HIGHLIGHTED TOPIC | Exercise and Inflammation

Immune function in sport and exercise

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Gleeson M. Immune function in sport and exercise. J Appl Physiol 103: 693–699, 2007; doi:10.1152/japplphysiol.00008.2007.—Regular moderate exercise is associated with a reduced incidence of infection compared with a completely sedentary state. However, prolonged bouts of strenuous exercise cause a temporary depression of various aspects of immune function (e.g., neutrophil respiratory burst, lymphocyte proliferation, monocyte antigen presentation) that usually lasts ~3–24 h after exercise, depending on the intensity and duration of the exercise bout. Postexercise immune function dysfunction is most pronounced when the exercise is continuous, prolonged (>1.5 h), of moderate to high intensity (55–75% maximum O$_2$ uptake), and performed without food intake. Periods of intensified training (overreaching) lasting 1 wk or more may result in longer lasting immune dysfunction. Although elite athletes are not clinically immune deficient, it is possible that the combined effects of small changes in several immune parameters may compromise resistance to common minor illnesses, such as upper respiratory tract infection. However, this may be a small price to pay as the anti-inflammatory effects of exercise mediated through cytokines and/or downregulation of toll-like receptor expression are likely mediators of many of the long-term health benefits of regular exercise.

cytokines; leukocytes; infection; inflammation; Toll-like receptors

THE AIM OF THIS REVIEW IS to provide an up-to-date summary of the known effects of exercise on immune function and infection risk and to point out some of the main flaws of research to date and challenges for the future. Exercise can have both positive and negative effects on immune function and susceptibility to minor illnesses. The relationship between exercise and susceptibility to infection has been modeled in the form of a “J”-shaped curve (28). This model suggests that, while engaging in moderate activity may enhance immune function above sedentary levels, excessive amounts of prolonged, high-intensity exercise may impair immune function. Although there is relatively little evidence available to suggest that there is any clinically significant difference in immune function between sedentary and moderately active persons, there is some fairly convincing epidemiological evidence that moderate habitual physical activity is associated with decreased infection incidence. For example, it has been reported that the regular performance of ~2 h of moderate exercise per day is associated with a 29% reduction in risk of picking up upper respiratory tract infection (URTI) compared with a sedentary lifestyle (25). In contrast, it has been reported that there is a 100–500% increase in risk of picking up an infection in the weeks following a competitive ultra-endurance running event (30, 35, 36). However, a recent study (7) failed to confirm these findings in a large cohort of marathon runners: no relation was found between training volume during 6 mo before a marathon race and the postrace incidence of self-reported URTI episodes, and there was no difference in infection incidence in the 3 wk after the race compared with before. Of interest though was the observation that the post-race URTI incidence in runners without URTI symptoms in the 3 wk preceding the race was 16% (and not different from prerace URTI incidence), whereas, in runners who experienced an URTI episode in the 3 wk before the race, 33% experienced an URTI episode after the race also (7). This suggests that the stress of the exercise may have allowed a reactivation of the virus responsible for the prerace infection. Furthermore, in none of these studies were infections clinically confirmed, so it cannot be ruled out that some of the reported symptoms (e.g., sore throat) were caused by noninfectious airway inflammation due to drying of the mucosal surfaces and/or the inhalation of dry air or pollutants.

Many studies have reported that various immune cell functions are temporarily impaired following acute bouts of prolonged, continuous heavy exercise (24, 28, 33, 38, 43, 45), and athletes engaged in intensive periods of endurance training appear to be more susceptible to minor infections. For example, according to some surveys, sore throats and flu-like symptoms are more common in athletes than in the general population, and, once infected, colds may last longer in athletes (18, 30, 34). This is obviously a concern for athletes, as it is generally recognized that even minor infections can result in a drop in exercise performance and the ability to sustain heavy training (40). More severe viral infections can be associated with the development of persistent fatigue (10). Even so, there are very few studies that have been able to demonstrate a direct association between any specific measure of exercise-induced impaired immune function and increased incidence of clinically confirmed infection.

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The circulating numbers and functional capacities of leukocytes may be decreased by repeated bouts of intense, prolonged exercise. The reason is probably related to increased levels of stress hormones during exercise (26) and entry into the circulation of less mature leukocytes from the bone marrow (13). Falls in the blood concentration of glutamine have also been suggested as a possible cause of the immunodepression associated with heavy training, although the evidence for this is less compelling (13). Also, during exercise, there is an increased production of reactive oxygen species, and some immune cell functions can be impaired by an excess of free radicals (31). During exercise, exposure to airborne pathogens is increased due to the higher rate and depth of breathing. An increase in gut permeability may also allow increased entry of gut bacterial endotoxins into the circulation, particularly during prolonged exercise in the heat. Hence the cause of the increased incidence of infection in athletes is likely to be multifactorial: a variety of stressors (physical, psychological, or environmental, nutritional) can suppress immune function (13), and these effects, together with increased exposure to pathogens, can make the athlete more susceptible to infection.

ACUTE EFFECTS OF EXERCISE ON IMMUNE FUNCTION

A single, acute bout of prolonged, strenuous exercise has a temporary depressive effect on immune function, and, in a few studies involving rather extreme exercise (marathons and ultramarathons), this has been associated with an increased incidence of infection in the weeks following the event. For example, several studies have described a substantially higher (two- to sixfold) frequency of self-reported symptoms of URTI in athletes who completed long-distance foot races compared with control runners who did not compete in the events (30, 34–36). An acute bout of physical activity is accompanied by responses that are remarkably similar in many respects to those induced by infection, sepsis, or trauma (32): there is a substantial increase in the number of circulating leukocytes (mainly lymphocytes and neutrophils), the magnitude of which is related to both the intensity and duration of exercise. There are also increases in the plasma concentrations of various substances that are known to influence leukocyte functions, including inflammatory cytokines, such as TNF-α, macrophage inflammatory protein-1, and IL-1β; anti-inflammatory cytokines IL-6, IL-10, and IL-1-receptor antagonist (IL-1ra); and acute phase proteins, including C-reactive protein (CRP). The large increase in plasma IL-6 concentration observed during exercise can be entirely accounted for by release of this cytokine from contracting muscle fibers (51). However, IL-6 production by monocytes (49) and IL-2 and IFN-γ (but not IL-4) production by T lymphocytes are inhibited during and for several hours after prolonged exercise (21, 32).

Hormonal changes also occur in response to exercise, including increases in the plasma concentration of several hormones [e.g., epinephrine (adrenaline), cortisol, growth hormone, and prolactin] that are known to have immunomodulatory effects. Muscle-derived IL-6 appears to be at least partly responsible for the elevated secretion of cortisol during prolonged exercise. Infusion of recombinant human IL-6 into resting humans to mimic the exercise-induced plasma levels of IL-6 increases plasma cortisol in a similar manner (50). In contrast, the same recombinant human IL-6 infusion does not change plasma catecholamine or insulin levels in resting healthy young subjects. Therefore, muscle-derived IL-6 may be partly responsible for the cortisol response to exercise, whereas other hormonal changes cannot be ascribed to IL-6. Stimulation of cortisol secretion by IL-6 may be due to an effect of IL-6 on the hypothalamus, stimulating the release of ACTH from the anterior pituitary gland, or by a direct effect of IL-6 on cortisol release from the adrenal glands; evidence for both mechanisms exists. In addition, it was recently demonstrated that relatively small increases in plasma levels of IL-6 induce the two anti-inflammatory cytokines IL-1ra and IL-10, together with CRP (50). During exercise, the increase in IL-6 precedes the increase in these two cytokines, arguing circumstantially for muscle-derived IL-6 to be the initiator of this response.

Whether humoral or cell-mediated immunity will dominate depends largely on the type of cytokines that are released by the activated T helper cells. T lymphocytes can be classed as type 1 or type 2 cells, depending on which cytokines they predominantly produce. Type 1 T cells produce mainly IFN-γ and tumor necrosis factor, and their actions activate macrophages and induce killer mechanisms, including T-cytotoxic cells, thus driving the immune system toward cell-mediated immune responses, which primarily provide protection against intracellular pathogens such as viruses. Type 2 cells mainly produce IL-4, IL-5, IL-10, and IL-13, which are necessary for promotion of humoral immunity, IgE-mediated allergic reactions, and activation of potentially tissue-damaging eosinophils. IL-4 and IL-13 primarily drive B-cell differentiation to antibody production, while IL-5 stimulates and primes eosinophils. Together with IL-4, IL-10 (which is also produced by monocytes and B cells) can inhibit type 1 T-cell cytokine production. Interestingly, it appears that exercise can influence the type 1/type 2 cytokine balance.

In accordance with the elevations of circulating IL-6, IL-10, and IL-1ra, strenuous exercise decreases the percentage of type 1 T cells in the circulation, whereas the percentage of type 2 cells does not change (21). Both cortisol and epinephrine suppress the type 1 T-cell cytokine production, whereas IL-6 directly stimulates type 2 T-cell cytokine production. Another important action of IL-6 is that it suppresses production of TNF-α, which is a potent activator of inflammation (48). As type 1 T cells promote cell-mediated immune responses, which primarily provide protection against viruses, exercise, possibly working through muscle-derived IL-6, may decrease virus protection in the host and thus may account for why athletes appear to be more prone to acquire URTI. However, it is very important to stress that the shift toward type 2 T-cell dominance might be beneficial, because it also suppresses the ability of the immune system to induce tissue damage and inflammation. Blood markers of inflammation are strongly associated with cardiovascular and metabolic disease in the middle-aged and elderly population, and inflammation has been implicated in the pathology of several chronic diseases. Thus elevated systemic levels of IL-6 during and following exercise could be one of the mechanisms by which regular exercise provides protection against the development of chronic diseases (Fig. 1). However, it could be argued that the relative importance of IL-6 in this context is likely to be rather small, as significant health benefits of regular exercise are apparent even when the exercise is of light-moderate intensity.
Phagocytic neutrophils appear to be activated by an acute bout of exercise, but show a diminished responsiveness to stimulation by bacterial lipopolysaccharide (including both reduced oxidative burst and diminished degranulation responses) after exercise, which can last for many hours (38, 42). Acute exercise temporarily increases the number of circulating natural killer (NK) cells, but, following exercise, NK cell counts drop to less than one-half of normal levels for a couple of hours; normal resting values are usually restored within 24 h (46). NK-cell cytolytic activity (per cell) falls after exercise, and, if the activity is both prolonged and strenuous, the decrease in NK cell counts and cytolytic activity may begin during the exercise session (46). During recovery from exercise, lymphokine-activated killer cell numbers and activity also fall below preexercise levels. Acute exercise has been shown to diminish the proliferative response of lymphocytes to mitogens (24) and decrease the expression of an early activation marker (CD69) in response to stimulation with mitogen (43). When the exercise bout is strenuous and very prolonged (>1.5 h), the number of circulating lymphocytes may be decreased below preexercise levels for several hours after exercise, and the T-lymphocyte CD4+/CD8+ ratio is decreased (2).

Another limitation in the interpretation of such studies, even when multiple parameters are assessed, is that presently no instruments are available to predict the cumulative effects of these factors. Thus separating cells from their extracellular milieu excludes the effects of exercise-induced chemical changes in the blood that will undoubtedly modify leukocyte function. The closest one can get to the in vivo condition is by performing measurements on whole blood, in which the proximity of the leukocytes and the extracellular milieu is retained. Another limitation in the interpretation of such studies, even where multiple parameters are assessed, is that presently no instruments are available to predict the cumulative effects of several small changes in immune system parameters on host resistance (19). Furthermore, it should be borne in mind that only 0.2% of the total leukocyte mass is circulating at any moment; the remainder is in lymphoid tissue, the bone marrow, and other tissues. It may thus be more important to assess the status of leukocytes in the skin, mucosa, and lymph nodes rather than in the blood.

**CHRONIC EFFECTS OF EXERCISE TRAINING ON IMMUNE FUNCTION**

Following an acute bout of exercise, changes in circulating leukocyte numbers and functions normally return to preexercise values within 3–24 h. Cross-sectional studies that have compared leukocyte numbers and functions in blood samples taken from athletes more than 24 h after their last training session with those of sedentary individuals have generally reported few differences. Thus, in the true resting state, immune function appears to be broadly similar in athletes compared with nonathletes. There is a weak suggestion of a slightly elevated NK cell count and cytolytic action in trained individuals (46), but these effects are small and unlikely to be of clinical significance. Levels of secretory immunoglobulins by B lymphocytes are inhibited, and delayed-type hypersensitivity responses to subdermal antigen injection (a marker of the cell-mediated immune response) are diminished (4). These changes during early recovery from exercise would appear to weaken the potential immune response to pathogens and have been suggested to provide an “open window” for infection, representing the most vulnerable time period for an athlete in terms of their susceptibility to contracting an infection (33).
The immune function in sport and exercise, including neutrophil and monocyte oxidative burst, T-lymphon immunoendocrine responses to endurance exercise. These studies in recent years have investigated the effects of short supercompensation and an increase in performance. Several investigators have noted a state of overreaching in which performance is temporarily reduced, weeks at certain stages of the season. This may induce a state of immune dysfunction does not appear to decrease in periods of very heavy training (12). Furthermore, moderate exercise training in healthy young adults does not reduce the initiation of a specific antibody response in vivo measures of immune function are probably more meaningful than in vitro individual cell-type functional measures, as they represent the whole system response to challenge.

Athletes commonly intensify their training for a few days or weeks at certain stages of the season. This may induce a state of overreaching in which performance is temporarily reduced, but, following a period of taper with only light training, results in supercompensation and an increase in performance. Several studies in recent years have investigated the effects of short periods of intensified training on resting immune function and on immunoendocrine responses to endurance exercise. These studies indicate that several indexes of leukocyte function, including neutrophil and monocyte oxidative burst, T-lymphocyte CD4⁻/CD8⁺, mitogen-stimulated lymphocyte proliferation and antibody synthesis, and NK-cell cytotoxic activity, are sensitive to increases in the training load in already well-trained athletes (15, 20, 21, 41, 55). Even following relatively short periods (1–3 wk) of intensified training, marked reductions in neutrophil function, lymphocyte proliferation, s-IgA, and the circulating number of T cells producing IFN-γ have been observed (12, 20, 21). Thus, with chronic periods of very heavy training, several aspects of both innate and adaptive immunity are depressed, but athletes are not clinically immune deficient. In other words, exercise-induced immune dysfunction does not put athletes in danger of serious illness, but it could be sufficient to increase the risk of picking up common infections such as URTI or influenza should the more serious illness occur.

Several longitudinal studies have monitored immune function in high-level athletes such as cyclists (1), swimmers (12, 15), and footballers (5, 8, 39) over the course of a competitive season. In a recent study of American football players, the incidence of URTI was increased during intense training, and it was reported that the secretion rate of s-IgA (which represents the amount of s-IgA available on the mucosal surfaces for protection against pathogens) was significantly and inversely related to URTI incidence (8). In an earlier, much cited study, the impact of long-term training on systemic and mucosal immunity was assessed prospectively in a cohort of elite Australian swimmers over a 7-mo training season in preparation for the national championships (12, 15). The results indicated significant depression of resting serum and salivary immunoglobulin concentrations in athletes, associated with long-term training at an intensive level. Furthermore, resting s-IgA concentrations at the start of the training period showed significant inverse correlation with infection rates, and the number of infections observed in the swimmers was predicted by the preseason and mean pretraining s-IgA levels. These studies on mucosal immunity in athletes are representative of the very small number of studies that have established a relationship between some surrogate measure of immune function and infection incidence in athletes. A few studies on soldiers during intensive periods of military training have also reported a negative relationship between s-IgA concentration and occurrence of URTI (6), although others have not (17, 53). In one recent study, an increased URTI incidence during 4 wk of intense military training was significantly correlated with decreased numbers of circulating NK cells (17). However, in these situations, the training often involves not only strenuous physical activity, but also dietary energy deficiency, sleep deprivation, and psychological challenges. These multiple stressors are likely to induce a pattern of immunoendocrine responses that amplify the exercise-induced alterations.

**THE POSTEXERCISE SORE THROAT: AIRWAY INFECTION OR INFLAMMATION?**

Self-reporting of symptoms of URTI using questionnaires has been used in a number of studies designed to evaluate the effects of acute, prolonged exercise (e.g., running a marathon) or periods of intensified training on infection incidence. However, this approach leaves such studies open to the criticism that the reporting of symptoms (e.g., sore throat, runny nose, congestion, fever) is subjective and that factors other than infection (e.g., allergies, inhalation of air pollutants, airway inflammation) could also cause some of these symptoms. Recently, a surveillance study was conducted over a 5-mo summer/autumn competition season to identify the pathogenic etiology and symptomatology of upper respiratory illness (URI) in highly trained elite athletes (n = 32), recreationally competitive athletes (n = 31), and untrained sedentary controls (n = 20) (47). Nasopharyngeal and throat swabs were collected on subjects presenting with two or more defined URI symptoms. Swabs were analyzed using microscopy, culture, and polymerase chain reaction testing for bacterial, viral, chlamydial, and mycoplasmal respiratory pathogens. The Wisconsin Upper Respiratory Symptom Survey (WURSS-44) questionnaire was administered to assess the daily symptomatology and functional impairment. A total of 37 URI episodes in 28 subjects were reported (9 controls, 7 recreationally competitive exercisers, and 21 elite athletes). The overall distribution mimicked the “J”-shaped curve with rate ratios for illness higher in both the control (1.93, 95% confidence interval: 0.72–5.18) and elite (4.50, 95% confidence interval: 1.91–10.59) cohorts than the referent recreationally competitive athlete cohort. However, of these 37 episodes, infectious agents were identified in only 11 (30%) (2 control, 3 recreationally competitive exercisers, and 6 elite athletes). No pathogens were identified in 26 episodes of URI. Specific global symptom, total symptom, and functional impairment severity scores were higher in subjects with an infectious URI episode, particularly on illness days 3–5. These findings strongly suggest that URI in elite athletes are seldom infectious, and the symptomatology is distinct between infectious and noninfectious episodes. In future research, noninfectious causes of URI should be considered and investigated to identify alternative mechanisms and mediators.
CAN EXERCISE-INDUCED IMMUNODEPRESSION BE PREVENTED, AND DO WE WANT TO PREVENT IT?

Studies from Bente Pedersen’s group in Copenhagen indicate that the release of IL-6 from contracting muscle can be attenuated by long-term antioxidant supplementation. In a recent single-blind, placebo-controlled study (8), it was reported that 4 wk of oral supplementation, with a combination of vitamin C (500 mg/day) and vitamin E (400 IU/day), markedly attenuated the release of IL-6 from active muscle and the plasma IL-6 and cortisol response to 3 h of dynamic two-legged, knee-extensor exercise at 50% of maximal power output compared with placebo. High levels of circulating IL-6 stimulate cortisol release, and this study provides some strong evidence that the mechanism of action of the antioxidant supplementation was via a reduction in IL-6 release from the muscle fibers of the exercising legs. Attenuating the IL-6 and cortisol response would be expected to limit the exercise-induced depression of immune function, and may be the mechanism that could explain the reported lower incidence of URTI symptoms in ultramarathon runners supplemented with vitamin C (alone or in combination with other antioxidants) compared with placebo (35, 36).

Consumption of carbohydrate during exercise also attenuates increases in plasma IL-6, catecholamines, ACTH, and cortisol (27, 29). Carbohydrate intake during exercise also attenuates the trafficking of most leukocyte and lymphocyte subsets, including the rise in the neutrophil-to-lymphocyte ratio, prevents the exercise-induced fall in neutrophil function, and reduces the extent of the diminution of mitogen-stimulated T-lymphocyte proliferation following prolonged exercise (16). Recently, it was shown that consuming 30–60 g of carbohydrate per hour during 2.5 h of strenuous cycling prevented both the decrease in the number and percentage of IFN-γ-positive T lymphocytes and the suppression of IFN-γ production from stimulated T lymphocytes observed on the placebo control trial (22). IFN-γ production is critical to antiviral defense, and it has been suggested that the suppression of IFN-γ production may be an important mechanism leading to an increased risk of infection after prolonged exercise bouts (32).

Pedersen’s group, however, have argued that the reduction in the IL-6 response to exercise may be a double-edged sword, as IL-6 has several metabolic effects and shared mechanisms exist regarding immune impairment and training adaptation (48). Attenuating the IL-6 response to exercise will also inhibit lipolysis (48), reduce the anti-inflammatory effects of exercise, and attenuate the expression of a number of metabolic genes in the exercised muscle (37). In other words, it is possible that antioxidant supplementation and/or carbohydrate ingestion during exercise sessions could limit adaptation to training. However, it can also be argued that carbohydrate intake during training allows the athlete to work harder and longer, and as yet there is no evidence that physiological and performance adaptations are impaired by carbohydrate intake during training sessions. Further research is needed to determine how nutrient intake might affect the transcriptional regulation of metabolic genes in skeletal muscle and what, if any, consequences this has for training adaptation or even long-term health benefits. The concern for athletes is that, although these nutritional interventions may reduce their risk of infection, another effect may be to limit their hard-earned adaptation to training.

A SMALL PRICE TO PAY FOR LONG-TERM HEALTH BENEFITS?

Blood markers of inflammation are strongly associated with chronic disease in the older population, and inflammation has been implicated in the pathology of several cardiovascular and metabolic diseases. Evidence is now emerging that exercise has anti-inflammatory effects. Individuals who are physically active on a regular basis have a reduction in the levels of biomarkers that are used to assess systemic inflammation. For example, higher levels of habitual physical activity are associated with lower mitogen-stimulated inflammatory cytokine production, lower skeletal muscle inflammatory protein content, lower adipokine production, and lower serum levels of
CRP (14). Thus, although extreme exercise stress may impair immune function and increase susceptibility to infection, this may not be entirely detrimental to the host and may, by reducing immune activation and subsequent inflammation, be one of the mechanisms through which regular exercise benefits long-term health (Fig. 1).

An accumulation of chronic, low-grade inflammation is common in individuals who live a sedentary lifestyle; however, the mechanism underlying this connection is not fully understood. A new and potentially important finding is that, following a prolonged bout of strenuous exercise, the expression of Toll-like receptors (TLRs) 1, 2, and 4 on monocytes is decreased for at least several hours (14). TLRs are highly conserved transmembrane proteins that play an important role in the detection and recognition of microbial pathogens, and they can also be activated by endogenous danger signals of tissue damage, such as heat shock proteins. The key product of TLR signaling in antigen-presenting cells is the production of inflammatory cytokines and proteins, and thus the TLR pathway plays an important role in mediating whole body inflammation (Fig. 2). Evidence is now emerging that TLRs may be involved in the link between a sedentary lifestyle, inflammation, and disease. Recent studies have shown that both acute aerobic and chronic resistance exercise bouts result in decreased monocyte cell-surface expression of TLRs (14, 23, 52). Prolonged exercise also results in a decreased induction of costimulatory molecules and cytokines following stimulation with known TLR activators (23). Furthermore, a period of chronic exercise training decreases both inflammatory cytokine production and the cell-surface expression of TLR4 on monocytes (52). Although these effects may contribute to postexercise immunodepression and the reported higher susceptibility to infection in athletes, this may be a small price to pay as, over the long term, a decrease in TLR expression may represent a beneficial effect, because it decreases the inflammatory capacity of leukocytes, thus altering whole body chronic inflammation and possibly reducing the risk of developing chronic disease. The precise physiological stimulus mediating an exercise-induced decrease in cell-surface TLR expression is not known; however, a number of possible signals have been implicated, including anti-inflammatory cytokines, stress hormones, and heat shock proteins (14).

SUMMARY

In summary, acute bouts of exercise cause a temporary depression of various aspects of immune function (e.g., neutrophil respiratory burst, lymphocyte proliferation, monocyte TLR, and major histocompatibility complex class II protein expression) that lasts ~3–24 h after exercise, depending on the intensity and duration of the exercise bout. Postexercise immune function depression is most pronounced when the exercise is continuous, prolonged (>1.5 h), of moderate to high intensity (55–75% maximum O2 uptake), and performed without food intake. Periods of intensified training (overreaching) lasting 1 wk or more can result in longer lasting immune dysfunction. Although elite athletes are not clinically immune deficient, it is possible that the combined effects of small changes in several immune parameters may compromise resistance to common minor illnesses such as URTI. Protracted immune depression linked with prolonged training may determine susceptibility to infection, particularly at times of major competitions. This is obviously a concern because of the potential impact of an infectious episode on exercise performance. It is not really a concern for the general population, as individuals do not need to indulge in heavy training loads to obtain the health benefits of exercise that may well be proven to be due, in large part, to its anti-inflammatory effects.

Hundreds of studies have now been conducted that confirm both acute and chronic effects of exercise on the immune system, but there are still very few studies that have been able to show a direct link between exercise-induced immune depression and increased incidence of confirmed illness in athletes. This is an important issue that needs to be addressed in future studies, although it must be recognized that this is a difficult task. Even among the general population, we do not know the impact of small changes in specific immune parameters on risk of infection. Most clinical studies have only been concerned with the risk of life-threatening illness in immunodeficient patients, not with the risks of picking up common infections such as colds and flu.

REFERENCES


