the exercise immunology.

### **Strategies to boost immune system in heavy trained athletes.**

Recovery procedures and training load distribution are the most obvious strategies to boost the immune system in heavy trained athletes. Apart of the many nutritional suggestions, there are less explored and quite inexpensive systems to improve immunity in heavy training athletes. First one is the organization of the training. The tetradic system proposed in the ancient times [28] warning the athletes and the trainers about the organization of the training week, to avoid overloads. As stated by Philostratus : "...after a first day of introductory mild-intensity training, the second day is dedicated to strenuous exercise, followed by a day of low intensity, and another day of mild intensity exercise ". A proper sleep was also recommended together with a regulate life habits and proper diet. Thus, yet in ancient time were well know the risk of overtraining. in lowering the body defenses. A proper sleep is necessary to boost immune system, but a question arises about which is a "proper" sleep. Sleep can be characterized both from duration than from quality. For example, training placed in late evening hours, due to the activation of the adrenergic system (hypothalamus-pituitary-adrenocortical axis), has been proven to be detrimental to a good sleep and to a

decrease in total sleep time and slow-wave sleep and REM sleep (the restoring sleep), while moderate training increase REM sleep [29]. The susceptibility window to infections after heavy training is a temporary phenomenon than can last from several hours to days [30], so, another important preventive measure to preserve the body in the susceptibility window, is to adopt physical measures during the recovery phases, for example hyperthermia (saunas) in the cold environments has been shown to be an effective method. Repetitive mild hyperthermia has been proven to be effective in elevating CD56(+) NKT and B and T cells after 7 days of daily exposure at 40 degrees [31,32]. After exercise, cryotherapy has shown to have some effect on immune system recovery [33], lowering peripheral inflammation. Many evidence exist about the efficacy of massage in improving the immune system response. Recent studies in animals [34] and in men [35] shown the efficacy of massage in boosting effects on T cell repertoire and in decrease noradrenergic innervation of lymphoid organs. Lifestyles intervention and psychological methods has also been proven to be effective in boost the immune system, for example meditation and methods to coping with life stressors [36,37]. Quite simple activities, such as breathing control can be helpful in reducing stress, boosting immune system [38, 39]. An emerging measure to boost immune system, is the so-called nature-based therapy. Using relaxing environment to decrease stress, ameliorating subjective (stress scales) and objective (lower catecholamines) has proven to be an effective way to restore and improve the immune system [40]. In this respect, social stress is known to be associated with a low immune system [41], and social situation of menace, panic or continuous pressure, can seriously impair the immune system. High level athletes must cope with high social pressure and thus stress, and this is also a possible concurrent cause of immunodepression. From this point on, the discourse about stress and thinking, become philosophic or even religious, and is beyond the scope of this review.

## Conclusions

Immunity is a complex interaction between organs and the environment, mediated by several genes, receptors, molecules, hormones, cytokines, antibodies, antigens, inflammation substances which in turn relate to psychological factors. Immune system response of heavy trained athletes has been theorized to follow a J or S shape dynamics in times, being high training loads effective in modify the immune response elevating the biological markers of immunity and the organism susceptibility to infections. The cascade of inflammatory markers of inflammation have as a main player the T cells systems. Training in cold environment put the athletes at risk and every manageable and affordable countermeasure must be considered by coaches and athletes. Athletes, who are considered healthier than normal population, are in fact prone to infections of the respiratory tract, due to lowering of the immune system in the time frames subsequent heavy training sessions. Apart of behavioral intervention to minimize the “open window” effect on infection, some recommendation can be found in the scientific literature on how to cope with stressors and boost the immune system in athletes which are on heavy training or after heavy competition. A key factor is a progression in training loads, a proper placement of training sessions, and allowing a proper recovery between training sessions. Relatively simple measures can be adopted, such as sleep hygiene and increase personal hygiene, reducing exposure to possible factors of infections, and

proper nutrition rich in vitamins, hot beverages in winter, sauna, massage as proper recovery intervention can be helpful in prevent illness together with vaccination. However, social factors are also emerging important determinant of susceptibility to inflammation, such as environmental pollution and cleanliness. Availability of food with high content of high-quality nutrients, and even economic income are determining factors of health. Further research is needed in the modeling of the immune response and on interaction between physiological and social factors involving the sphere of humanities sciences into the model of the immune response.

## Declarations

### Competing Interests:

The author declares no competing interests.

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