運動與免疫

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中文摘要

急性的單一運動能夠導致許多暫時性免疫功能的抑制（中性白血球呼吸釋放，淋巴球增生，單核球主要組織相容抗原複合物第二類分子的表現），這種現象通常在運動後會維持~3-24小時，單視運動的強度與持續的時間而定。長時間（＞1.5 小時）中到高強度（55-75% VO_2max）的運動且在沒有攝取任何食物的情況下，所引起的抑制作用最爲明顯。持續一周或者更長的增強訓練（過度延長），逐漸地導致免疫功能的抑制。雖然優秀的運動員在臨床上沒有免疫缺陷，但是在綜合一些免疫參數的小改變，可能減低對於常見小疾病的抵抗力，例如上呼吸道的感染。長時間的免疫功能抑制與長期的訓練具相關性，可能導致可疑的感染，特別是在重要比賽的時候。爲維持免疫功能，運動員應攝取良好的均衡飲食，以達到他們對能量、碳水化合物、蛋白質以及微量營養素的需求。長時間高強度的運動中，攝取碳水化合物能夠減低壓力荷爾蒙的上升，並且能減低運動所引起的免疫功能抑制的現象。最近的研究發現抗氧化的維生素補充，可以降低運動所引起的壓力與白血球功能損害。

翻譯：巫錦霖博士
張素華

註：本文爲 Michael Gleeson 教授受邀於 2005 年國際運動健康科學學術研討會發表專題演講之全文。經 Gleeson 教授同意及研討會承辦單位國立台灣體育學院運動健康科學學系授權後刊登，特此聲明並致謝意。

Exercise and Immunity

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Abstract

Acute bouts of exercise cause a temporary depression of various aspects of immune function (e.g. neutrophil respiratory burst, lymphocyte proliferation, monocyte MHC class II expression) that usually lasts ~3-24 hours after exercise depending on the intensity and duration of the exercise bout. Post-exercise immune function depression is most pronounced when the exercise is continuous, prolonged (>1.5 hours), of moderate to high intensity (55-75% VO_2max) and performed without food intake. Periods of intensified training (overreaching) lasting one week or more result in chronically depressed immune function. 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. Protracted immune depression linked with prolonged training may determine susceptibility to infection, particularly at times of major competitions. To maintain immune function, athletes should eat a well balanced diet sufficient to meet their energy, carbohydrate, protein and micronutrient requirements. Consuming carbohydrate during prolonged strenuous exercise attenuates rises in stress hormones and appears to limit the degree of exercise-induced immune depression. Recent evidence suggests that antioxidant vitamin supplementation may also reduce exercise stress and impairment of leukocyte functions.

Introduction

Athletes engaged in heavy training programs, particularly those involved in endurance events, appear to be more susceptible than normal to infection. 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 for longer in athletes (13, 27, 31). There is some convincing evidence that this increased susceptibility to infection arises due to a depression of immune system function and there are several detailed reviews on the subject available (10, 20, 41).

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 and entry into the circulation of less mature leukocytes from the bone marrow. Falls in the blood concentration of glutamine have also been suggested as a possible cause of the immunodepression associated with heavy training, though the evidence for this is less compelling. Inflammation caused by muscle damage may be another factor. 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 (28). 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 and these effects together with increased exposure to pathogens can make the athlete more susceptible to infection.

The relationship between exercise and susceptibility to infection has been modelled in the form of a 'J' shaped curve (24). This model suggests that while engaging in moderate activity may enhance immune function above sedentary levels, excessive amounts of prolonged high-intensity exercise induce detrimental effects on immune function. However, although the literature provides strong evidence in support of the latter point (10, 20, 24, 30, 35, 41), relatively little evidence is

available to suggest that there is any clinically significant difference in immune function between sedentary and moderately active persons. Thus, it may be more realistic to 'flatten' out the portion of the curve representing this part of the relationship. Recently an epidemiological study on infection incidence and habitual physical activity reported that the regular performance of about 2 hours of moderate exercise per day was associated with a 29% reduction in risk of picking up upper respiratory tract infection compared with a sedentary lifestyle (21). 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 (27, 32, 33).

Acute effects of exercise on immune function

A single, acute bout of prolonged strenuous exercise has a temporary depressive effect on immune function and this has been associated with an increased incidence of infection. For example, several studies have described a substantially higher (2-6 fold) frequency of self-reported symptoms of upper respiratory tract infection (URTI) in athletes who completed long distance foot races compared with control runners who did not compete in the events (27, 31, 32, 33). 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 (10, 29): 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 and anti-inflammatory cytokines such as tumour necrosis factor-α, interleukin (IL)-1β, IL-6, IL-10, macrophage inflammatory protein-1 and IL-1-receptor antagonist (IL-1ra), acute phase proteins like C-reactive protein and activated complement fragments. The large increases in plasma IL-6 concentration observed during exercise can be entirely accounted for by release of this cytokine from contracting muscle fibres (46). However, IL-6 production by monocytes (44) and IL-2 and IFN-γ (but not IL-4) production by T lymphocytes are inhibited during and for several hours after

prolonged exercise (16, 29). These cytokine changes suggest a shift in the TH1/TH2 balance towards a TH2 response which would be expected to decrease defence against intracellular pathogens.

Hormonal changes also occur in response to exercise, including rises in the plasma concentration of several hormones (e.g. 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 (rhIL-6) into resting humans to mimic the exercise-induced plasma levels of IL-6 increases plasma cortisol in a similar manner (45). In contrast, the same rhIL-6 infusion does not change plasma adrenaline, noradrenaline 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 C-Reactive Protein (45). During exercise the increase in IL-6 precedes the increase in the these two cytokines, arguing circumstantially for muscle-derived IL-6 to be the initiator of this response. IL-6 and IL-4 stimulate monocytes and macrophages to produce IL-1ra, which inhibits the effect of IL-1. Type 2 T lymphocytes, monocytes and B cells are the main producers of IL-10 and together with IL-4 it can inhibit type 1 T cell cytokine production. In accordance with this, strenuous exercise decreases the percentage of type 1 T cells in the circulation, whereas the percentage of type 2 T cells does not change. Both cortisol and adrenaline suppress the type 1 T cell cytokine production, whereas IL-6 directly stimulates type 2 T cell cytokine production. Type 1 T cells drive the immune system towards protection against intracellular pathogens such as viruses therefore, 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.

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 (35, 38). Acute exercise temporarily increases the number of circulating NK cells but following exercise NK cell counts drop to less than half of normal levels for a couple of hours; normal resting values are usually restored within 24 hours (42). NK cell cytolytic activity (per cell) falls after exercise and if the activity is both prolonged and vigorous, the decrease in NK cell counts and cytolytic activity may begin during the exercise session (42). During recovery from exercise lymphokine activated killer (LAK) cell numbers and activity also fall below pre-exercise levels. Acute exercise has been shown to diminish the proliferative response of lymphocytes to mitogens (20) and decrease the expression of an early activation marker (CD69) in response to stimulation with mitogen (39). When the exercise bout is strenuous and very prolonged (>1.5 hours), the number of circulating lymphocytes may be decreased below pre-exercise levels for several hours after exercise and the T-lymphocyte CD4+/CD8+ ratio is decreased (2, 32).

Antigen presenting cell (APC) function is also affected by exercise: exercise-induced reductions in macrophage MHC class II expression and antigen-presenting capacity have been documented (49). Both T memory (CD45RO+) and T naive (CD45RA+) cells increase temporarily during exercise, but the CD45RO/CD45RA ratio tends to increase due to the relatively greater mobilisation of the CD45RO+ subset (8, 18). Following prolonged strenuous exercise the production of immunoglobulins by B-lymphocytes is inhibited and DTH responses (as measured using the CMI multitest) are diminished (4). After prolonged exercise, the plasma concentration of glutamine has been reported to fall by about 20% and may remain depressed for some time. 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 (30). A new and potentially important finding is that following a prolonged bout of strenuous exercise the expression of some toll-like receptors (TLRs) on monocytes is decreased (19). TLRs enable antigen presenting cells to recognise pathogens and control the activation of the adaptive immune response (40). Prolonged exercise also results in a decreased induction of co-stimulatory molecules and cytokines following stimulation with known TLR ligands (19). These effects may represent a mechanism through which exercise stress impairs immune function and increases susceptibility to infection.

Can exercise-induced immunodepression be prevented?

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 (7) it was reported that 4 weeks 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 hours 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 antioxiodant supplementation was via a reduction in IL-6 release from the muscle of the exercising legs. Attenuating the IL-6 and cortisol response would be expected to limit the exercise-induced depression of immune function and this may be the mechanism for the reported lower incidence of URTI symptoms in ultramarathon runners supplemented with vitamin C compared with placebo (32, 33).

Consumption of carbohydrate (CHO) during exercise also attenuates rises in plasma IL-6, catecholamines, ACTH and cortisol (23, 25). CHO intake during exercise also attenuates the trafficking of most leukocyte and lymphocyte subsets, including the rise in the

neutrophil: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 (12). Very recently, it was shown that consuming 30-60 g of CHO per hour during 2.5 h of strenuous cycling prevented both the decrease in the number and percentage of interferon (IFN)-γ positive T lymphocytes and the suppression of IFN-γ production from stimulated T lymphocytes observed on the placebo control trial (16). IFN-γ production is critical to antiviral defence 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 (29).

Pedersen's group, however, have argued that the reduction in the IL-6 response to exercise may be two-edged sword as IL-6 has several metabolic effects and shared mechanisms exist regarding immune impairment and training adaptation (43). Attenuating the IL-6 response to exercise will also inhibit lipolysis (43), reduce the anti-inflammatory effects of exercise and attenuate the expression of a number of metabolic genes in the exercised muscle (34). In other words, it is possible that antioxidant supplementation and/or CHO ingestion during exercise sessions could limit adaptation to training. However, it can also be argued that CHO 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 CHO 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. 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.

Chronic effects of exercise training on immune function

The effects of exercise training on immune function have been investigated using (a) cross-sectional studies that have compared immune function in athletes and non-athletes (sedentary people); (b) longitudinal studies that have reported the effect of a training program - typically 4-12

weeks duration - in previously sedentary people; (c) short-term longitudinal studies that have reported the effect of a period - typically 1-3 weeks - of intensified training on immune function in already well trained athletes; (d) longitudinal studies that have monitored immune function in athletes over the course of a competitive season lasting typically 4-10 months and (e) Cross-sectional studies that have compared immune function in athletes diagnosed as "overtrained" with healthy athletes.

Following an acute bout of exercise changes in circulating leukocyte numbers and functions normally return to pre-exercise values within 12-24 hours. Cross-sectional studies that have compared leukocyte numbers and functions in blood samples taken from athletes more than 24 hours after their last training session with those of sedentary individuals have generally reported very few differences. Thus, in the true resting state immune function appears to be broadly similar in athletes compared with non-athletes and clinically normal levels are observed in most athletes (26). However, circulating numbers of leukocytes are generally lower in endurance athletes at rest compared with sedentary people. A low blood leukocyte count may arise from the haemodilution (expansion of the plasma volume) associated with training, or may represent increased apoptosis (programmed cell death) or altered leukocyte kinetics including a diminished release from the bone marrow. Indeed, the large increase in circulating neutrophil numbers that accompanies a bout of prolonged exercise could, over periods of months or years of heavy training, deplete the bone marrow reserve of these important cells. Certainly, the blood population of these cells seems to be less mature than those found in sedentary individuals (14, 35) and the phagocytic and oxidative burst activity of stimulated neutrophils has been reported to be lower in well trained cyclists compared with age and weight-matched sedentary controls (3).

Some studies have indicated that well trained individuals have a lower serum complement concentration compared with sedentary controls (20) but this may only reflect a training-induced haemodilution. There is a weak suggestion of a slightly elevated NK cell count and cytolytic action in trained individuals (42) but these effects are small and unlikely to be of any clinical significance.

Levels of secretory immunoglobulins such as salivary IgA (s-IgA) vary widely between individuals and although some early studies indicated that s-IgA concentrations are lower in endurance athletes compared with sedentary individuals (47), the majority of studies indicate that the levels are generally not different in athletes compared with non-athletes except when athletes are engaged in heavy training (9).

Longitudinal studies in which previously sedentary people are subjected to weeks or months of exercise training have shown that marked changes in immune function do not occur provided that blood samples are taken at least 24 hours after the last exercise bout. Furthermore, moderate exercise training in healthy young adults does not appear to have an effect on the initiation of a specific antibody response to vaccination or delayed type hypersensitivity (DTH) responses as measured by the swelling that arises 48 hours after injecting antigens into the skin using the CMI multitest (4).

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 indices of neutrophil function appear to be sensitive to the training load. A 2-week period of intensified training in already well-trained triathletes was associated with a 20% fall in the LPS-stimulated neutrophil degranulation response (37). Other leukocyte functions including T-lymphocyte $CD4^+/CD8^+$ ratios, mitogen-stimulated lymphocyte proliferation and antibody synthesis and natural killer cell cytotoxic activity have been shown to sensitive to increases in the training load in already well-trained athletes (48). Levels of secretory immunoglobulins such as salivary IgA are lower in athletes engaged in heavy training (9). However, exercise training in healthy young adults does not appear to have an effect on the initiation of a specific antibody response to vaccination or DTH responses as measured with the CMI multitest (4).

Thus, with chronic periods of 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 depression does not put athletes in danger of serious illness, but it can be sufficient to increase the risk of picking up common infections.

Several studies have examined changes in immune function during intensive periods of military training. However, this 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. Several studies have documented a fall in s-IgA concentration and some, though not all have observed a negative relationship between s-IgA concentration and occurrence of URTI.

S-IgA was evaluated as a marker of the severity of stress during a 19-day Royal Australian Air Force (RAAF) survival course, during which the 29 participants experienced hunger, thirst, boredom, loneliness, and extreme heat and cold combined with demanding physical effort (6). Dietary restriction, consumption of alcohol, body mass loss, occurrence of URTI, and negative emotions were negatively associated with s-IgA or the ratio of s-IgA to Albumin and the authors concluded that this ratio is a useful marker of the severity of stresses encountered during stressful training.

Few studies have investigated the effects of intensified training on multiple markers of immune function. However, in one such study (16, 17), seven healthy endurance-trained men completed three trials consisting of cycling exercise at a work rate equivalent to 74% VO_{2max} until volitional fatigue. The trials took place in the morning, before and after a 6-day period of intensified training (IT) and after 2 weeks of light recovery training (RT). Normal training (NT) consisted of ~10 hours of cycling per week; during the ITP, training load was increased on average by 73%. During RT, exercise was limited to no more than 4 h per week for 2 weeks. Training intensity and duration were confirmed by the use of heart rate monitors. The percentage and number of T-cells producing IFN-γ was lower at rest following the IT period compared with normal training. *Ex vivo* stimulated

neutrophil oxidative burst activity and lymphocyte proliferation fell after acute exercise and were markedly depressed at rest after the IT period compared with normal training. *Ex vivo* stimulated monocyte oxidative burst activity was unchanged after acute exercise, but was lower at rest following the IT period compared with normal training. Following all acute exercise trials the circulating number of IFN-γ^+ T-cells and the amount of IFN-γ produced per cell was decreased. The 6 days of intensified training did not affect resting s-IgA concentration, but the latter was significantly lower at the end of RT (s-IgA values were 74.2 ± 13.1, 64.6 ± 12.5 and 49.0 ± 10.4 mg/L during NT, IT and RT, respectively). Except for s-IgA, all measured immune parameters were back to normal after 2 weeks of RT. These results indicate that (a) acute exhaustive exercise causes a temporary fall in several aspects of immune cell function and a decrease in IFN-γ production by T cells; (b) resting immune function is decreased after only 6 days of intensified training and these effects are reversible with two weeks of relative rest; (c) in general the immune response to an acute bout of exhaustive exercise is not affected by the weekly training load.

Several longitudinal studies have monitored immune function in high-level athletes over the course of a competitive season. In one 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-month training season in preparation for national championships (11). The results indicated significant suppression of resting serum IgA, IgG and IgM and salivary IgA concentration in athletes associated with long-term training at an intensive level. Furthermore, resting saliva IgA concentrations at the start of the training period showed significant correlations with infection rates and the number of infections observed in the swimmers was predicted by the preseason and mean pre-training IgA levels. The studies on mucosal immunity in elite Australian swimmers by Maree Gleeson and colleagues (10, 11) are representative of a very small number of studies that have established a relationship between some measure of immune function and infection incidence in athletes. Among the markers of systemic immunity that were also measured there were no significant changes in numbers or percentages of B or T cell subsets, but there was a

significant fall in natural killer (NK) cell numbers and percentages in the swimmers over the training season.

In a study on competitive cyclists, the total number of leukocytes, T lymphocyte subsets, mitogen-induced lymphocyte proliferation and IL-2 production, adherence capacity and oxidative burst activity of neutrophils were measured at rest at the beginning of a training season and after six months of intensive training and a racing season, cycling approximately 500 km a week (1). Baseline values of the tested immune parameters were within the range observed in non-trained healthy controls. At the end of the season significant decreases in absolute numbers of CD3+ and CD4+ cells, diminished IL-2 production and reduced fMLP and PMA stimulated oxidative burst activity of neutrophils were noted.

There are only a few studies that have examined immunological changes in professional football players before, during and after a full season. A competitive season in 15 Belgian professionals did not produce any change in the total number of leukocytes but increased neutrophil counts and decreased CD4+ T-lymphocyte counts (5). There was also a slight decrease in T-cell proliferation and a significant decrease in neutrophil function. On the other hand, training and competitions did not induce significant changes in the number of NK cells nor NK cytotoxic activity (5). In 13 Portuguese players at the end of the season total leukocyte and neutrophil numbers and CD8+ cells were increased compared to pre-season values and the CD4/CD8 ratio was decreased (36). In an unpublished study of an English premier league squad that were monitored during the 2001-2002 season we found that the mean total leukocyte, neutrophil, monocyte and lymphocyte counts and the CD4/CD8 ratio did not change. During the season, however, the concentrations of some lymphocyte subpopulations were changed: CD45RO+ (memory) T cells showed significant decreases, falling to very low levels by the end of the season whereas the numbers of CD45RA+ (naïve) T cells increased. CD45RO expression on T cells also fell after 22 and 33 weeks and a significant fall in NK cells was evident at the end of the season. During the competitive period, salivary IgA concentration and MHCII expression on monocytes were lowest at

11 weeks when form (wins/losses ratio and league position) was lowest. Plasma cortisol levels were unchanged at the end of the season but testosterone levels were ~20% lower than pre-season. Cells positive for CD45RO are actually a mixture of memory cells (important in long-term recognition of antigens and in generating the acquired immune response to recall antigens) and short-term activated T cells. The loss these cell types and the fewer number of circulating NK cells could be viewed as disadvantageous to the body's defence against viral infection.

There are several possible causes of the diminution of immune function associated with heavy training. One mechanism may simply be the cumulative effects of repeated bouts of intense exercise with the consequent elevation of stress hormones, particularly glucocorticoids such as cortisol, causing temporary immunosuppression. It is known that both acute glucocorticosteroid administration (22) and exercise (16, 29) cause a temporary inhibition of IFN-γ production by T-lymphocytes and it has been suggested that this may be an important mechanism in exercise-induced depression of immune cell functions (29). When exercise is repeated frequently there may not be sufficient time for the immune system to recover fully.

Conclusions

In summary, acute bouts of exercise cause a temporary depression of various aspects of immune function (e.g. neutrophil respiratory burst, lymphocyte proliferation, monocyte MHC class II expression) that lasts ~3-24 hours after exercise depending on the intensity and duration of the exercise bout. Post-exercise immune function depression is most pronounced when the exercise is continuous, prolonged (>1.5 hours), of moderate to high intensity (55-75% VO_2max) and performed without food intake. Periods of intensified training (overreaching) lasting one week or more result in chronically depressed immune function. 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. Hundreds of studies have now been conducted that confirm both acute and chronic effects of exercise on the immune system, yet there are still very few studies that have been able to show a direct link between exercise-induced immune depression and increased incidence of illness in athletes. This is an important issue that needs to be addressed in future studies, though it must be recognised 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 (15). 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.

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