Physical exercise, immune response and susceptibility to infections – current knowledge and growing research areas

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Abstract

This review presents state-of-the-art knowledge and identifies knowledge gaps for future research in the area of exercise-associated modifications of infection susceptibility. Regular moderate-intensity exercise is believed to have beneficial effects on immune health through lowering inflammation intensity and reducing susceptibility to respiratory infections. Infection-promoting consequences are attributed to strenuous exercise as performed by professional athletes. In about half of the athletes presenting respiratory symptoms, no causative pathogen can be identified. Acute bouts of exercise enhance release of proinflammatory mediators thus probably leading to appearance of infection-like respiratory symptoms. Studies assessing influence of regularly repeated exercise on immune response and systemic inflammation are far less numerous than those regarding acute exercise effects. This identifies another knowledge gap requiring further assessment both in recreational and in professional athletes Additionally, ambient and environmental conditions modify systemic inflammatory response and infection susceptibility in particular in outdoor athletes. Both acute and chronic regular exercise influence humoral and cellular immune response mechanisms resulting in decreased specific and non-specific response in competitive athletes. Most promising areas of further research in exercise immunology include: detailed immunological characterization of infection-prone and infection-resistant athletes; efficacy of nutritional and pharmaceutical interventions as countermeasures to infections' symptoms; and influence of various exercise loads on susceptibility to infections with respiratory viruses, including SARS-CoV-2. Establishing uniform definition of "elite athlete' shall hopefully allow for comparable and straightforward interpretation of data coming from different studies and settings.

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Regular moderate-intensity exercise is believed to have beneficial effects on immune health through lowering inflammation intensity and reducing susceptibility to respiratory infections. Infection-promoting consequences are attributed to strenuous exercise as performed by professional athletes. In about half of the athletes presenting respiratory symptoms, no causative pathogen can be identified. Acute bouts of exercise enhance release of proinflammatory mediators thus probably leading to appearance of infection-like respiratory symptoms. Studies assessing influence of regularly repeated exercise on immune response and systemic inflammation are far less numerous than those regarding acute exercise effects. This identifies another knowledge gap requiring further assessment both in recreational and in professional athletes Additionally, ambient and environmental conditions modify systemic inflammatory response and infection susceptibility in particular in outdoor athletes. Both acute and chronic regular exercise influence humoral and cellular immune response mechanisms resulting in decreased specific and non-specific response in competitive athletes. Most promising areas of further research in exercise immunology include: detailed immunological characterization of infection-prone and infection-resistant athletes; efficacy of nutritional and pharmaceutical interventions as countermeasures to infections' symptoms; and influence of various exercise loads on susceptibility to infections with respiratory viruses, including SARS-CoV-2. Establishing uniform definition of "elite athlete' shall hopefully allow for comparable and straightforward interpretation of data coming from different studies and settings.

Introduction & overview

Regular physical exercise is recommended as part of the lifestyle modifications scheme aimed to reduce morbidity and mortality associated with the so-called civilization diseases. Until recent years the paradigm of beneficial influence of regular recreational exercise training was predominant, while noxious consequences used to be attributed to strenuous exercise as performed by professional athletes. Regular moderate exercise training has also been considered protective with regard to common respiratory infections and systemic low-grade inflammation(1,2). However, endurance sports, such as long-distance running and triathlon, keep becoming more and more popular in the general society. Questionnaire-based studies among runners have

documented increased incidence of upper respiratory tract infections (URTIs) symptoms during the days directly following participation in the event(3,4) Elite athletes frequently report URTI symptoms but their infectious etiology could be confirmed in only about 30-45% of cases. It has been suggested, that in subjects in whom the pathogen could not be identified, infection-like symptoms developing after exercise may be attributed to exercise-induced airway inflammation.

Therefore, spreading the knowledge and raising the awareness about influence of exercise training on the immune system and infection susceptibility is of high importance.

As part of a project of the Workng Group "Allergy, Asthma and Sports" within the EAACI Asthma Section, we hereby review the current literature, aiming at presenting state-of-the-art knowledge and identifying knowledge gaps for the purpose of future research.

Infections in exercising subjects – prevalence, epidemiology, pathogens

Elite athletes frequently report upper and lower respiratory symptoms but – as it was mentioned above - their infectious etiology can be confirmed roughly in half of cases. Spence et al in a prospective surveillance study have analyzed nasopharyngeal and throat swabs acquired during 37 symptomatic episodes in 28 elite and non-elite athletes confirming bacterial or viral etiology in 11 episodes (6). Viral pathogens identified included rhinoviruses and adenoviruses, whereas *M. pneumoniae, S.aureus* and *S.pneumoniae* were confirmed as bacteria responsible for URTI symptoms (6).

Cox et al identified viral or bacterial pathogen in 30% of oropharyngeal swab samples taken from elite Australian athletes with upper respiratory symptoms (URS)(7). Involvement of a single viral pathogen was ascertained in 26% of cases, whereas a bacterial cause was confirmed in 3% of infectious episodes. Most frequently detected viral pathogens included: rhinovirus (10%), influenza virus (10%), parainfluenza viruses 1,2 and 3 (6%) and coronaviruses (3%)(7).

Data published to date indicate that pathogen identification is possible in approximately 45% cases of upper respiratory symptoms in athletes (5). Similar proportion has been also described regarding URS in general population (8).

Infection-like syndromes in athletes - when no pathogen can be identified Development of symptoms during remaining infection-like incidents may possibly be attributed to activation of inflammatory process. This phenomenon can be accompanied by changes in synthesis and release of innate immunity proteins with proinflammatory, anti-inflammatory as well as immunomodulatory properties. Exercise, especially the strenuous one and/or performed in unfavorable ambient conditions, contributes to development of an inflammatory response. Exercise-induced inflammatory responses have been described both locally and on a systemic level.

Exercise and systemic inflammation

The effect of an acute exercise bout on systemic inflammatory parameters has been well established and confirmed in several studies. A single bout of intensive exercise training is associated with increased synthesis and release of acute phase proteins and proinflammatory cytokines (IL-6, TNF-α, IL-1β, MIP-1α). Increased serum levels of anti-inflammatory cytokines (e.g., IL-10, IL-1ra) have been observed as a secondary phenomenon (2,9–12). Serum levels of periostin, a hallmark of type 2 inflammation, were not increased within 1 hour after acute bout of exercise. In a study assessing serum cytokine responses to treadmill running exercise, resting levels of anti-inflammatory and immunomodulatory cytokines (IL-1ra, IL-10) were higher in URTI symptoms-free subjects. In contrast, acute exercise-induced IL-6 release was more pronounced in subjects prone to develop respiratory symptoms. This suggests presence of some dysregulation in cytokine balance and impairment of anti-inflammatory mechanisms in infection-prone exercisers.

An acute endurance or ultra-endurance exercise are possible good models for studies on exercise-induced inflammatory cytokine response. Interestingly, it has been recently shown that modulation of inflammatory cytokine response profile caused by 40-km run can be different from that induced by a 171-km ultra-endurance

race. Although both races led to significant increase in serum MIP-1β, MCP-1, IL-6, IL-8 and TNF-α, plasma IL-17A and IL-1β levels were notably higher only after a 171-km trail. (14) In the light of these observations, further research is to be undertaken with particular focus on pro- and anti-inflammatory effects of participation in extreme sports events.

Studies on systemic inflammatory cytokines in regular exercisers report varying findings. Henson et al have observed lack of significant difference between adolescent tennis players and non-athletic controls in terms of serum/plasma IL-1ra and respiratory infections over 2.5 months. During training season significant decrease in intracellular IL-2 and IL-4 production had been described in Italian footballers (16). In parallel , a Portuguese study in kayakers revealed lower plasma IL-1β, IL-18, IFN-γ and IL-1ra levels off-training season as compared to training season, which speaks in favor of beneficial anti-inflammatory effect of regular albeit intensive exercise (17). In a small study, significantly higher resting serum levels of periostin in elite swimmers compared to asthmatics or healthy subjects were described (13).

A recent systematic review and meta-analysis of 19 randomized controlled trials investigating effect of regular exercise on inflammatory cytokine response revealed that anti-inflammatory effect of regular moderate exercise may be due to decreased levels of inflammasome activation-related cytokines (IL-1β and IL-18) (18). Enhanced release of IL-1ra, upon acute bouts of exercise has also been reported (11,19). However, IL-1ra levels tend to decrease post-exercise in athletes reporting four or more episodes of upper respiratory infections per year (11). In a study involving Polish speed skaters, athletes considered less prone to URTIs basing on questionnaire data, had significantly higher serum IL-1ra during winter training period which seems concordant with the anti-inflammatory spectrum of IL-1ra activity (20).

Apart from the exercise as a stimulus *per se* , the influence of ambient conditions in which the exercise is performed on systemic inflammatory markers has also been studied. Changes in serum pro- and anti-inflammatory cytokines were reported in subjects exercising in warm and humid conditions (21). Observations in speed skaters suggest that unfavorable ambient conditions during winter outdoor activity - and not exercise load *per se* – may constitute primary factor modifying systemic inflammation (20).

In general, studies assessing influence of regularly repeated exercise on immune and inflammatory parameters at a systemic level are far less numerous than those regarding effects of an acute exercise bout. This can, therefore, be identified as one of knowledge gaps requiring further assessment both in recreational and in professional athletes performing exercise characterized by different patterns and intensity. During future research planning, provisions should be made for the fact that immune cells are not the sole source of inflammatory proteins (e.g., IL-6, periostin) (22,23) and considerable involvement of muscles as source of proteins released upon exercise must be taken into account during interpretation of results of serum/plasma assessments.

The effect of exercise on airway inflammation

Apart from investigations at the systemic level, potential influence of exercise on inflammation in upper and lower airways has been studied using non- or semi-invasive airway samplings such as nasal lavage fluid (NLF) and exhaled breath condensate (EBC) . Data acquired so far are, however, inconclusive, partly due to considerable differences in sampling methodology.

TNF-α, a pleiotropic pro-inflammatory cytokine released by a wide spectrum of cells, can be increased at both mRNA and protein level in the asthmatic airways. Mast cell-derived TNF-α has been postulated as playing a role in the pathophysiology of airway smooth muscle contraction (as reviewed in (32) and (33)). A bout of exercise induces a serum TNF-α increase followed shortly by a secondary release of interleukin 10 (IL-10) and IL-1ra. In a small study of swimmers and speed skaters (n=15) no considerable influence of acute bout of exercise on the levels of inflammatory mediators in exhaled breath condensate (EBC) was observed (29), a similar cytokine pattern disbalance was seen in lower airways of elite athletes and asthmatics. Namely, baseline TNF-α levels in EBC in non-asthmatic athletes were comparable to those observed in non-exercising asthmatics. Moreover, this was accompanied by decreased levels of anti-inflammatory IL-1ra in EBC of both athletes and asthmatics. Increased intensity of inflammation in the airways, particularly

neutrophilic as reflected by increased cell counts and sputum MPO, was also described in subjects exposed to unfavorable ambient conditions on high altitudes(30). In another study, baseline sputum mRNA expression of multiple pro-inflammatory proteins was not increased in athletes, but swimming training session induced considerable increase in IL-1β, IL-6 and TNF-α mRNA expression (31). Neutrophilic airway inflammation has been consistently described in different studies performed in winter athletes (34). Inflammatory changes in athletes' airways are reflected in considerable frequency of non-specific bronchial hyperresponsiveness observed in more than 40% of athletes, in particular those performing inter outdoor sports (20,34–36).

During interpretation of data reflecting local exercise-associated airway inflammation, several coexisting factors should be considered. Inflammatory changes in the airways may result independently from separate influence of exercise and environmental conditions. Influence of atopy *per se* on local airway inflammation cannot be neglected, either. The extent of contribution of each factor to airway inflammation can be determined with high degree of accuracy only if studies are specifically designed in order to include this influence.

Influence of exercise on cellular immune response mechanisms

Exercise activates various physiological mechanisms leading to alterations in number and functions of innate immunity cells. These mechanisms include: oxidative stress, increased metabolic rate, increased release of heat shock proteins, catecholamines, cortisol and insulin-like growth factor (2). Short lasting bout of exercise induces rapid and considerable yet transient increase in neutrophil numbers directly after exercise. After several hours a second wave of increased neutrophil number may be seen, depending on intensity and duration of exercise (37,38). The initial increase in neutrophils results from the release of marginal pool cells, while later increase is due to the exercise-associated cortisol action on bone marrow. Acute bout of exercise has ambiguous influence on neutrophils' function. Degranulation, phagocytic properties and oxidative burst activity are increased in spontaneous conditions, but may be decreased after acute exercise (2) .

A more recent study has shown that in elite athletes oxidative stress markers decrease

after exercise (39). Although acute bout of exercise performed at high intensity (>60% of maximal oxygen uptake) may result in oxidative stress due to reactive oxygen species (ROS) being generated excessively by enhanced oxygen consumption (40)(a phenomenon known as exercise-induced oxidative stress), several studies have demonstrated that continuous aerobic training reduces ROS production and increases antioxidant defenses .

An acute bout of exercise causes transient increase in peripheral monocytes (44–49) probably due to their release from marginal pool . In addition, changes in monocytic surface proteins and cytokine expression can be observed following a single exercise bout, with the pro-inflammatory CD14+/CD16+ phenotype predominance (50,51). Acute bout of exercise has also been reported to decrease the expression of Toll-like receptors (TLR) 1, 2 and 4 (52–54) accompanied by increased LPS-induced release pro-inflammatory cytokines (51).

Regarding tissue macrophages, stimulatory effects of exercise on their phagocytosis, anti-tumor activity, reactive oxygen and nitrogen metabolism and chemotaxis were described . Tissue macrophages are characterized with diversity and plasticity. In response to various stimuli they may present pro- or anti-inflammatory phenotype referred to as M1 and M2, respectively. The M1 phenotype results from stimulation by TLR ligands and IFN-γ whereas the M2 phenotype is an effect of alternative stimulation of macrophages by IL-4/IL-13 (55). Increased switching from M1 to M2 macrophage phenotype is one of the postulated mechanisms of anti-inflammatory and somewhat bronchoprotective action of exercise (56). To date, the impact of acute exercise on macrophage polarizations has mainly been studied in animal models and M1-to-M2 macrophage phenotype switching was observed (57). Studies investigating the effects of exercise on macrophage polarization were performed in several tissues, however, they mainly assessed the influence of prolonged physical activity programs (56,58). In a small sample of Taiwanese footballers, acute aerobic exercise caused decrease of proinflammatory M1 phenotype with no effect on M2 phenotype markers (59). Considering the paucity of human studies targeting influence of acute bout of exercise on macrophage polarization and – through

this - on tissue inflammation, it is highly desirable that these issues be addressed in the nearest future. We can identify this area as an unfilled gap and potentially promising research niche in the field of exercise immunology.

Studies targeting dendritic cells (DCs) in the context of acute exercise are not numerous, either. Due to their role in educating naïve T cells during differentiation, DCs can influence the intensity and nature of Th-dependent response. Studying the murine model of asthma, Mackenzie et al assessed the influence of a single bout of moderate exercise on DC maturation and activation (60). Under these conditions, DC maturation was decreased which was evidenced by altered expression of MHC-II, CD80, CD83 and CD86. In the rat model of acute exercise, Liao et al described an increase only in DC number but not functional modifications as assessed by surface molecules' expression (61). In another study, the same group found some functional activities to be increased post-exercise in rats (e.g., MHC-II expression, cytokine production). In a study performed in healthy human adults, LaVoy et al reported that acute exercise bout may contribute to increased generation of monocyte-derived DC in 8-day culture setting, which can constitute a useful tool of acquiring DC for research and immunotherapy purposes (49). Taken together, data published to date indicate that both DC number and function can be modified by acute exercise. Considering important role of these cells in regulation of immune response (including development of type 2 inflammation), impact of exercise on DCs definitely deserves more research interest with particular stress on human studies.

Lymphocytosis induced by acute bout of exercise has been well-documented in human studies. Both T CD4+ and T CD8+ increase in number after acute strenuous exercise in an intensity proportionate manner. However, T CD4+ cells increase in larger absolute numbers due to their higher baseline count in peripheral blood, whereas higher β2-adrenergic receptor density on the surface of T CD8+ cells makes them highly responsive to exercise and leads to larger relative post-exercise increase in their number (63). Both T cell subsets react differently to variable recovery periods between single exercise bouts. T CD4+ and CD8+ lymphocytes may equally fail to return to baseline numbers should the recovery period be shortened. However, subsequent acute exercise leads to more prominent increase in T CD8+ as compared to T CD4+ cell numbers (64).

Exercise-induced shifts in Treg numbers appear to be dependent on exercise intensity and duration. Presently, no consistent data exist on the effect of acute exercise on TCD4+CD25+FoxP3+ cell numbers (63) nor is anything known on the mechanism which might underlie potential effects on Treg cells. For instance, it is postulated that the apparent decline in Tregs observed after triathlon or marathon may be due either to cell apoptosis or their redistribution into peripheral tissues. Recently, a biphasic response of Treg count to acute exercise was described (65)), which adds more to the complexity of the picture and confirms that modulation of Treg-dependent response through acute exercise remains an open field for research.

Considering the influence of chronic exercise training on T cell numbers, significant decrease has been observed in case of IFN-γ+ T cells whereas no considerable impact of exercise upon type 2 (I.e., IL-4+ T cells) was noted in elite cyclists during their training period (66). Decreased Th1 and Treg cells numbers accompanied by increased Th2 numbers were seen four weeks after marathon participation in trained runners as compared with non-running controls (67). These shifts may underlie the increased infection rate in elite athletes. Lastly, a Chinese transcriptome study showed that regular endurance exercise may contribute to transcriptional changes resulting in downregulation of genes coding for proinflammatory proteins (68).

Effects of both acute and chronic exercise on immune response cells' numbers and functions are summarized in **Tables 1 and 2** .

Exercise and humoral immune response

Decreased efficiency of humoral immune response on a mucosal level is consistently associated with physical exercise and manifests predominantly with lowered secretory IgA (sIgA) levels in saliva. Recently, the significance of other salivary antibacterial proteins in exercise-induced modifications of immune response has been discussed . Results of numerous studies have shown increased susceptibility to URTIs in the period directly following participation in a long-distance run (3,4,69,70). Moreover, an association of decreased salivary IgA with increased probability of URTIs has been observed in studies involving elite athletes (71,72)

During the periods of intensive training as a part of sports (71–74) and military (75–77) curriculum, shifts in salivary IgA are observed; decreased sIgA is accompanied by increased infection susceptibility, although the correlation is not always clear and evident (2). In addition, other interfering factors should be considered during interpretation of data regarding influence of short bout of exercise on sIgA levels and susceptibility to infections. These factors include: type and pattern of exercise, its duration as well as general subject's fitness. An extremely intensive training regime is frequently associated with other potential modifiers of immune response, such as increased energy expenditure, sleep deprivation, altitude above sea level and psychological stressors (2,78–80) .

Moderate physical activity as a part of lifestyle modification leads to increase in salivary IgA levels. This further confirms beneficial anti-inflammatory and immunomodulatory influence of regular physical activity performed at a non-elite level (81,82).

Contradictory results have been observed regarding serum concentrations of immunoglobulins. According to several authors, serum IgG's increase in endurance athletes shortly after acute exercise bout as well as over longer periods of repeated trainings (83–86). Other studies have shown, however, considerable falls in serum IgG associated with strenuous exercise, such as 75 km run, 3-week rugby training camp or 14-week running training program (87–90). Serum IgM studies brought similarly ambiguous results: both decreases (83,87–89) and increases (84,91) under intensive exercise conditions have been described. Few studies in which serum IgD levels – as a marker of B cell activation - were assessed have also brought conflicting results (83,84). Shifts in IgE levels under strenuous exercise conditions have not been extensively studied, either. A large inter-subject variability in exercise-associated changes in IgE were observed, which is probably due to genetically conditioned intensity of IgE synthesis and release . Regarding moderate intensity physical training, it has been suggested that it may induce a decrease in both total and allergen specific IgE levels (92).

Potential research gaps

Association of shifts in salivary IgA with modified susceptibility to respiratory infections has been established. However, unresolved issues still remain with regard to the role of factors often accompanying strenuous exercise (to list just a few: psychological stress, sleep deprivation, concomitant medication and dietary supplements) and potentially influencing immune status. In what regards exercise-associated changes in serum levels of other immunoglobulin isotypes, results of not abundant studies are often contradictory, therefore, a potential, largely not addressed research area is still open.

Exercise load and susceptibility to infections

Association of exercise load and URTI susceptibility can be presented as the so-called "J-shaped curve model" hypothesizing that although regular moderate doses of physical activity have beneficial effects on health, excessive amounts or intensities of physical activity have opposite, negative consequences (69) **(Figure 1)** . Although the "J" shaped curve hypothesis relating amount of exercise and risk of disease has been accepted by athletes, coaches and scientists, the available evidence is insufficient to support it (93). Recently, a modification was proposed to the J-curve model and an "S-shaped" graphic presentation of interactions between exercise intensity and URTI susceptibility was proposed (94,95) **(Figure 2)** . This S-curve model takes into account suggestions based on previous reports on increased infection rate only in athletes reporting pre-race symptoms (96). Moreover, these authors postulate that athletes with high training load should be analyzed separately from the "true" elite athletes. Assumption that in the latter ones an excessive training volume does not coincide with increased susceptibility to infections can be supported by data from pilot training log analysis covering a 16-year time span (95). Furtherly, a combined model has been proposed that includes additional issues highlighted by Moreira et al, indicating that J-curve model may be applicable solely to less-fit individuals whereas the classical curve would tend to flatten as the fitness level increases (97). It should also be mentioned that acute bout of exercise may be considered as a set of positive stimuli leading to enhancement of immune response and immune protection, contributing to enhanced performance (98).

In the context of exercise load-related infection susceptibility, several issues may be considered not yet elucidated and requiring further research. The role of pre-existing, sometimes latent or clinically silent, URTI in the development of what is later reported as upper respiratory symptoms, should be cleared up in order to avoid blurring of the clinical picture and interpretation of irrelevant data. Establishing a uniform definition of "elite" athlete will help to compare results from different studies and settings.

In the context of URTI susceptibility, the influence of exercise on the microbiome cannot be neglected. There are data confirming that exercise (recreational and endurance) modifies gut microbial diversity (99,100) and that prebiotic supplementation may influence exercise-induced bronchial hyperresponsiveness (101), although not influencing allergic inflammation markers (102). Although several environmental factors (e.g., smoking) have been identified as possible modifiers of airway microbiome, data on influence of exercise are not abundant and not conclusive with regard to specific taxa (103).

Finally, not only clinical data and reports, but also immunological parameters should be addressed in more numerous studies assuming stratification based on training load.

6.1 Allergic athletes and susceptibility to infections

An increasing proportion of young athletes are atopic, i.e. show signs of IgE-mediated allergy which is, along with the sport event, a major risk factor for asthma and respiratory symptoms in athletes (104,105). The relative importance of allergy is growing, also because pollen exposure may become more prolonged and intense with global warming (106). A mixed type of eosinophilic and neutrophilic airway inflammation seems to affect especially swimmers, ice-hockey players, and cross-country skiers (107). The inflammation may represent a multifactorial aggression, in which both allergic and irritant mechanisms play a role. In allergic athletes, high level competition seems to exacerbate at least some components of the allergic immune response, such as airway hyperresponsiveness and airway inflammation. The question remains about how excessive exercise affects the Th1/Th2 balance. If exercise drives a Th2 response then a more difficult to control phenotype in the elite allergic athlete may be expected.

Growing points and areas for developing research Immunological changes associated with exercise form a potentially promising field of research with many gaps to be filled. Detailed assessment of microbiome involved in pathogenesis of respiratory symptoms in athletes is one of the most obvious and evident challenges that exercise immunologists and sports scientists are currently confronted with. Studies looking at the impact of exercise or physical activity on susceptibility to infection varied widely in respect to subjects, exercise load and methods (93). Further elucidation of processes lying behind respiratory symptoms without an ascertained pathogen is one of considerable research gaps. In this aspect, few studies have so far addressed the impact of regular chronic exercise training on humoral and cellular immunity in humans. Infection-like symptoms in subjects in whom no pathogen can be identified are not fully explained regarding underlying inflammatory mechanism, therefore, the role of pre-existing silent or latent infections should be taken into consideration in future studies. Over last 18 months, the COVID-19 pandemics created challenges for medical professionals irrespective of specialty (108). In the context of exercise training, key issues to be addressed are:

- Influence of regular training of different intensities on susceptibility to SARS-CoV-2 infection (109)
- Influence of COVID-19 infection on sports performance (110,111)
- Maintainig immune health during restrictions caused by pandemic and temporarily limited access to sports facilities (112)
- Return to regular exercise after COVID-19 infection (113) Establishing a uniform definition of "elite athlete" will contribute to a more comparable and straightforward interpretation of data coming from different studies and settings. Hence, issues to be tackled include:

1. Are the athletes who show more "immunodepression" more prone to URTIs during the weeks following exercise?
2. Which are the clinically relevant outcomes to assess and predict meaningful exercise-induced immunodepression?

3. Is downregulation of non-specific immunity after intense exercise a normal protective response, with mild immunodepression being an attempt to limit inflammation?
4. When should the exercise-associated changes in non-specific immunity be considered pathological?
5. What are the differences between healthy and illness prone athletes in the above-mentioned context?
6. What is the efficacy, if any, of nutritional or pharmaceutical interventions as countermeasures to URTI symptoms? In conclusion, exercise - depending on its pattern, intensity and environmental conditions - modifies various aspects of immune response. The degree of clinical relevance of these modifications and the ways they may impact the sports performance remain promising field for future research.**Figure 1**A J-shaped model describing relationship between exercise load and the risk of URTI. Modified after Nieman**Figure 2**An S-shaped relationship between training load and infection rate, proposed by Malm (modified after) REFERENCES

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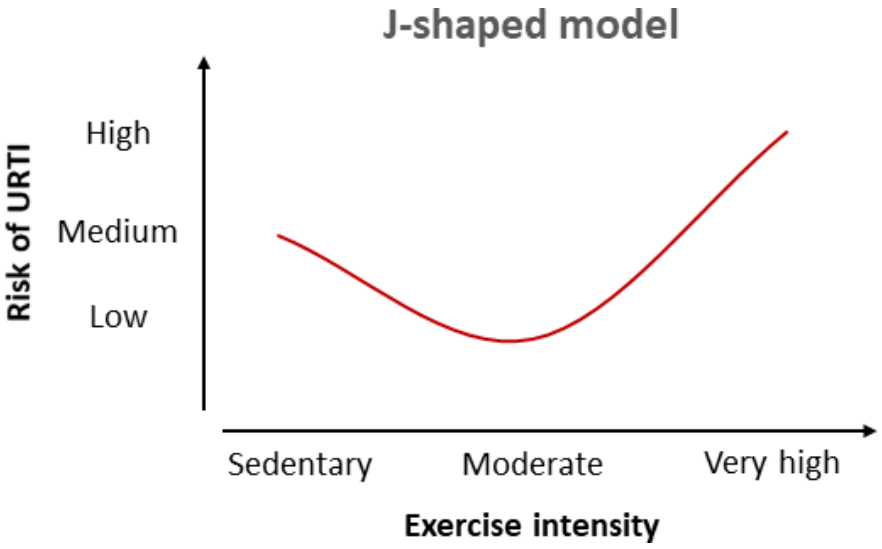

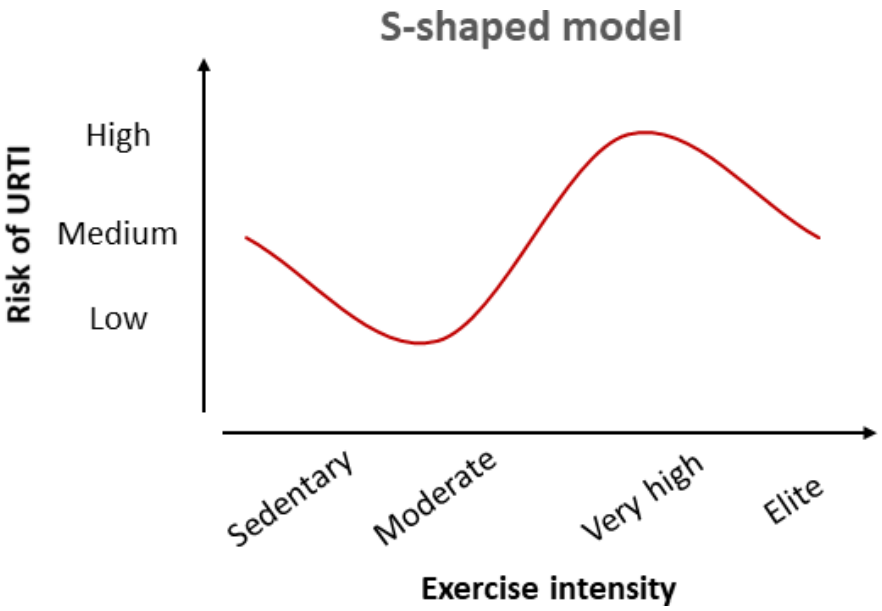

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