REVIEW ARTICLE

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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. However, strenuous exercise, as performed by professional athletes, may promote infection: in about half of athletes presenting respiratory symptoms, no causative pathogen can be identified. Acute bouts of exercise enhance the release of pro-inflammatory mediators, which may induce infection-like respiratory symptoms. Relatively few studies have assessed the influence of regularly repeated exercise on the immune response and systemic inflammation compared to the effects of acute exercise. Additionally, ambient and environmental conditions may modify the systemic inflammatory response and infection susceptibility, particularly 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. The most promising areas of further research in

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exercise immunology include detailed immunological characterization of infection-prone and infection-resistant athletes, examining the efficacy of nutritional and pharmaceutical interventions as countermeasures to infection symptoms, and determining the influence of various exercise loads on susceptibility to infections with respiratory viruses, including SARS-CoV-2. By establishing a uniform definition of an "elite athlete," it will be possible to make a comparable and straightforward interpretation of data from different studies and settings.

1 | INTRODUCTION & OVERVIEW

Regular physical exercise is one of the lifestyle modifications aimed at reducing morbidity and mortality associated with civilization diseases such as obesity, diabetes, cardiovascular disease, and cancer. Until recent years, regular recreational exercise training was believed to have a beneficial influence, while strenuous exercise, as performed by professional athletes, had possibly harmful consequences.

Regular moderate exercise training has also been considered protective against common respiratory infections and systemic low-grade inflammation.[1,2] Over recent years, however, sports associated with high-intensity exercise, such as long-distance running (marathon or ultramarathon) and triathlon, are gaining popularity in general society. Most participants in such activities form a somewhat distinct population, being predominantly Caucasian males, aged around 40 years, usually holding Bachelor's or Master's degree.[3,4] Among the comorbidities and medical conditions in this group, allergies were self-reported in 25% of those studied and exercise-induced asthma symptoms in 13%.[3] Questionnaire-based studies among long-distance runners have documented an increased incidence of upper respiratory tract infection (URTI) symptoms during the days directly following an event[5,6] Elite athletes frequently report URTI symptoms, but an infectious etiology could only be confirmed in about 30%–45% of cases.[7,8] It has been suggested that in subjects in whom no pathogen could be identified, the development of infection-like symptoms after exercise may be attributed to exercise-induced airway inflammation.[7] Such inflammation can contribute to the development of bronchoconstriction in exercising subjects, considerably influencing their sports performance.[9]

Therefore, there is a need to raise awareness of the influence of exercise training on the immune system and susceptibility to infection.

As part of a project of the "Allergy, Asthma and Sports" Working Group within the EAACI Asthma Section, this paper presents the current understanding of the effect of physical exercise on the immune system and identifies areas for future research based on a review of current literature.

2 | INFECTIONS IN EXERCISING SUBJECTS—PREVALENCE, EPIDEMIOLOGY, PATHOGENS

Elite athletes frequently report upper respiratory symptoms; however, their infectious etiology can only be confirmed in around half of cases. A prospective study by Spence et al of nasopharyngeal and throat swabs acquired during 37 symptomatic episodes in 28 elite and non-elite athletes confirmed a bacterial or viral etiology in 11 episodes; the identified viral pathogens responsible for URTI symptoms included rhinoviruses and adenoviruses, as well as the bacteria *M. pneumoniae*, *S. aureus*, and *S. pneumoniae*.[8]

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

Studies indicate that pathogen identification is possible in approximately 45% cases of URS in athletes.[7] A similar proportion has been also described in the general population.[11]

3 | INFECTION-LIKE SYNDROMES IN ATHLETES—WHEN NO PATHOGEN CAN BE IDENTIFIED

The development of symptoms during non-infectious URS may possibly be attributed to the activation of the inflammatory process. This phenomenon can be accompanied by changes in the synthesis and release of pro-inflammatory and anti-inflammatory factors, as well as proteins with immunomodulatory properties. Strenuous exercise performed in unfavorable ambient conditions, for example, excessive cold or heat, humidity, and exposure to air pollutants, contributes to the development of an inflammatory response. Such exercise-induced inflammatory responses have been described both locally and on a systemic level.[7,10,12–14]

3.1 | Exercise and systemic inflammation

Several studies have confirmed that acute exercise can influence systemic inflammation. A single bout of intensive exercise training is associated with the increased synthesis and release of pro-inflammatory cytokines, with increased serum levels of anti-inflammatory cytokines (e.g., IL-10 and IL-1ra) being observed as a secondary phenomenon.[2,12,15–17] Serum levels of periostin, a hallmark of type 2 inflammation, were not increased within 1 h after acute exercise.[18] 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 symptom-free subjects.[12] In contrast, acute exercise-induced IL-6 release was more pronounced in subjects prone to developing respiratory symptoms. This finding suggests that infection-prone exercisers may be subject to some dysregulation in cytokine balance and impairment of anti-inflammatory mechanisms.

Acute endurance or ultra-endurance exercises are good models for studies on the exercise-induced inflammatory cytokine response. A recent study of the effect of long-distance running on cytokine levels and leukocyte number involving 11 trail finishers (five female; mean age 37.5 ± 9.0 years) and 12 ultra-trail finishers (four female; 38.3 ± 6.9 years) found the 40 km run to modulate the inflammatory cytokine response to a different degree than the 171 km ultra-endurance race.[19] Although both races led to significant increase in serum MIP-1β, MCP-1, IL-6, IL-8, and TNF-α, notably higher plasma IL-17A and IL-1β were only observed after the 171 km trail. In the light of these observations, further research is needed into the 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 report no significant difference between adolescent tennis players and non-athletic controls in terms of serum/plasma IL-1ra and respiratory infections over 2.5 months.[20] During training season, a significant decrease in intracellular IL-2 and IL-4 production has been described in Italian footballers,[21] while lower plasma IL-1β, IL-18, IFN-γ, and IL-1ra levels have been noted in Portuguese kayakers during the off-training season as compared to training season; this suggests that regular intensive exercise may have a beneficial anti-inflammatory effect.[22] In addition, significantly higher resting serum levels of periostin were noted in nine elite swimmers compared to ten asthmatic non-athletes and seven healthy subjects.[18] The authors suggest that increased resting serum periostin in athletes may result from airway injury in response to repetitive stimuli during strenuous exercise. Such injuries would persist also after the training season, and increased periostin levels would, in such case, be unrelated to type 2 inflammation.

A recent systematic review and meta-analysis of 19 randomized controlled trials investigating the effect of regular exercise on inflammatory cytokine response found that regular moderate exercise may exert its anti-inflammatory effect by reducing the levels of inflammasome activation-related cytokines (IL-1β and IL-18).[23]

Enhanced IL-1ra release has also been reported following acute bouts of exercise.[12,24] However, IL-1ra levels tend to decrease post-exercise in athletes reporting four or more episodes of upper respiratory infections per year.[12] In a study involving Polish speed skaters, athletes considered less prone to URTIs, basing on a self-reporting survey, had significantly higher serum IL-1ra during the winter training period. This seems concordant with the anti-inflammatory spectrum of IL-1ra activity.[25]

Apart from the exercise as a stimulus *per se*, the ambient conditions in which the exercise is performed may also influence systemic inflammatory markers. Changes in serum pro- and anti-inflammatory cytokine levels have been reported in subjects exercising in warm and humid conditions.[26] In addition, in a study of speed skaters who had been predominantly training at outdoor ice rinks during winter, almost twice as many demonstrated BHR to methacholine, as compared with the summer period. Although the skaters were subjected to a similar exercise load during both seasons, their serum IL-1ra levels negatively correlated with ambient air temperature during winter but not during summer. Furthermore, serum IL-1ra was only found to positively correlate with exercise load in the winter training season. These observations suggest that unfavorable ambient conditions during winter outdoor sports activity, and not exercise load *per se*, may constitute the primary factor modifying systemic inflammation.[25]

A microarray-based transcriptome study of peripheral blood leukocyte response to regular endurance exercise training involving 12 young (aged 18.4 ± 1 years on average) athletes and 12 matched sedentary controls with equal (50/50%) gender distribution found that regular endurance exercise may induce transcriptional changes. These changes resulted in the downregulation of genes involved in the inflammatory and immune response and concomitant upregulation of the genes related to ribosomal protein production and mitochondrial energetics.[27]

In general, most studies assessing the influence of exercise on immune and inflammatory parameters at the systemic level are based on acute exercise rather than regular exercise. Hence, there is a need for more research on different patterns and intensity of exercise among recreational and professional athletes. However, future studies should consider the fact that immune cells are not the sole source of inflammatory proteins (e.g., IL-6, periostin),[28,29] that muscles have considerable involvement as sources of proteins released into serum upon exercise. Current data regarding the influence of acute and chronic regular exercise on systemic inflammation are shown in Figure 1.

3.2 | The effect of exercise on airway inflammation

Apart from investigations at the systemic level, the potential influence of exercise on inflammation in the 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).[18,30–37] However, the data acquired so far are inconclusive, partly due to considerable differences in sampling methodology.
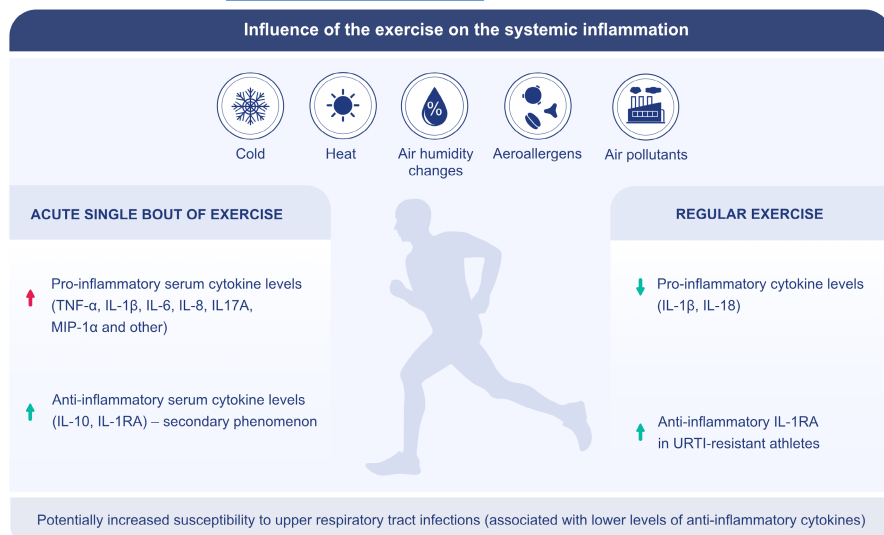
FIGURE 1 Exercise, both acute and regular, can influence systemic inflammation. Levels of anti-inflammatory mediators vary between athletes susceptible and resistant to upper respiratory infections. Influence of cold and warm/humid ambient conditions on systemic inflammation in athletes has been described
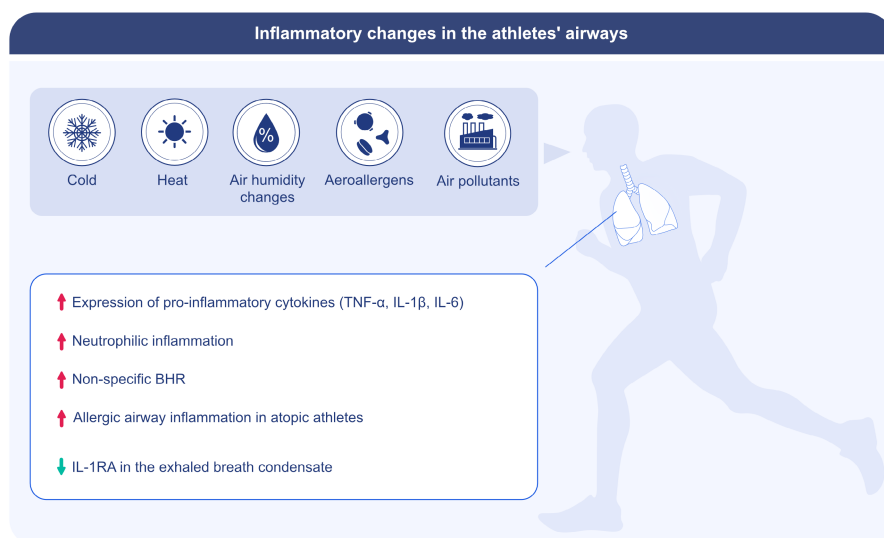

FIGURE 2 Inflammatory changes in athletes' airways can result from the presence of various ambient and environmental factors. Apart from the influence of exercise, local changes in the airways can result from external factors acting independently of physical exercise

TNF-α, a pleiotropic pro-inflammatory cytokine released by a wide spectrum of cells, can be increased at both the 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 [38,39]. 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), acute exercise was not found to have any considerable influence on the levels of inflammatory mediators in exhaled breath condensate (EBC).[35] Interestingly, in this study, an imbalance in cytokine levels similar to that noted in the lungs of asthmatics was observed in the lower airways of swimmers and speed skaters: The non-asthmatic athletes demonstrated comparable baseline EBC TNF-α levels to non-exercising asthmatics, and this was accompanied by decreased levels of anti-inflammatory IL-1ra in EBC in both athletes and asthmatics. Increased inflammation, particularly neutrophilic, as reflected by increased cell counts and sputum myeloperoxidase (MPO), was also detected in

the airways of subjects exposed to unfavorable ambient conditions at high altitudes.[36] Athletes demonstrated a considerable increase in pro-inflammatory IL-1β, IL-6, and TNF-α mRNA expression in sputum after a swimming training session.[37] Neutrophilic airway inflammation has been consistently described in studies on winter athletes.[40] Inflammatory changes in the airways of athletes are reflected in a considerable frequency of non-specific bronchial hyperresponsiveness; this was observed in more than 40% of tested athletes and was more prevalent in those performing winter outdoor sports.[25,40–42]

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 the influences of exercise and environmental conditions. In addition, atopy may also have an influence *per se* on local airway inflammation. The contribution of each factor to airway inflammation can only be accurately determined if they all are included in the study design.

3.3 | Allergic inflammation in athletes

An increasing proportion of young athletes are atopic, that is, show signs of IgE-mediated allergy; this is, along with repeated exercise, a major risk factor for asthma and respiratory symptoms in athletes.[43,44] The relative importance of allergy is also growing; for example exposure to pollen may become more prolonged and intense with global warming.[45] A mixed type of eosinophilic and neutrophilic airway inflammation seems to have a particularly strong influence on swimmers, ice-hockey players, and cross-country skiers.[46] Such inflammation may represent a multifactorial problem involving both allergic and irritant mechanisms such as cold and dry air, humidity, and air pollutants. 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.[47,48] The question of how excessive exercise affects the Th1/Th2 balance remains. If exercise drives the Th2 response, then it may be expected that the phenotype may be more difficult to control in an elite allergic athlete.

The effects of exercise and variable extrinsic factors on inflammatory pathways within the airways are shown in Figure 2.

4 | INFLUENCE OF EXERCISE ON CELLULAR IMMUNE RESPONSE MECHANISMS

Exercise activates various physiological mechanisms leading to alterations in the number and function of innate immunity cells. These mechanisms include oxidative stress, increased metabolic rate, and the increased release of heat shock proteins, catecholamines, cortisol, and insulin-like growth factor.[2] A short bout of exercise induces a rapid and considerable, yet transient, increase in peripheral blood neutrophil numbers directly afterward. This may be followed by a second wave of increased neutrophil number after several hours, depending on the intensity and duration of exercise.[49,50] The initial increase in neutrophils results from the release of marginal pool cells, while the later increase is due to the influence of exercise-associated cortisol on bone marrow. An acute bout of exercise has an ambiguous influence on neutrophil 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 found that oxidative stress markers decrease in elite swimmers after exercise.[51] Although an acute bout of exercise performed at high intensity (>60% of maximal oxygen uptake) may result in oxidative stress, caused by reactive oxygen species (ROS) generation due to enhanced oxygen consumption[52] (a phenomenon known as exercise-induced oxidative stress), several studies have demonstrated that continuous aerobic training reduces ROS production and increases antioxidant defenses.[52–55]

An acute bout of exercise causes a transient increase in peripheral monocytes[56–61] probably due to their release from the peripheral pool.[2] In addition, a single exercise bout results in changes in monocytic surface proteins and cytokine expression, with the pro-inflammatory CD14+/CD16+ phenotype predominating.[62,63] Acute bouts of exercise have also been reported to decrease the expression of Toll-like receptors (TLR) 1, 2, and 4[64–66] accompanied by increased LPS-induced release of pro-inflammatory cytokines.[63]

Exercise also stimulates the phagocytosis, anti-tumor activity, reactive oxygen and nitrogen metabolism and chemotaxis of tissue macrophages.[2] Tissue macrophages are characterized with diversity and plasticity, and may present a pro- or anti-inflammatory phenotype, known as M1 or M2, respectively, in response to various stimuli. The M1 phenotype results from stimulation by TLR ligands and IFN-γ, and M2 phenotype due to alternative stimulation of macrophages by IL-4/IL-13.[67] It has been proposed that the switch from the M1 to M2 macrophage phenotype may be one of the postulated bases of the anti-inflammatory and somewhat bronchoprotective action of exercise.[68] To date, the impact of acute exercise on macrophage polarizations has mainly been studied in animal models, in which M1-to-M2 macrophage phenotype switching has been observed.[69] Studies investigating the effects of exercise on macrophage polarization have been performed in several tissues; however, they have mainly assessed the influence of prolonged physical activity programs.[68,70] In a small sample of 14 male Taiwanese footballers (aged 19.9 ± 1.4 years), acute aerobic exercise caused a decrease in the pro-inflammatory M1 phenotype with no effect on M2 phenotype markers.[71] Considering the paucity of human studies targeting influence of acute bout of exercise on macrophage polarization and, hence, on tissue inflammation, there is a pressing need for such research. Indeed, this appears a potentially promising research niche in the field of exercise immunology.

Few studies have targeted dendritic cells (DCs) in the context of acute exercise. Due to their role in educating naïve T cells during differentiation, DCs can influence the intensity and nature of the Th-dependent response. In a murine model of asthma, Mackenzie et al assessed the influence of a single bout of moderate exercise on DC maturation and activation.[72] Under these conditions, DC maturation was decreased, as evidenced by altered expression of MHC-II, CD80, CD83, and CD86.

Studies in two different rat models (Fischer 344 and Sprague-Dawley)[73,74] yielded conflicting results regarding the influence of long-term periodized exercise training on the functional activities of dendritic cells. In the first model (Fischer 344), an increase in DC number was observed, but no functional modifications, as indicated by surface molecule expression.[73] In the second model, the functional activities (e.g., MHC-II expression, cytokine production) were found to be increased post-exercise.[74]

In a study on healthy human adults, LaVoy et al reported that an acute exercise bout may contribute to increased generation of monocyte-derived DC following 8-day culture, which can constitute a useful tool for acquiring DC for research and immunotherapy purposes.[61] Taken together, data published to date indicate that both DC number and function can be modified by acute exercise. Considering the important role of these cells in the regulation of the immune response (including the development of type 2 inflammation), the

impact of exercise on DCs definitely deserves more research interest, with particular stress on human studies.

The induction of lymphocytosis by acute bouts 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; in contrast, due to the higher β2-adrenergic receptor density on the surface of T CD8+ cells, they are more responsive to exercise and demonstrate greater relative post-exercise increases.[75] Both T-cell subsets react differently to variable recovery periods between single exercise bouts. While CD4+ and CD8+ lymphocytes equally fail to return to baseline numbers after short recovery periods, subsequent acute exercise leads to a more prominent increase in T CD8+ than T CD4+ cell numbers.[76]

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[75] nor is anything known on the mechanism which might underlie the potential effects on Treg cells. For instance, it is postulated that the apparent decline in Tregs observed after a triathlon or marathon may be due either to cell apoptosis or their redistribution into peripheral tissues. Recently, Treg count was found to demonstrate a biphasic response to acute exercise[77]; there is hence a need for more research into the modulation of Treg-dependent response through acute exercise.

In elite cyclists during their training period, repeated exercise was found to result in a significant decrease in IFN-γ+ T cells but not on type 2 cells (i.e., IL-4+ T cells).[78] Trained runners demonstrated decreased Th1 and Treg cell numbers and increased Th2 numbers 4 weeks after marathon participation compared with non-running controls.[79] These shifts may underlie the increased infection rate in elite athletes.[75,79]

The effects of both acute and chronic exercise on immune response cell numbers and functions are summarized in Tables 1 and 2.

5 | EXERCISE AND HUMORAL IMMUNE RESPONSE

Physical exercise is associated with decreased efficiency of humoral immune response on a mucosal level, manifesting predominantly as 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.[2] Numerous studies have shown increased susceptibility to URTIs in the period directly following participation in a long-distance run.[5,6,80,81] Moreover, decreased salivary IgA has been associated with an increased chance of URTIs in elite athletes.[82,83]

Shifts in salivary IgA are often observed during periods of intensive training as part of sports[82–85] and military[86–88] curricula; decreased sIgA is often noted, accompanied by increased infection susceptibility, although this correlation is not always clear and evident.[2] In addition, other interfering factors should be considered when interpreting data regarding the influence of short bouts of exercise on sIgA levels and susceptibility to infection: These include the type, pattern and duration of exercise, and the general fitness of the subject. An extremely intensive training regime is frequently associated with other potential modifiers of the immune response, such as increased energy expenditure, sleep deprivation, altitude above sea level, and psychological stressors.[2,89–91]

Moderate physical activity leads to an increase in salivary IgA levels. This further confirms the beneficial anti-inflammatory and immunomodulatory influence of regular physical activity performed at a non-elite level.[92,93]

Contradictory results have been observed regarding serum concentrations of immunoglobulins. Several studies have noted an increase in serum IgG in endurance athletes shortly after acute exercise, as well as over longer periods of repeated training.[94–97] However, other studies have noted considerable falls in serum IgG following strenuous exercise, such as a 75 km run, 3-week rugby training camp, or 14-week running training program.[98–101] Serum IgM studies yielded similarly ambiguous results: Both decreases[94,98–100] and increases[95,102] have been described under intensive exercise conditions. The few studies assessing serum IgD level, a marker of B cell activation, have also brought conflicting results.[94,95] Similarly, the shifts in IgE level associated with strenuous exercise have not been extensively studied. Large inter-subject variability in exercise-associated changes in IgE has also been observed; this is probably due to genetically conditioned intensity of IgE synthesis and release.[94] It has also been suggested that moderate-intensity physical training may induce a decrease in both total and allergen-specific IgE levels.[103]

TABLE 1 Influence of exercise on immune response cells number in human studies

Cells	Type of exercise	Nature of influence	References
Neutrophils	Acute	Biphasic increase	49,50
Monocytes	Acute	Transient increase	56-61
CD4+ T cells	Acute	Increase	75,76
CD8+ T cells	Acute	Increase	75,76
T_{reg} cells	Acute	Increase, decrease or no effect	75,77
	Chronic	Decrease	79
Type 1 T cells (IFNγ +)	Chronic	Decrease	78,79
Type 2 T cells (IL–4 +)	Chronic	Increase or no effect	78,79

TABLE 2 Influence of exercise on innate immunity cell function in human studies

| Cells	Type of exercise	Nature of influence	References
Neutrophils	Acute	Unstimulated: increased degranulation, phagocytosis and oxidative burst; Bacterial stimulation: decreased degranulation and burst activity	2,51,52
	Chronic	Reduced ROS production and increased antioxidant defenses	52-54
Monocytes	Acute	Increased pro-inflammatory phenotype CD14+CD16+; Decreased expression of TLR1, TLR2 and TLR4	62-66
Macrophages	Acute	Decreased expression of markers of pro-inflammatory M1 phenotype (no effect on M2 phenotype)	71
	Chronic	Differentiation into anti-inflammatory M2 phenotype	68,70
Dendritic cells	Acute	Increased generation of monocyte-derived DC in culture	61
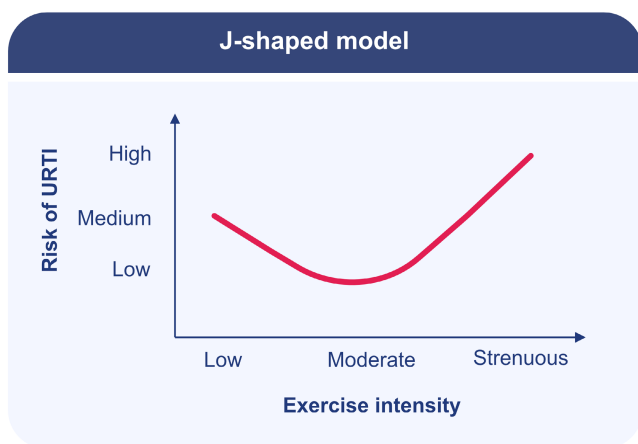
FIGURE 3 J-shaped model describing relationship between exercise load and the risk of URTI. Modified after Nieman[80]

A relationship has been established between shifts in salivary IgA and changes in susceptibility to respiratory infections. However, the precise influence of factors commonly accompanying strenuous exercise (to list just a few: psychological stress, sleep deprivation, concomitant medication, and dietary supplements) on immune status remains unclear. Despite the apparent value of salivary IgA as a potential biomarker of RTI susceptibility in the context of exercise, recent studies emphasize the need to control for the above-listed confounding factors.[104] Few studies have examined exercise-associated changes in the serum levels of other immunoglobulin isotypes, and their results are often contradictory. As such, this interesting and relatively unaddressed research area remains open.

6 | EXERCISE LOAD AND SUSCEPTIBILITY TO INFECTIONS

Exercise load is widely believed to have a J-shaped relationship with URTI susceptibility, that is, regular moderate doses of physical activity have beneficial effects on health, while excessive amounts or intensities of physical activity have opposite, negative consequences[80] (Figure 3); however, the available evidence is insufficient to support it.[105] A more recent modification based on previous reports on increased infection rate in athletes reporting pre-race symptoms is that the relationship may be more "S-shaped".[106–108] The time of infection could be of importance in eliciting respiratory symptoms in athletes. It may happen that, in an athlete performing several session per day, exercise takes place before and after inoculation; this creates the possibility that RTI symptoms can result from greater infection susceptibility due to exercise, or due to exacerbation of symptoms of an existing infection[107] Moreover, it is postulated that athletes with high training load should be analyzed separately from the "true" elite athletes. Data from a pilot training log analysis covering a 16-year time span suggest that, in the latter, an excessive training volume does not coincide with increased susceptibility to infections.[107] However, it should be noted that the data were acquired in a small group of athletes (eleven in total with the initial concept based on data acquired from a single athlete) with the use of self-filled training logbooks, sickness days, and injuries. In addition, the precise definition of an *elite athlete* still remains unclear, thus complicating study design and data interpretation.[109–112]

Following Moreira et al, a combined model has also been proposed indicating that the J-curve model may be applicable solely to less-fit individuals, whereas the classical curve would tend to flatten as the fitness level increases.[113] It should also be mentioned that an acute bout of exercise may be considered as a set of positive stimuli enhancing the immune response and immune protection, and that can contribute to enhanced performance.[114]

The issue of exercise load-related infection susceptibility requires further research. These studies should clarify the role of pre-existing URTI, which can be sometimes latent or clinically silent, in the development as upper respiratory symptoms. In addition, establishing a uniform definition of *elite athlete* will allow greater comparisons between studies.

Exercise may well have a significant effect on the microbiome. Studies suggest that both endurance and non-endurance exercise modify gut microbial diversity[115,116] and that prebiotic supplementation may influence exercise-induced bronchial hyperresponsiveness,[117] but not allergic inflammation markers.[118] Although several

factors, such as genetics, smoking, alcohol consumption, lifestyle, and physical activity, have been identified as possible modifiers of the airway microbiome, no specific relationships have been observed between exercise and specific taxa.[119]

Finally, clinical data, reports, and immunological parameters should be addressed in more numerous studies assuming stratification based on training load.

7 | GROWING POINTS AND AREAS FOR DEVELOPING RESEARCH

The immunological changes associated with exercise constitute a promising area of research (Box 1), and there is a need for a detailed assessment of the microbiome involved in the pathogenesis of respiratory symptoms in athletes. Studies of the impact of exercise or physical activity on susceptibility to infection have varied widely with regard to subjects, exercise load, and methods.[105] In addition, few studies have addressed the impact of regular chronic exercise on humoral and cellular immunity in humans, and the processes and inflammatory mechanisms underlying the occurrence of respiratory symptoms without an ascertained pathogen require further research. As such, future studies should consider the role of pre-existing silent or latent infections.

While sex-related differences in physiology, pathophysiology, genetics, pharmacology, and disease management are gaining importance, this is not currently a routine approach in the field of exercise science. However, sex hormones, menstrual cycle phase, oral contraception, and other factors may modulate the effect of exercise training on immune pathways.[120,121] Hence, more studies should account for the effect of sex when planning and designing clinical research in sports and exercise science.

Over the last 18 months, the COVID-19 pandemic has created challenges for all medical professionals, irrespective of their specialism.[122] In the context of exercise training, key issues to be addressed are as follows:

- Influence of regular training of different intensities on susceptibility to SARS-CoV-2 infection[123]
- Influence of COVID-19 infection on sports performance[124,125]
- Maintaining immune health during restrictions caused by pandemic and temporarily limited access to sports facilities[126]
- Return to regular exercise after COVID-19 infection[127]

As noted above, establishing a uniform definition of *elite athlete* will allow greater standardization of data and study design. With this in mind, various issues need to be tackled:

- Are the athletes who show greater "immunodepression" more prone to URTIs during the weeks following participation in a competition?
- Which clinically relevant outcomes can be used to assess and predict meaningful exercise-induced immunodepression?

> **BOX 1** **Summary of current research gaps and unmet needs with regard to influence of physical exercise on immune response and infections susceptibility.**
>
> - Development of more sensitive methods to identify pathogens in the airways of the athletes who present upper respiratory symptoms
> - Design and conduction of studies assessing the influence of a regular, repeated exercise (characterizing with different patterns and intensities)
> - Assessment of the influence of ambient and environmental conditions locally on athletes' airways in addition to the effects elicited by exercise
> - Exploration of the influence of various forms of exercise on allergic inflammation and development of allergic symptoms
> - Further assessment and validation of salivary IgA as a biomarker of susceptibility to infection in exercisers
> - Investigating the influence of exercise on airway and gut microbiome
> - Assessment of susceptibility to infections in regular exercisers taking into account stratification of the studied subjects based on exercise pattern and intensity as well as influence of the factors associated with environment and lifestyle
> - Addressing possible inter-gender differences in the outcome of exercise influence on immune parameters in the future studies

- Is downregulation of non-specific immunity after intense exercise a normal protective response, with mild immunodepression being an attempt to limit inflammation?
- When should the exercise-associated changes in non-specific immunity be considered pathological?
- What are the differences between illness-resistant and illness-prone athletes in the above-mentioned context?
- What is the efficacy, if any, of nutritional or pharmaceutical interventions as countermeasures to URTI symptoms?

In conclusion, the pattern, intensity, and environmental conditions of exercise influence various aspects of the immune response. The degree of clinical relevance of these modifications and the ways they may impact sports performance remain promising fields for future research.

AUTHOR CONTRIBUTION

MK conceived the idea of the manuscript and prepared the outline and first draft. SS designed Figure 3 and included amendments and new contents to the manuscript on all stages of its development. MB, SDG, LD, ZD, MLK, AM, MR, and MC provided amendments and

new contents to the manuscript at all stages of its development. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

Apart from academic affiliations, ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies. In the past 3 years, ZD received honoraria, consultancy and speaker fees from Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, Sanofi-Genzyme. SS is currently employed by Galenus Health, with no relation to this work. The remaining authors declare no COI with regard to this manuscript.

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