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Exercise and Immunity: Clinical Studies

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ABSTRACT

Moderate to heavy exercise workloads have contrasting influences on immune function. Moderate exercise training has been associated with favorable perturbations in immunity and a reduction in incidence of upper respiratory tract infection (URTI). More research is needed to establish whether or not a link exists between moderate exercise-induced perturbations in immunity and improvements in other clinical outcomes such as cancer, heart disease, type 2 diabetes, arthritis, and aging. Epidemiological data indicate that endurance athletes are at increased URTI risk during periods of heavy training and the 1–2 week period following race events. For several hours subsequent to heavy exertion, components of both the innate (e.g., natural killer cell activity and neutrophil oxidative burst activity) and adaptive (e.g., T- and B-cell function) immune system exhibit suppressed function. Some attempts have been made through nutritional means (e.g., glutamine, vitamins C and E, and carbohydrate supplementation) to attenuate immune changes following intensive exercise and thus lower URTI risk. Carbohydrate supplementation during heavy exercise has emerged as the most effective countermeasure, and attenuates increases in blood neutrophil counts, stress hormones, and inflammatory cytokines.

I. INTRODUCTION

Exercise immunology is a relatively new area of scientific endeavor, with 80% of articles published during the past decade (Nieman, 2003). Growing evidence indicates that physical activity does influence immune function and as a consequence risk of certain types of infection, in particular the most common of all, upper respiratory tract infections (URTI). This chapter will summarize recent investigations showing that in contrast to moderate physical activity, prolonged and intensive exertion causes numerous negative changes in immunity and an increased risk of URTI.

A. Exercise, Immune Changes, and Clinical Outcomes

The link between exercise-induced perturbations in immunity and improvements in other clinical outcomes such as cancer, heart disease, type 2 diabetes, arthritis, and aging has not been investigated as thoroughly as with URTI. More research is needed to determine if immune alterations during exercise training help explain the lowered risk of chronic disease. For example, although epidemiological and experimental studies with animal models suggest that physical activity may protect against several forms of cancer, evidence linking this to enhanced immunity is limited and controversial (Fairey et al., 2005). Hoffman-Goetz and Husted (1995) more than a decade ago proposed that although various exercise-induced mechanical and hormonal changes best explain the relationship to reduced risk of colon, breast, and prostate cancer in

physically active individuals, several potential immu-nological effects may be contributing factors. These include exercise-induced immune modulation of cyto-kines; activation and changes in signal transduction of natural killer (NK) cells, macrophages, neutrophils, and tumor-infiltrating lymphocytes; changes in the expression of cell adhesion molecules; and alterations in prostaglandins. Accumulating evidence indicates that exercise training causes changes in pro- and anti-inflammatory cytokine levels and activity that may influence both the prevention and treatment of certain types of carcinomas (Allgayer et al., 2004). This area of research endeavor is highly complex, and more research is needed.

Immune senescence or age-associated immune defi-ciency appears to be partly responsible for the afflic-tions of old age. Elderly persons are more susceptible to many infections, autoimmune disorders, and cancers when compared with younger adults. A new and growing area of research endeavor is the study of the relationship between physical activity and immune senescence. One study of adults over the age of 65 years showed that a 10-month exercise program enhanced the antibody titer response to an influenza immunization (Kohut et al., 2004), thus showing that exercise can have some immediate benefits for the elderly. Regular physical activity may also attenuate the age-related decrease in T lymphocyte function (Smith et al., 2004). Very few studies have been con-ducted in this area, but the available data taken together suggest that exercise training may need to be long term and of sufficient volume to induce changes in body weight and fitness before any change in immunity can be expected in old age (Kohut and Senchina, 2004; Nieman et al., 1993). In other words, because the aging process is so dominant in old age, long-term physical activity combined with leanness and other positive lifestyle habits may be necessary before immune func-tion is enhanced.

Type 2 diabetes and cardiovascular disease are associated with chronic low-grade systemic inflamma-tion. During exercise, IL-6 is produced by muscle fibers and stimulates the appearance in the circulation of other anti-inflammatory cytokines such as IL-1ra and IL-10 (Petersen and Pedersen, 2005). IL-6 also inhibits the production of the pro-inflammatory cytokine TNF-alpha and stimulates lipolysis and fat oxidation. With weight loss from energy restriction and exercise, plasma levels of IL-6 fall, skeletal muscle TNF-alpha decreases, and insulin sensitivity improves (Ferrier et al., 2004; Ryan and Nicklas, 2004). Thus, IL-6 release from the exercising muscle may help mediate some of the health benefits of exercise including metabolic control of type 2 diabetes (Petersen and Pedersen,

2005). The exercise-induced cytokine links between adipose and muscle tissues clearly warrant further study (Tomas et al., 2004).

II. EXERCISE, IMMUNITY, AND URTI RISK

Upper respiratory tract infections are the most frequently occurring illnesses in humans worldwide. More than 200 different viruses cause the common cold, and rhinoviruses and coronaviruses are the cul-prits 25–60% of the time. The U.S. Centers for Disease Control and Prevention has estimated that more than one billion URTIs occur annually in the United States, a leading cause of lost school and work days. The average person has two or three respiratory infec-tions each year, with young children suffering six to seven.

Among elite athletes and their coaches, a common perception is that heavy exertion lowers resistance and is a predisposing factor to URTI. In a 1996 survey by the Gatorade Sports Science Institute of 2,700 high school and college coaches and athletic trainers, 89% checked "yes" to the question, "Do you believe over-training can compromise the immune system and make athletes sick?" (personal communication, Gato-rade Sports Science Institute, Barrington, IL).

Conversely, there is also a common belief among fitness enthusiasts that regular exercise confers resis-tance against infection. In a survey of 170 non-elite marathon runners (personal best time, average of 3 hours 25 minutes) who had been training for and par-ticipating in marathons for an average of 12 years, 90% reported that they definitely or mostly agreed with the statement that they "rarely get sick" (unpublished observations). A survey of 750 masters athletes (ranging in age from 40 to 81 years) showed that 76% perceived themselves as less vulnerable to viral illnesses than their sedentary peers (Shephard et al., 1995).

Although the relationship between exercise and URTI and other types of infections has been explored since early in the twentieth century (Baetjer, 1932), the number of well-designed epidemiological and exercise training experimental trials on humans is still small, limiting our understanding of this important topic (Nieman, 1997a, 2003).

Data from animal studies have been difficult to apply to the human condition but in general have sup-ported the finding that one or two periods of exhaus-tive exercise following inoculation lead to a more frequent appearance of infection and a higher fatality rate (but results differ depending on the pathogen, with some more affected by exercise than others) (Friman et al., 1995; Pedersen and Bruunsgaard, 1995).

Davis et al. (1997), for example, exposed mice to rest, 30 minutes of moderate exercise, or 2.5–3 hours of exhaustive exercise following intranasal infection with the herpes simplex virus (HSV-1). Mice exercised to fatigue had a greater overall mortality during a 21-day period than did controls or moderately exercised mice.

In humans, it is well established that various measures of physical performance capability are reduced during an infectious episode (Friman et al., 1995). Several case histories have been published demonstrating that sudden and unexplained deterioration in athletic performance can be traced to either recent URTI or subclinical viral infections that run a protracted course. In some athletes, a viral infection may lead to a debilitating state known as "post-viral fatigue syndrome" (Maffulli et al., 1993; Parker et al., 1996). The symptoms include lethargy, easy fatigability, and myalgia, and can persist for several months.

A. Exercise-Induced Changes in Immune Function

Together, these data imply that there is a relationship between exercise and infection, and that heavy exertion may suppress various components of immunity. Research data on the resting immunity of athletes and non-athletes, however, are limited and present a confusing picture at present (Nieman, 1997b). For example, the few studies available suggest that the innate immune system responds differentially to the chronic stress of intensive exercise, with natural killer cell activity tending to be enhanced while neutrophil function is suppressed (Nieman et al., 1995b, 1999; Pyne et al., 1995; Smith and Pyne, 1997). The adaptive immune system (resting state) in general seems to be largely unaffected by athletic endeavor.

Each acute bout of cardiorespiratory endurance exercise leads to transient but significant changes in immunity and host defense (Gabriel and Kindermann, 1997; Hoffman-Goetz and Pedersen, 1994; Nieman et al., 1997b, 2002a, 2003a, 2004; Pedersen and Brunsgaard, 1995). Natural killer cell activity, various measures of T- and B-cell function, upper airway neutrophil function, and salivary IgA concentration have all been reported to be suppressed for at least several hours during recovery from prolonged, intense endurance exercise (Bruunsgaard et al., 1997; Gabriel and Kindermann, 1997; Mackinnon and Hooper, 1994; Müns, 1993; Nieman et al., 1995a, 1995c, 2001, 2003b; Shinkai et al., 1993). During this "open window" of decreased host protection, viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection (Figure 1).
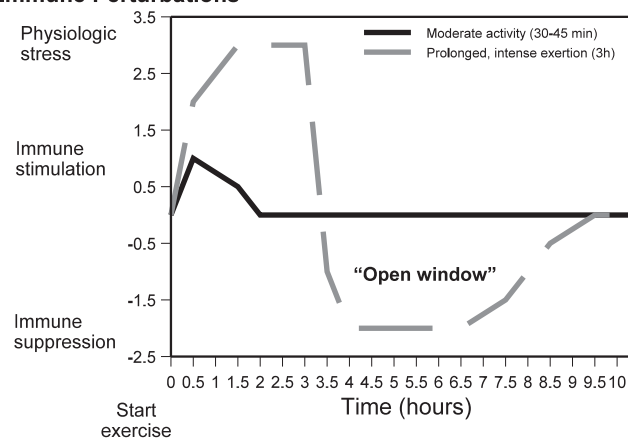
Immune Perturbations

FIGURE 1 The "open window theory": Moderate exercise causes mild immune changes; in contrast, prolonged, intensive exercise (90 minutes or longer) leads to a downturn in immunosurveillance that increases the likelihood for opportunistic upper respiratory tract infections.

Although this is an attractive hypothesis, no one has yet demonstrated conclusively that athletes showing the most extreme immunosuppression are those that contract an infection (Lee et al., 1992; Mackinnon et al., 1993). In one study, salivary IgA secretion rate decreased by nearly half in a group of 155 ultramarathon runners following a 160 km race (Nieman et al., 2006). Nearly one in four runners reported an URTI episode during the 2-week period following the race, and the decrease in sIgA secretion rate was significantly greater in these runners (54%) compared to those not reporting URTI (31%). It is doubtful, however, that sIgA output alone can be used to predict URTI at the individual athlete level. In this study, the overall predictive value for URTI was 55%, indicating that sIgA output was more useful at the group compared to the individual level, and that other factors need to be discovered and combined with sIgA before URTI risk can be predicted for individual athletes.

B. Heavy Exertion and URTI: Epidemiological Evidence

Understanding the relationship between exercise and infection has potential implications for public health, and for the athlete, it may mean the difference between being able to compete or performing at a subpar level or missing the event altogether because of illness. It has been proposed that the relationship between exercise and URTI may be modeled in the form of a "J" curve (Nieman, 1997a) (Figure 2). This model suggests that although the risk of URTI may decrease below that of a sedentary individual when
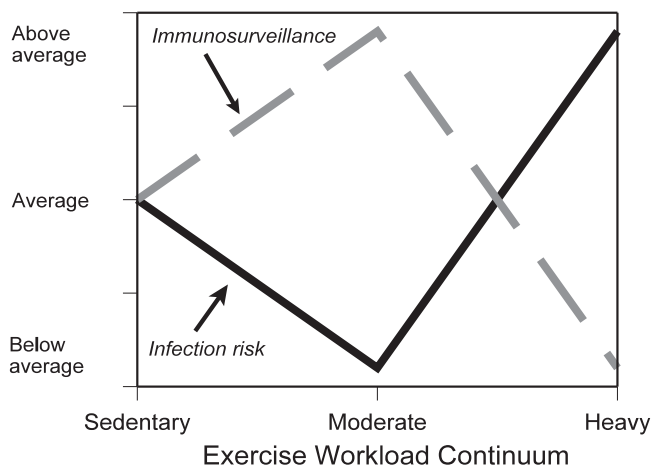
FIGURE 2 Model on the relationship between exercise workload, risk of upper respiratory tract infection (URTI), and immunosurveillance.

one engages in moderate exercise training, risk may rise above average during periods of excessive amounts of high-intensity exercise.

The model in Figure 2 also suggests that immunosurveillance mirrors that relationship between infection risk and exercise workload. In other words, it makes sense that if regular moderate exercise lowers infection risk, it should be accompanied by enhanced immunosurveillance. On the other hand, when an athlete engages in unusually heavy exercise workloads (e.g., overtraining or a competitive endurance race event), infection risk should be related to diminished immunosurveillance.

At present, there is more evidence, primarily epidemiological in nature, exploring the relationship between heavy exertion and infection, and these data will be reviewed first followed by a section on moderate exercise training and infection (Table 1). Much more research using larger subject pools and improved research designs is necessary before this model can be wholly accepted or rejected. The epidemiological studies summarized in Table 1 all used self-reported URTI data (primarily retrospective, with two studies using 1-year daily logs). None have attempted to verify symptomatology using viral identification or verification by physicians. There is some concern that the symptoms reported by endurance athletes following competitive race events may reflect those associated with an inflammatory response rather than URTI (Castell et al., 1997; Drenth et al., 1995; Nehlsen-Cannarella et al., 1997). Nonetheless, the data are consistent in supporting the viewpoint that heavy exertion increases the risk of URTI, while moderate exercise training is associated with a decreased risk.

Several epidemiological reports suggest that athletes engaging in marathon-type events and/or very heavy training are at increased risk of URTI (Table 1). Nieman et al. (1990a) researched the incidence of URTI in a group of 2,311 marathon runners who varied widely in running ability and training habits. Runners retrospectively self-reported demographic, training, and URTI episode and symptom data for the 2-month period (January, February) prior to and the 1-week period immediately following the 1987 Los Angeles Marathon race. During the week following the race, 12.9% of the marathoners reported an URTI compared to only 2.2% of control runners who did not participate (odds ratio, 5.9, using a logistic regression model that controlled for various training and demographic variables). Forty percent of the runners reported at least one URTI episode during the 2-month winter period prior to the marathon race. Controlling for various confounders, it was determined that runners training more than 96 km/wk doubled their odds for sickness compared to those training less than 32 km/wk.

Linde (1987) studied URTI in a group of 44 elite orienteers and 44 non-athletes of the same age, sex, and occupational distribution during a 1-year period. Athletes and controls recorded symptoms of sickness using daily logs for 1 year. The orienteers experienced significantly more URTI episodes during the year in comparison to the control group (2.5 vs. 1.7 episodes, respectively). While one-third of the controls reported no URTI during the year-long study period, this applied to only 10% of the orienteers. The average duration of symptoms in the group of orienteers was 7.9 days compared to 6.4 days in the control group (NS). The control group had the expected seasonal variation with the peak incidence in winter and relatively few cases in summer, while the orienteers tended to show a more even distribution.

Heath et al. (1991) also followed a cohort of runners (N = 530) who self-reported URTI symptoms daily for 1 year. The average runner in the study was about 40 years of age, ran 32 km/wk, and experienced a rate of 1.2 URTI per year. Controlling for various confounding variables using logistic regression, the lowest odds ratio for URTI was found in those running less than 16 km/wk. The odds ratio more than doubled for those running more than 27 km/wk. This study demonstrated that total running distance for a year is a significant risk factor for URTI, with risk increasing as the running distance rises.

Peters and Bateman (1983) studied the incidence of URTI in 150 randomly selected runners who took part in a 56 km Cape Town race in comparison to matched controls who did not run. Symptoms of URTI occurred in 33.3% of runners compared with 15.3% of controls

TABLE 1   Epidemiological Research on the Relationship Between Intense, Prolonged Exercise and Upper Respiratory Tract Infection (URTI)

Investigators	Subjects	Method of determining URTI	Major finding
Peters and Bateman (1982)	141 South African marathon runners vs. 124 live-in controls	2-week recall of URTI incidence and duration after 56 km race	URTI incidence twice as high in runners after 56 km race vs. controls (33.3% vs. 15.3%)
Linde (1987)	44 Danish elite orienteers vs. 44 matched non-athletes	URTI symptoms self-recorded in daily log for 1 year	Orienteers vs. controls had 2.5 vs. 1.7 URTIs during year
Nieman et al. (1989)	294 California runners training for race	2-month recall of URTI incidence; 1 week recall after winter 5, 10, 21 km races	Training 42 vs. 12 km/wk associated with lower URTI; no effect of race participation on URTI
Peters (1990)	108 South African marathon runners vs. 108 live-in controls	2-week recall of URTI incidence and duration after 56 km race	URTI incidence 28.7% in runners vs. 12.9% in controls after 56 km race
Nieman et al. (1990a)	2,311 Los Angeles marathon runners	2-month recall of URTI incidence during training for marathon; 1-week recall after winter race	Runners training ≥97 vs. <32 km/wk at higher URTI risk; odds ratio 5.9 for participants vs. non-participants 1 week after 42.2 km race
Heath et al. (1991)	530 runners, South Carolina	1-year daily log using self-reported, pre-coded, symptoms	Increase in running distance positively related to increased URTI risk
Peters et al. (1993)	84 South African marathon runners vs. 73 non-runner controls	2-week recall of URTI incidence and duration after 90 km race	URTI incidence 68% in runners vs. 45% in controls after 56 km race; 33% in runners using vitamin C vs. 53% of controls
Nieman (1993) (unpublished data)	170 North Carolina marathon runners	1-week recall of URTI incidence after summer marathon race	URTI reported by only 3% of marathoners during week after summer race
Peters et al. (1996)	178 South African runners vs. 162 controls	2-week recall of URTI incidence and duration after 90 km race	URTI incidence 40.4% in placebo runners vs. 15.9% using vitamin C (500 mg/d for 3 weeks). Vitamin A and E had no additional effect
Castell et al. (1996)	151 endurance athletes in the United Kingdom	1-week recall of URTI incidence after heavy exertion	URTI reported by 81% of athletes using placebo vs. 49% using a glutamine-based beverage
Nieman et al. (2002a)	91 marathon runners, North Carolina	15-day recall of URTI incidence after marathon race event	URTI reported by 17% of marathoners; post-race sIgA: protein lower in URTI vs. non-URTI group
Nieman et al. (2006)	155 ultramarathoners, Western U.S. 160 km	2-week recall of URTI incidence after 160 km race event	URTI reported by 24% of athletes; sIgA decrease was 54% in URTI vs. 31% in non-URTI group

during the 2-week period following the race, and were most common in those who achieved the faster race times. The most prevalent symptoms after the race were reported to be sore throats and nasal symptoms. Of the total number of symptoms reported by the runners, 80% lasted for longer than 3 days, suggesting an infective origin.

Several subsequent studies from this group of researchers have confirmed this finding (Peters, 1990; Peters et al., 1993, 1996). During the 2-week period following the 56 km Milo Korkie Ultramarathon in Pretoria, South Africa, 28.7% of the 108 subjects who completed the race reported non-allergy–derived URTI symptoms as compared to 12.9% of controls (Peters, 1990). In another study, 68% of runners reported the development of symptoms of URTI within 2 weeks after the 90 km Comrades Ultramarathon (Peters et al., 1993). Using a double-blind placebo research design, it was determined that only 33% of runners taking a 600 mg vitamin C supplement daily for 3 weeks prior to the race developed URTI symptoms. The incidence of URTI was greatest among the runners who trained the hardest coming into the race (85% vs. 45% of the low- or medium-training status runners).

In subsequent research, vitamin C, but not vitamin A and E, supplements have not been found to alter URTI rates following ultramarathon competitions (Peters et al., 1996; Peters-Futre, 1997). As summarized in Table 1, 15.9% of runners using vitamin C supplements (500 mg/day) reported URTI during the 2-week

period following the 1993 90 km Comarades ultra-marathon in comparison to 40.4% of runners using placebo, 20–26% of runners using vitamin C with vitamin E and beta carotene, and 24.4% of controls on placebo. The authors suggested that because heavy exertion enhances the production of free oxygen radicals, vitamin C, which has antioxidant properties, may be required in increased quantities (Peters et al., 1993; Peters-Futre, 1997). Other researchers have reported reduced URTI rates following marathon race events in runners consuming beverages containing glutamine, an amino acid used by various cells of the immune system (Castell et al., 1996, 1997).

Predicting what runners will obtain URTI following an endurance race event from demographic and immune function parameters has proven to be a difficult task. Table 1 summarizes two studies that showed that URTI was more likely in runners experiencing low salivary IgA output during and after competing in a 160 km race event (Nieman et al., 2002a; 2006).

URTI risk following a race event may depend on the distance, with an increased incidence conspicuous only following marathon or ultramarathon events. For example, Nieman et al. (1989) were unable to establish any increase in prevalence of URTI in 273 runners during the week following 5 km, 10 km, and 21.1 km events as compared to the week before. URTI incidence was also measured during the 2 winter-month period prior to the three races, and in this group of recreational runners, 25% of those running 25 or more km/wk (average of 42 km/wk) reported at least one URTI episode, as opposed to 34% training less than 25 km/wk (average of 12 km/wk) (p = 0.09). These findings suggest that, in recreational running, an average weekly distance of 42 versus 12 km is associated with either no change in or even a slight reduction of URTI incidence. Further, they suggest, that racing 5 km to 21.1 km is not related to an increased risk of sickness during the ensuing week.

URTI rates after endurance races may also vary depending on the season. As summarized in Table 1, only 3% of marathon runners reported URTI symptoms during the week after the July 1993 Grandfather Mountain Marathon (Boone, NC).

Together, these epidemiological studies imply that heavy acute or chronic exercise is associated with an increased risk of URTI. The risk appears to be especially high during the 1- or 2-week period following marathon-type race events. Among runners varying widely in training habits, the risk for URTI is slightly elevated for the highest distance runners, but only when several confounding factors are controlled.

Thus, it makes sense that URTI risk may be increased when the endurance athlete goes through repeated cycles of unusually heavy exertion; has been exposed to novel pathogens; and has experienced other stressors to the immune system including lack of sleep, severe mental stress, malnutrition, or weight loss. A 1-year retrospective study of 852 German athletes showed that risk of URTI was highest in endurance athletes who also reported significant stress and sleep deprivation (Konig et al., 2000). In other words, URTI risk is related to many factors, and when brought together during travel to important competitive events, the athletes may be unusually susceptible.

The majority of endurance athletes, however, do not report URTI after competitive race events. For example, only 1 in 7 marathon runners reported an episode of URTI during the week following the March 1987 Los Angeles Marathon, compared to 2 in 100 who did not compete (Nieman et al., 1990a). When athletes train hard, but avoid overreaching and overtraining, URTI risk is typically unaltered. For example, during a 2.5-month period (winter/spring) in which elite female rowers trained 2–3 hours daily (rowing drills, resistance training), incidence of URTI did not vary significantly from that of non-athletic controls (Nieman et al., 2000a).

C. Moderate Exertion, URTI, and Immune Function

What about the common belief that moderate physical activity is beneficial in decreasing URTI risk? Very few studies have been carried out in this area, and more research is certainly warranted to investigate this interesting question.

At present, there are few published epidemiological reports that have retrospectively or prospectively compared incidence of URTI in large groups of moderately active and sedentary individuals. A 1-year epidemiological study of 547 adults demonstrated a 23% reduction in risk of URTI in those engaging in regular versus irregular moderate-to-vigorous physical activity (Matthews et al., 2002). In healthy elderly subjects, URTI symptomatology during a 1-year period was inversely related to energy expended during moderate physical activity (Kostka et al., 2000). In Project PRIME, a randomized clinical trial that investigated interventions to increase physical activity, the odds ratio for reporting URTI symptoms was 0.50 (95% C.I., 0.28 to 0.91) among participants who engaged in a minimum of 150 minutes per week of moderate and vigorous activity compared with less active participants (Strasner et al., 2001).

Three randomized experimental trials have provided important data in support of the viewpoint that moderate physical activity may reduce URTI symptomatology (Table 2). In one randomized, controlled

TABLE 2   **Exercise Training Studies on the Relationship Between Moderate Exercise and Upper Respiratory Tract Infection (URTI)**

Investigators	Subjects	Method of determining URTI	Major finding
Nieman et al. (1990b)	36 mildly obese, inactive women, California	Daily logs using self-reported, pre-coded, URTI symptoms for 15 weeks during winter season	Walking group reported fewer days with URTI symptoms than controls (5.1 vs. 10.8)
Nieman et al. (1993)	42 elderly women (30 inactive, 12 athletes), North Carolina	Daily logs using self-reported, pre-coded, URTI symptoms for 12 weeks during fall season	Incidence of URTI 8% in athletes; inactives randomized to 12 weeks walking vs. controls, 21% in walkers, 50% in sedentary controls
Nieman et al. (1998a)	90 overweight and 30 normal-weight women	Daily logs using self-reported, pre-coded URTI symptoms for 12 weeks during winter season	Number of days with URTI symptoms, 9.4 ± 1.1, 5.6 ± 0.9, and 4.8 ± 0.9 in overweight walkers, overweight controls, and normal-weight controls

study of 36 women (mean age 35 years), exercise subjects walked briskly for 45 minutes, 5 days a week, and experienced one-half the days with URTI symptoms during the 15-week period compared to that of the sedentary control group (5.1 ± 1.2 vs. 10.8 ± 2.3 days, $p = 0.039$) (Nieman et al., 1990b).

The effect of exercise training (five 45-minute walking sessions/week at 60–75% maximum heart rate) and/or moderate energy restriction (4.19–5.44 MJ or 1,200–1,300 kcal per day) on URTI was studied in non-obese, physically active women (N = 30) and obese women (N = 91, body mass index 33.1 ± 0.6 kg/m^2) randomized to one of four groups: control, exercise, diet, exercise and diet (Nieman et al., 1998a). All subjects self-reported symptoms of sickness in health logs using a pre-coded checklist. Energy restriction had no significant effect on URTI incidence, and subjects from the two exercise groups were contrasted with subjects from the two non-exercise groups. The number of days with symptoms of URTI for subjects in the exercise groups was reduced relative to the non-exercise groups (5.6 ± 0.9 and 9.4 ± 1.1 sickness days, respectively), similar to that of the non-obese controls (4.8 ± 0.9). Figure 3 summarizes the combined data set from these two training studies.

In a study of elderly women, the incidence of the common cold during a 12-week period in the fall was measured to be lowest in highly conditioned, lean subjects who exercised moderately each day for about 1.5 hours (8%) (Nieman et al., 1993). Elderly subjects who walked 40 minutes, 5 times/week had an incidence of 21%, as compared to 50% for the sedentary control group ($X = 6.36$, $p = 0.042$). These data suggest that elderly women not engaging in cardiorespiratory exercise are more likely than those who do exercise regularly to experience an URTI during the fall season.

During moderate exercise or vigorous exercise that incorporates rest intervals, several positive changes
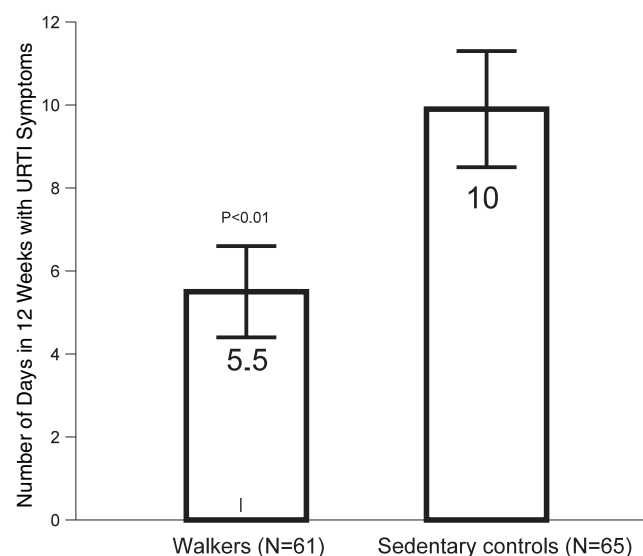
FIGURE 3   The number of URTI symptom days was decreased by approximately half through a walking program (5 days per week, 45 minutes per session, for 15 weeks).

occur in the immune system (Nehlsen-Cannarella et al., 1991; Nieman, 2000; Nieman and Nehlsen-Cannarella, 1994; Nieman et al., 2005a). Stress hormones, which can suppress immunity, and pro- and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise. Although the immune system returns to pre-exercise levels very quickly after the exercise session is over, each session represents a boost in immune surveillance that appears to reduce the risk of infection over the long term.

Although public health recommendations must be considered tentative, the data on the relationship between moderate exercise, enhanced immunity, and lowered risk of sickness are consistent with guidelines

urging the general public to engage in near-daily brisk walking.

III. ATHLETIC ENDEAVOR AND URTI

Endurance athletes are often uncertain of whether they should exercise or rest during an infectious episode. There are few data available in humans to provide definitive answers. Most clinical authorities in this area recommend that if the athlete has symptoms of a common cold with no constitutional involvement, then regular training may be safely resumed a few days after the resolution of symptoms.

Mild exercise during sickness with a common cold does not appear to be contraindicated. Weidner et al. (1997), for example, have shown that rhinovirus-caused upper respiratory illness does not impair short duration submaximal or maximal exercise performance. In addition, moderate exercise training did not influence URTI symptomatology (Weidner et al., 1998; Weidner and Schurr, 2003). However, it should be cautioned that rhinoviruses account for only 40% of URTI, and further research is needed with other pathogens to determine their relationship to exercise. Some clinicians feel that if there are symptoms or signs of systemic involvement (fever, extreme tiredness, muscle aches, swollen lymph glands, etc.), then 2–4 weeks should probably be allowed before resumption of intensive training (Friman et al., 1995; Nieman, 1997a).

For elite athletes who may be undergoing heavy exercise stress in preparation for competition, several precautions may help them reduce their risk of URTI. Considerable evidence indicates that two other environmental factors—improper nutrition and psychological stress—can compound the negative influence that heavy exertion has on the immune system (Nieman, 1997a; Shephard and Shek, 1995). Based on current understanding, the athlete is urged to eat a well-balanced diet, keep other life stresses to a minimum, avoid overtraining and chronic fatigue, obtain adequate sleep, and space vigorous workouts and race events as far apart as possible.

Immune system function may be suppressed during periods of rapid weight loss, so when necessary, the athlete is advised to lose weight slowly during noncompetitive training phases (Nieman et al., 1998a; Shade et al., 2004). Cold viruses are spread by both personal contact and breathing the air near sick people. Therefore, if at all possible, athletes should avoid being around sick people before and after important events. If the athlete is competing during the winter months, a flu shot is recommended.

A. Nutritional Strategies

Nutrition impacts the development of the immune system, both in the growing fetus and in the early months of life. Nutrients are also necessary for the immune response to pathogens so that cells can divide and produce antibodies and cytokines. Many enzymes in immune cells require the presence of micronutrients, and critical roles have been defined for zinc; iron; copper; selenium; and vitamins A, B6, C, and E in the maintenance of optimum immune function.

Although endurance athletes may be at increased infection risk during heavy training or competitive cycles, they must exercise intensively to contend successfully. Athletes appear less interested in reducing training workloads, and more receptive to ingesting nutrient supplements that have the potential to counter exercise-induced inflammation and immune alterations (Nieman, 2001; Shephard and Shek, 1995).

The influence of a growing list of nutritional supplements on the immune and infection response to intense and prolonged exercise has been assessed. Supplements studied thus far include zinc, dietary fat, plant sterols, antioxidants (e.g., vitamins C and E, beta-carotene, N-acetylcysteine, and butylated hydroxyanisole), glutamine, and carbohydrate. Except for carbohydrate beverages, none of these supplements has emerged as an effective countermeasure to exercise-induced immune suppression. Antioxidants and glutamine have received much attention, but the data thus far do not support their role in negating immune changes after heavy exertion. At this point, athletes should eat a varied and balanced diet in accordance with the Food Guide Pyramid and energy needs, and be assured that vitamin and mineral intake is adequate for both health and immune function.

1. Carbohydrate Supplements

Research during the 1980s and early 1990s established that a reduction in blood glucose levels was linked to hypothalamic-pituitary-adrenal activation, an increased release of adrenocorticotrophic hormone and cortisol, increased plasma growth hormone, and increased plasma epinephrine levels (Murray et al., 1991). Stress hormones have an intimate link with some aspects of immune function (Figure 4).

Several studies with runners and cyclists have shown that carbohydrate beverage ingestion plays a role in attenuating changes in immunity when the athlete experiences physiologic stress and depletion of carbohydrate stores in response to high intensity (~75–80% VO_{2max}) exercise bouts lasting longer than 90 minutes (Nehlsen-Cannarella et al., 1997; Nieman et al., 1997a, 1997c, 1998b, 2003a). In particular, carbo-
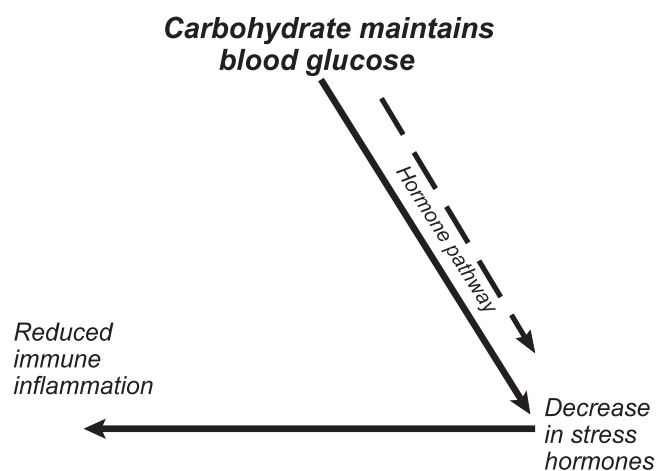
Carbohydrate maintains blood glucose

Hormone pathway

Reduced immune inflammation

Decrease in stress hormones

FIGURE 4 Carbohydrate supplementation during exercise attenuates plasma stress hormone, blood neutrophil count, and plasma cytokine responses.

hydrate ingestion (about one liter per hour of a typical sports drink) compared to a placebo has been linked to reduced change in blood immune cell counts, and lower pro- and anti-inflammatory cytokines. However, carbohydrate ingestion during intense and prolonged exercise is largely ineffective in countering post-exercise decrements in NK and T-cell function, and salivary IgA output.

Overall, these data indicate that physiological stress to some aspects of the immune system is reduced when endurance athletes use carbohydrate during intense exertion lasting 90 minutes or more. Does this mean that endurance athletes using carbohydrate beverages during marathon-type race events will lower their risk of sickness afterwards? One study suggests this is so, but more research is needed (Nieman et al., 2002a).

2. Antioxidants

Heavy exertion increases the generation of free radicals and reactive oxygen species (ROS) through several pathways including oxidative phosphorylation, increase in catecholamines, prostanoid metabolism, xanthine oxidase, and NAD(P)H oxidase (Urso and Clarkson, 2003). Neutrophils and macrophages migrate to the site of contraction-induced muscle damage, infiltrate the muscle tissue, activate the release of cytokines, and produce additional ROS. Most ROS are neutralized by a sophisticated antioxidant defense system consisting of a variety of enzymes and non-enzymatic antioxidants including vitamin A, E, and C; glutathione; ubiquinone; and flavonoids. Intensive and sustained exercise, however, can create an imbalance between ROS and antioxidants, leading to oxida-

tive stress that not only causes lipid peroxidation and protein oxidation, but may also impact immune function.

Can antioxidant supplements attenuate exercise-induced changes in immune function and infection risk? Several double-blind placebo studies of South African ultramarathon runners demonstrated that vitamin C (but not E or beta-carotene) supplementation (about 600 mg/day for 3 weeks) was related to fewer reports of URTI symptoms (Peters, 1990; Peters et al., 1993, 1996; Peters and Bateman, 1983; Peters-Futre, 1997). This has not been replicated, however, by other research teams. Himmelstein et al. (1998), for example, reported no alteration in URTI incidence among 44 marathon runners and 48 sedentary subjects randomly assigned to a 2-month regimen of 1,000 mg/day of vitamin C or placebo. Most randomized, placebo-controlled studies have been unable to demonstrate that vitamin C supplements modulate immune responses following heavy exertion (Nieman et al., 1997b; Nieman et al., 2000b, 2002b).

Vitamin E functions primarily as a non-specific, chain-breaking antioxidant that prevents the propagation of lipid peroxidation. The vitamin is a peroxyl radical scavenger and protects polyunsaturated fatty acids within membrane phospholipids and in plasma lipoproteins. The effect of vitamin E supplementation on the inflammatory and immune response to intensive and prolonged exercise is largely unstudied and equivocal. Cannon et al. (1991) found that vitamin E supplementation of 800 IU/day for 48 days attenuated endotoxin-induced IL-6 secretion from mononuclear cells for 12 days after running downhill on an inclined treadmill. Singh et al. (1999) showed no effect of vitamin E supplementation (4 days, 800 IU/day) on the increase in plasma IL-6 following a 98-minute treadmill run at 65–70% VO_{2max} to exhaustion. Petersen et al. (2002) reported no influence of vitamin E and C supplementation (500 mg and 400 mg, respectively, for 14 days before and 7 days after) on the plasma cytokine response to a 5% downhill 90-minute treadmill run at 75% VO_{2max}.

Two months of vitamin E supplementation at a dose of 800 IU/day α-tocopherol did not effect increases in plasma cytokines, perturbations in other measures of immunity, or oxidative stress in triathletes competing in the Triathlon World Championship race event (Nieman et al., 2004). To the contrary, athletes in the vitamin E compared to placebo group experienced greater lipid peroxidation and increases in plasma levels of several cytokines following the triathlon. Despite these indications that vitamin E exerted pro-oxidant and pro-inflammatory effects, race performance did not differ between athletes in the vitamin E

and placebo groups. In general, vitamin E supplementation to counter immune suppression and oxidative stress in endurance athletes cannot be recommended.

3. *Glutamine*

Glutamine, a non-essential amino acid, has attracted much attention by investigators (Mackinnon and Hooper, 1996; Rhode et al., 1995, 1998). Glutamine is the most abundant amino acid in the body, and is synthesized by skeletal muscle and other tissues. Glutamine is an important fuel for lymphocytes and monocytes, and decreased amounts *in vitro* have a direct effect in lowering proliferation rates of lymphocytes.

Reduced plasma glutamine levels have been observed in response to various stressors, including prolonged exercise. Since skeletal muscle is the major tissue involved in glutamine production and is known to release glutamine into the blood compartment at a high rate, it has been hypothesized that muscle activity may directly influence the immune system by altering the availability of this immune cell fuel substrate.

Whether exercise-induced reductions in plasma glutamine levels are linked to impaired immunity and host protection against viruses in athletes is still unsettled, but the majority of studies have not favored such a relationship (Nieman and Pedersen, 2000). For example, in a crossover, placebo-controlled study of eight males, glutamine supplementation abolished the post-exercise decrease in plasma glutamine concentration but still had no influence relative to placebo on exercise-induced decreases in T- and natural killer cell function (Rhode et al., 1998).

One problem with the glutamine hypothesis is that plasma concentrations following exercise do not decrease below threshold levels that are detrimental to lymphocyte function as demarcated by *in vitro* experiments. In other words, even marathon-type exertion does not deplete the large body stores of glutamine enough to diminish lymphocyte function.

In summary, there is growing evidence that prolonged intensive exercise is associated with an increased risk of URTI, in contrast to a decreased risk with moderate exercise training. Attempts have been made to alter the elevated URTI risk and suppressed immunity that have been associated with heavy exertion through chemical and nutritional means, with the most promising results thus far reported for carbohydrate supplementation. Further research is needed to establish the relationship of other nutrient supplements to changes in both immune function and host protection against URTI pathogens.

IV. CONCLUSIONS

By far, the most important finding that has emerged from exercise immunology studies during the past 2 decades is that positive immune changes take place during each bout of moderate physical activity. Over time, this translates to fewer days of sickness with the common cold and other upper respiratory tract infections. This is consistent with public health guidelines urging individuals to engage in near-daily physical activity of 30 minutes or greater.

The future of exercise immunology is determining whether or not exercise-induced perturbations in immunity help explain improvements in other clinical outcomes such as cancer, heart disease, type 2 diabetes, arthritis, and aging. This is an exciting new area of scientific endeavor, and preliminary data suggest that immune changes during exercise training are one of multiple mechanistic factors.

Risk of upper respiratory tract infections can increase when athletes push beyond normal limits. The infection risk is amplified when other factors related to immune function are present, including exposure to novel pathogens during travel, lack of sleep, severe mental stress, malnutrition, or weight loss.

Should the athlete exercise when sick? In general, if the symptoms are from the neck up (e.g., the common cold), moderate exercise is probably acceptable and some researchers would argue even beneficial, while bedrest and a gradual progression to normal training are recommended when the illness is systemic (e.g., the flu). If in doubt as to the type of infectious illness, individuals should consult a physician.

Many components of the immune system exhibit adverse change after prolonged, heavy exertion lasting longer than 90 minutes. These immune changes occur in several compartments of the immune system and body (e.g., the skin, upper respiratory tract mucosal tissue, lung, blood, and muscle). During this "open window" of impaired immunity (which may last between 3 and 72 hours, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection. Of the various nutritional countermeasures that have been evaluated thus far, ingestion of carbohydrate beverages during intense and prolonged exercise has emerged as the most effective. However, carbohydrate supplementation during exercise decreases exercise-induced increases in plasma cytokines and stress hormones, but is largely ineffective against other immune components including natural killer and T-cell function.

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