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Review

The compelling link between physical activity and the body's defense system

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Abstract

This review summarizes research discoveries within 4 areas of exercise immunology that have received the most attention from investigators: (1) acute and chronic effects of exercise on the immune system, (2) clinical benefits of the exercise–immune relationship, (3) nutritional influences on the immune response to exercise, and (4) the effect of exercise on immunosenescence. These scientific discoveries can be organized into distinctive time periods: 1900–1979, which focused on exercise-induced changes in basic immune cell counts and function; 1980–1989, during which seminal papers were published with evidence that heavy exertion was associated with transient immune dysfunction, elevated inflammatory biomarkers, and increased risk of upper respiratory tract infections; 1990–2009, when additional focus areas were added to the field of exercise immunology including the interactive effect of nutrition, effects on the aging immune system, and inflammatory cytokines; and 2010 to the present, when technological advances in mass spectrometry allowed system biology approaches (i.e., metabolomics, proteomics, lipidomics, and microbiome characterization) to be applied to exercise immunology studies. The future of exercise immunology will take advantage of these technologies to provide new insights on the interactions between exercise, nutrition, and immune function, with application down to the personalized level. Additionally, these methodologies will improve mechanistic understanding of how exercise-induced immune perturbations reduce the risk of common chronic diseases.

Keywords: Aging; Exercise; Immunology; Infection; Inflammation; Mass Spectrometry; Nutrition

1. Introduction to exercise immunology

Although exercise immunology is considered a relatively new area of scientific endeavor with 90% of papers published after 1990,[1] some of the earliest studies were published well over a century ago. For example, in 1902, Larrabee[2] provided evidence that changes in white blood cell differential counts in Boston marathon runners paralleled those seen in certain diseased conditions. He also observed that "the exertion had gone far beyond physiological limits and our results certainly show that where this is the case we may get a considerable leukocytosis of the inflammatory type."[2]

The immune system is very responsive to exercise, with the extent and duration reflecting the degree of physiological stress imposed by the workload. This review paper summarizes the research discoveries within 4 areas of exercise immunology that have received the most consideration: acute and chronic effects of exercise on the immune system, clinical benefits of this exercise–immune relationship, nutritional influences on the immune response to exercise, and the exercise effect on immunosenescence (Fig. 1).[3–7]

These scientific discoveries can be organized into distinctive time periods (Fig. 2). The earliest exercise immunology studies (1900–1979) focused on exercise-induced changes in basic immune cell counts and function.[5] The human immunodeficiency virus was identified as the cause of the AIDS in 1984. One of the markers for AIDS diagnosis was the CD4 antigen on helper T cells that required a flow cytometer for detection. Many medical universities acquired flow cytometers in the 1980s, and these instruments became available to exercise investigators, initiating the modern era of exercise immunology research. Another impetus was the publication of a brief review in a special issue of the *Journal of the American*

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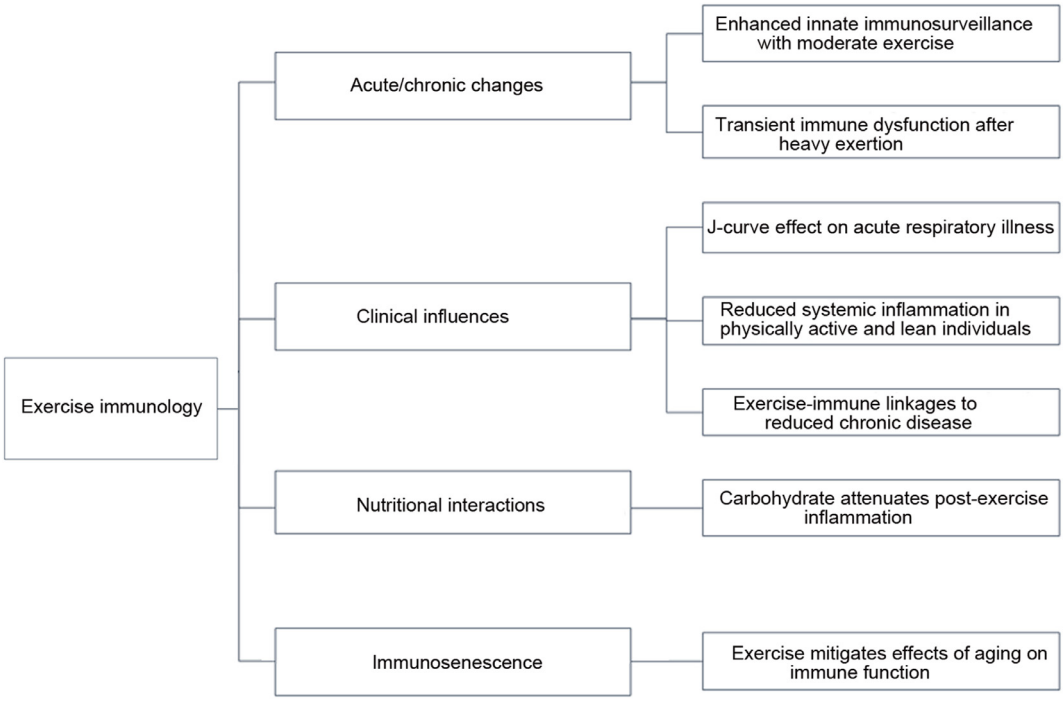

Fig. 1. Key research areas and basic findings in exercise immunology.

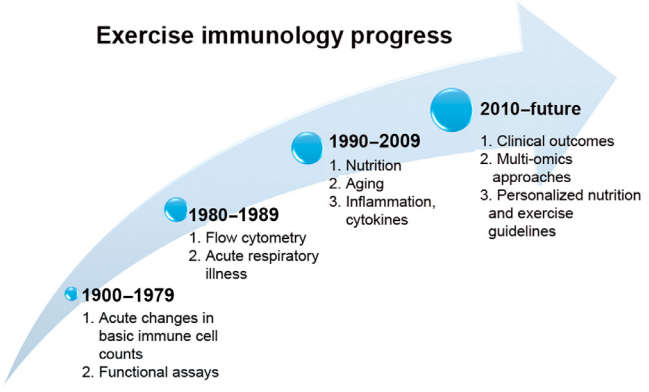

Fig. 2. Exercise immunology research can be organized into 4 distinctive periods.

Medical Association for the 1984 Olympic Games in Los Angeles.[8] This review concluded there was "no clear experimental or clinical evidence that exercise will alter the frequency or severity of human infections... Further studies will be needed before it can be concluded that exercise affects the host response to infection in any clinically meaningful way."[8] This conclusion was consistent with the existing evidence at that time and at the same time provided a framework for future investigations. During the same time period (1980–1989), seminal papers were published with evidence that heavy exertion was associated with transient immune dysfunction, elevated inflammatory biomarkers, and an increased risk of upper respiratory tract infections (URTIs).[9–18] For example, acute bouts of intense and prolonged exercise were linked by several early exercise immunology pioneer investigators to suppressed salivary immunoglobulin A (IgA) output, decreased natural killer cell (NK) lytic activity, reduced T- and B-cell function, and a 2- to 6-fold increased URTI risk during the 1–2 week postrace time period.[9–18] In 1989, the International Society of Exercise Immunology was founded, leading to biannual conferences and the highly successful *Exercise Immunology Review* journal (www.isei.dk).[5]

During the time period from 1990 to 2009, additional focus areas were added to the field of exercise immunology, including the interactive effect of nutrition,[7,19,20] effects on the aging immune system,[21–23] and influences on inflammatory cytokines.[24–27] With advances in mass spectrometry and genetic testing technology since 2010, increasing attention is being focused on metabolomics, proteomics, lipidomics, gut microbiome characterization, and genomic approaches to exercise immunology, and how this information can be used to provide personalized exercise and nutrition guidelines.[28–33] Additionally, acute and chronic exercise-induced immune changes are now being described as important mechanistic pathways for elucidating reduced cancer and heart disease risk among the physically active.[34–36]

2. Acute and chronic effects of exercise on the immune system

The acute immune response to exercise depends on the intensity and duration of effort. For the purposes of this review, moderate and vigorous exercises are differentiated using an intensity threshold of 60% of the oxygen update and heart rate reserve, and a duration threshold of 60 min. Exercise immunology investigators had an early focus on the large perturbations of basic leukocyte subsets associated with the physiological stress of athletic endeavor.[2,9–14,27] Increasing attention is being directed to the enhanced immunosurveillance of distinct immune cell subtypes during

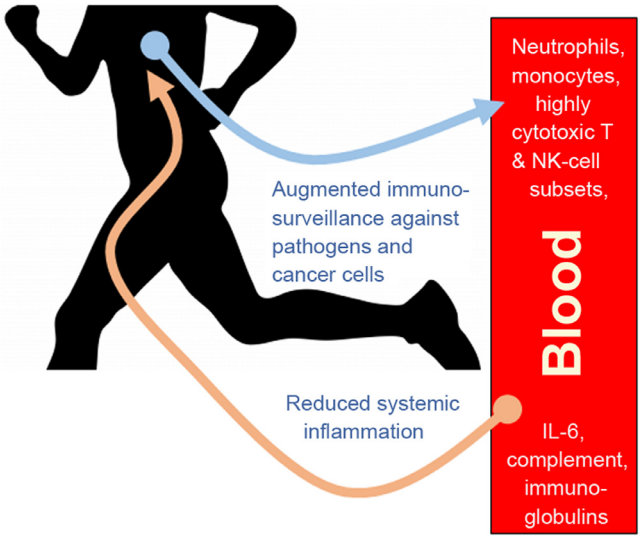

Fig. 3. Acute exercise stimulates the interchange of innate immune system cells and components between lymphoid tissues and the blood compartment. Although transient, a summation effect occurs over time, with improved immunosurveillance against pathogens and cancer cells and decreased systemic inflammation.

exercise bouts of less than 60 min that have potential prevention and therapeutic value.[37–48]

2.1. *Enhanced immunosurveillance with acute exercise bouts of less than 60 min*

During moderate- and vigorous-intensity aerobic exercise bouts of less than 60 min duration, the antipathogen activity of tissue macrophages occurs in parallel with an enhanced recirculation of immunoglobulins, anti-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells, and immature B cells, all of which play critical roles in immune defense activity and metabolic health (Fig. 3).[37–40,44–47] Acute exercise bouts preferentially mobilize NK cells and $CD8^+$ T lymphocytes that exhibit high cytotoxicity and tissue migrating potential.[38,46,48] Stress hormones, which can suppress immune cell function, and proinflammatory cytokines, indicative of intense metabolic activity, do not reach high levels during short duration, moderate exercise bouts.[40] Over time, these transient, exercise-induced increases in selective lymphocyte subsets enhance immunosurveillance and lower inflammation, and may be of particular clinical value for obese and diseased individuals.[41–43]

In general, acute exercise is now viewed as an important immune system adjuvant to stimulate the ongoing exchange of leukocytes between the circulation and tissues.[37] An ancillary benefit is that acute exercise may serve as a simple strategy to enrich the blood compartment of highly cytotoxic T-cell and NK cell subsets that can be harvested for clinical use.[38,44–46] Metabolically, moderate exercise induces small, acute elevations in IL-6 that exert direct anti-inflammatory effects, improving glucose and lipid metabolism over time.[49,50] Another benefit may include an enhanced antibody-specific response when vaccinations are preceded by an acute exercise bout, but more research is needed with better study designs to control for potential confounding influences.[51]

2.2. *Transient immune dysfunction after heavy exertion*

The measurement of immune responses to prolonged and intensive exercise by athletes continues to receive high attention. Taken together, the best evidence supports that high exercise training workloads, competition events, and the associated physiological, metabolic, and psychological stress are linked to immune dysfunction, inflammation, oxidative stress, and muscle damage.[9–14,24,27,52–54] NK cell and neutrophil function, various measures of T- and B-cell function, salivary IgA output, skin delayed-type hypersensitivity response, major histocompatibility complex II expression in macrophages, and other biomarkers of immune function are altered for several hours to days during recovery from prolonged and intensive endurance exercise.[52–58] The contrast in the magnitude of immune responses between a 30- to 45-min walking bout and 42.2-km marathon race is summarized in Fig. 4.[3,4,27,40,52–57] These immune changes occur in several compartments of the immune system and body including the skin, upper respiratory tract mucosal tissue, lung, blood, muscle, and peritoneal cavity. Although some investigators have challenged the clinical significance and linkage between heavy exertion and transient immune dysfunction,[58] the majority of investigators in the field of exercise immunology have supported the viewpoint that the immune system reflects the magnitude of physiological stress experienced by the exerciser.[3–5,27,54,56,57]

Recent improvements in mass spectrometry technology and bioinformatics support have improved the capacity to use a systems biology approach when measuring the complex interactions between exercise stress and immune function within the human athlete.[29–33,59–63] Metabolomics, proteomics, and lipidomics have revealed that metabolism and immunity are inextricably interwoven and has led to a new area of research

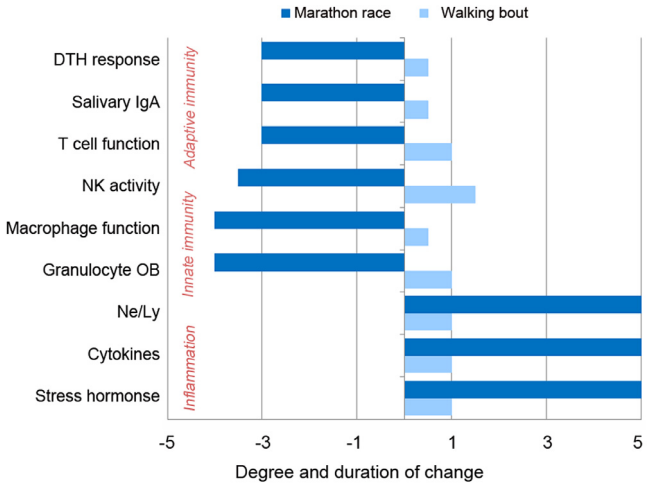

Fig. 4. The contrast in acute immune responses to heavy exertion (e.g., a marathon race) and a 30- to 45-min walking bout. DTH = delayed-type hypersensitivity; IgA = immunoglobulin A; Ne/Ly = neutrophil/lymphocyte ratio; NK = natural killer; OB = oxidative burst.

endeavor termed immunometabolism.[33,64] In a typical study with human athletes exercising intensely for more than 2 h, significant increases in at least 300 identified metabolites can be measured as body glycogen stores are depleted and an extensive increase occurs in numerous and varied lipid superpathway metabolites, including oxidized derivatives called oxylipins.[32,60–62] Exercise-induced muscle tissue injury and inflammation elicit a strong innate immune response involving granulocytes, monocytes, and macrophages. Immune-specific proteins are produced to regulate the innate immune response, with oxylipins involved in initiating, mediating, and resolving this process.[29,30,60,63] Most of the expressed immune-related proteins including lysozyme C, neutrophil elastase and defensin 1, proteins S100-A8/A12, cathelicidin antimicrobial peptide, α-actinin-1, and profilin-1 are involved with pathogen defense and immune cell chemotaxis and locomotion. Other proteins including serum amyloid A-4, myeloperoxidase, complements C4B and C7, plasma protease C1 inhibitor, α-2-HS-glycoprotein, and α-1-acid glycoprotein 2 increase chronically during recovery and are involved in the inflammatory acute phase response.[30]

This profound, exercise-induced perturbation in metabolites, lipid mediators, and proteins more than likely has a direct influence on immune function, decreasing the capacity of immune cells to increase oxygen consumption rates after activation.[31] In response to an acute immunologic challenge such as exercise stress, cells of the immune system must be able to engage in growth and proliferation to generate effector cells that produce specific molecules such as cytokines and the proteins listed in the previous paragraph.[64] Immune activation is associated with oxygen and biosynthetic demands, and immune cells must engage in metabolic reprogramming to generate sufficient energy to fuel these demands. Although more research is needed, preliminary data support that immune cell metabolic capacity is decreased during recovery from physiologically demanding bouts of intensive exercise, resulting in transient immune dysfunction.[31,33] Immunonutrition support, especially increased intake of carbohydrate and polyphenols, has been shown to counter these exercise-induced decrements in immune cell metabolic capacity.[31,33]

2.3. Illness risk and high exercise workloads

The potential linkage between prolonged, intensive exercise and increased risk for illness has been an active area of research since the 1980s.[3,65–69] Early epidemiologic studies indicated that athletes engaging in marathon and ultramarathon race events and/or very heavy training were at increased risk of URTI.[17,67] (Table 1). For example, in a large group of 2311 endurance runners, nearly 13.0% reported illness during the week after the Los Angeles Marathon race compared with 2.2% of control runners (odds ratio (OR) = 5.9; 95% confidence interval (CI): 1.9–18.8).[17] Forty percent of the runners reported at least 1 illness episode during the 2-month winter period before the marathon race, and those running more than 96 km/week *vs.* less than 32 km/week doubled their odds for illness. A 1-year retrospective study of 852 German athletes showed that URTI risk was highest in endurance athletes who also reported significant stress and sleep deprivation.[70] These seminal studies indicated that illness risk may be increased when an athlete participates in competitive events, goes through repeated cycles of unusually heavy exertion, or experiences other stressors to the immune system including lack of sleep and mental stress. The direct connection between exercise-induced immune changes and infection risk has not yet been established, and will require long-term studies with large cohorts. More research is needed to more clearly demonstrate the linkage between heavy exertion, illness symptoms, and pathogen-based illnesses, and the relative importance of associated factors such as travel, pathogen exposure, exercise-induced immune perturbations, sleep disruption, mental stress, and nutrition support.[3,4]

As illness data from additional studies mounted,[71–77] several athletic organizations including the International Olympic Committee (IOC) and the International Association of Athletics Federation (IAAF) initiated acute illness surveillance systems to delineate the extent of the problem and underlying risk factors.[65,78–89] The stated goal was to improve illness prevention and treatment procedures.[65,80] The IOC has also focused on the inappropriate management of both internal (e.g., psychological responses) and external loads (e.g., training and competition workloads). Load management is a key strategy, according to the IOC, to decrease illness incidence and associated downturns in exercise performance, interruptions in training, missed competitive events, and risk of serious medical complications. The wealth of acute illness epidemiologic data collected during international competition events has revealed that 2%–18% of elite athletes experience illness episodes, with higher proportions for females and those engaging in endurance events (Table 1).[78–89] At least one-half of the acute illness bouts involve the respiratory tract, with other affected systems including the digestive tract, skin tissues, and the genitourinary tract.[65] Significant illness risk factors include female gender, high levels of depression or anxiety, engaging in unusually intensive training periods with large fluctuations, international travel across several time zones, participation in competitive events especially during the winter, lack of sleep, and low diet energy intake.[65,68–92] The decrease in exercise performance after an URTI can last 2–4 days, and runners who unwisely start an endurance race with systemic URTI symptoms are 2–3 times less likely to complete the race.[65,92,93] Paralympic athletes have unique preexisting medical conditions that predispose them to an increased risk of illness, and the incidence rate of illness is high in the Summer (10.0–13.2 episodes per 1000 athlete-days) and Winter (18.7 episodes per 1000 athlete-days) Paralympic Games.[94]

Athletes must train hard for competition and are interested in strategies to keep their immune systems robust and illness rates low despite the physiologic stress experienced. The ultimate objective is to achieve performance goals with little interruption from illness and fatigue from training-induced subclinical immune dysfunction. Several training, hygienic, nutritional, and psychological strategies are recommended, and these require the coordinated involvement of the medical staff, coaches, and athletes.[4,6,65,95] The medical staff should develop and implement an illness prevention program, with a focus on full preventative precautions for high-risk individuals such as female endurance athletes. Adjustments to

Table 1.
Research on the relationship between vigorous exercise and illness.

Investigator	Study population	Research design	Key finding
Peters and Bateman[67]	141 ultramarathon runners and 124 controls (aged 18−65 years)	Participants reported 2-week recall of illness symptoms after 56-km race	Illness incidence 2× higher in runners after race *vs.* controls (33% *vs.* 15%).
Nieman et al.[21]	1828 marathon runners and 134 runner controls (aged 36.9 ± 0.2 years)	Participants reported illness symptoms 2 months before and 1 week after March 42.2-km race	Illness incidence 6× higher in runners who finished race *vs.* controls (13% *vs.* 2%). Runners training ≥97 km/week *vs.* <32 km/week at higher URTl risk.
Heath et al.[69]	530 runners (aged 39.4 years)	Participants reported training log and illness symptoms every month for 1 year	Running >485 miles/year (780 km/year) increased risk of illness.
Konig et al.[70]	852 German athletes (aged 23.6 ± 9.5 years)	Participants retrospectively reported illness episodes over past 12 months	Illness incidence 2× higher in endurance sports (OR = 2.2); 2× higher with stress (OR = 2.0); and nearly 2× with sleep deprivation (OR = 1.7).
Spence et al.[71]	20 elite triathletes/cyclists, 30 recreational triathletes/cyclists, 20 sedentary controls (aged 18−34 years)	Participants followed for 5 months in summer/autumn; reported daily illness symptoms	Illness incidence 4× higher in elite athletes and 2× greater in controls *vs.* recreational athletes. Higher number of illness days in elite athletes (311 days) and control (137 days) and recreational (92 days).
Gleeson et al.[72]	75 endurance trained university students (aged 18−35 years)	Participants followed for 4 months in winter; reported weekly illness symptoms	Greater illness incidence in high and medium *vs.* low training groups (2.4 ± 2.6 episodes and 2.6 ± 2.2 episodes *vs.* 1.0 ± 1.7 episodes).
Rama et al.[73]	19 elite swimmers *vs.* 11 nonathlete controls (aged 17.6 ± 1.0 years)	Participants followed for 7 months in winter; reported daily illness symptoms	67% of illness episodes occurred during high volume training in swimmers *vs.* no illness in control at same time points.
Hellard et al.[74]	28 elite swimmers (aged 16−30 years)	Participants followed for 4 years; monitored weekly for illness	Illness increased 1.08× (95%CI: 1.01−1.16) every 10% increase in resistance training and 1.10× (95%CI: 1.01−1.19) for every 10% increase in high-load training.
Svendsen et al.[75]	42 elite cross-country skiers (aged 24 ± 4 years)	Participants followed for 8 years; reported illness symptoms daily for 10 days after the Tour de Ski race	Illness incidence was 3× higher in skiers who raced the Tour de Ski *vs.* non-competing skiers (48% *vs.* 16%).
Raysmith and Drew[77]	33 international track and field athletes	Participants reported illness symptoms during 6 months preceding competition for 5 years	Illness incidence was 23%; one-half of illnesses occurred 2 months before competition. Better performing athletes had a lower incidence of illness.
Drew et al.[78]	132 elite athletes preparing for the Olympics	3 months before competition, participants reported illness symptoms during a 1-month time period	Illness symptoms in 100% athletes (46% upper respiratory). Risk factors were female sex, low energy availability.
Prien et al.,[79] Timpka et al.[80]	1551 elite athletes preceding World Championship competition	Participants retrospectively reported illness symptoms during 4 weeks preceding competition	Illness incidence ranged from 5% to 13%.
Engebretsen et al.,[81,82] Palmer-Green and Elliott,[83] Soligard et al.[84,85]	27,245 elite athletes during an international Olympic competition	Medical staff reported illness symptoms during competition event (<4 weeks)	Illness incidence ranged from 5% to 18%; Risk factor was female sex.
Mountjoy et al.,[86,87] Prien et al.[79]	5293 elite aquatics athletes during the international World Championships	Medical staff reported illness symptoms during competition event (<4 weeks)	Illness incidence ranged from 7% to 13%.
Alonso et al.,[88,89] Timpka et al.[80]	3305 elite track and field athletes during the international World Championships	Medical staff reported illness symptoms during competition event (<4 weeks)	Illness incidence ranged from 2% to 7%; 10× greater illness incidence in endurance events *vs.* speed/power events.

Abbreviations: CI = confidence interval; OR = odds ratio; URTI = upper respiratory tract infections.

the guidelines can be applied based on how each individual athlete responds. Here is a summary of the most important guidelines provided from consensus statements:[4,6,65,95]

2.3.1. Training and competition load management

a. Develop a detailed, individualized training and competition plan that also provides for sufficient recovery using sleep, nutrition, hydration, and psychological strategies.
b. Use small increments when changing the training load (typically less than 10% weekly).
c. Develop a competition event calendar that is based on the health of the athlete.
d. Monitor for early signs and symptoms of over-reaching, overtraining, and illness.
e. Avoid intensive training when ill or experiencing the early signs and symptoms of illness (which can make the illness more severe and prolonged).
f. Participate in ongoing illness surveillance systems by sport agencies.

2.3.2. Hygienic, lifestyle, nutritional, and behavioral strategies

a. Minimize pathogen exposure by avoiding close contact with infected individuals in crowded, enclosed spaces, and not sharing drinking or eating implements. Avoid exercise sessions in poorly ventilated clubs and gymnasium facilities. The medical staff should isolate infected athletes.
b. Limit hand-to-face contact (i.e., self-inoculation) and wash hands regularly and effectively. The medical staff should educate the athletes to minimize pathogen spread to others (e.g., sneezing and coughing into the crook of the elbow).
c. Follow other hygienic practices to limit all types of infections including safe sex and the use of condoms, wearing open footwear when using public facilities to limit skin infections, using insect repellents, and covering the arms and legs with clothing at dawn or dusk.
d. Maintain vaccines needed for home and foreign travel, with a focus on annual influenza vaccination.
e. Follow strategies that facilitate regular, high-quality sleep.
f. Avoid excessive alcohol intake.
g. Consume a well-balanced diet with sufficient energy to maintain a healthy weight, with a focus on grains, fruits, and vegetables to provide sufficient carbohydrate and polyphenols that reduce exercise-induced inflammation and improve viral protection.

2.3.3. Psychological load management

a. Follow stress management techniques that decrease the extraneous load of life hassles and stresses.
b. Develop coping strategies that minimize the internalized impact of negative life events and emotions.
c. Periodically monitor psychological stresses using available instruments.

3. Clinical influences of immune responses to chronic exercise

Each bout of moderate physical activity promotes improved but transient immunosurveillance and, when repeated on a regular basis, confers multiple health benefits including decreased illness incidence and dampened systemic inflammation.[95]

3.1. J-curve relationship between exercise and URTIs

Table 2 summarizes published evidence from randomized clinical trials and epidemiologic studies on the inverse relationship between moderate exercise training and URTI incidence. The randomized clinical trials (8 weeks to 1 year in length) are consistent in demonstrating that study participants assigned to moderate exercise programs experience reduced URTI incidence and duration.[21,96–100] The magnitude of reduction in URTI symptom days with near-daily moderate exercise in these randomized clinical trials (typically 40%–50%) exceeds levels reported for most medications and supplements, and bolsters public health guidelines urging individuals to be physically active on a regular basis. The protective effect of moderate activity on illness incidence contrasts with the increased illness risk linked with prolonged and intensive exercise, as summarized in the J-curve model (Fig. 5).[95] The IOC consensus group provided support for the J-curve model, but cautioned that the right side of the model may not apply to elite athletes on the highest level, where high training loads are not consistently associated with an increased risk of illness.[65]

Retrospective and prospective epidemiologic studies have measured illness incidence in large groups of individuals engaging in self-selected and varied physical activity workloads (Table 2).[101–104] Collectively, the epidemiologic studies summarized in Table 2 consistently show reduced URTI rates (weighted mean, 28%) in high *vs.* low physical activity and fitness groups. Fig. 6 summarizes the results from a group of 1002 adults (aged 18–85 years; 60% female and 40% male) studied for 12 weeks (one-half during the winter, one-half during the fall), with monitoring of URTI symptoms and severity using the validated Wisconsin Upper Respiratory Symptom Survey.[103,105] The number of days with URTI was 43% lower in subjects engaging in an average of 5 or more days per week of aerobic exercise (20 min bouts or longer) compared with those who were largely sedentary ($\leq$1 day/week), and 46% lower when comparing subjects in the highest *vs.* lowest tertile for perceived physical fitness. This relationship persisted, even after adjustment for confounders such as age, education level, marital status, gender, body mass index (BMI), and perceived mental stress.

Physical activity may lower rates of infection for other types of viral and bacterial diseases, but more data are needed. Several epidemiologic studies suggest that regular physical activity is associated with decreased mortality and incidence rates for influenza and pneumonia.[106–109] These findings are in accordance with rodent-based studies demonstrating a positive link between chronic exercise and improved host responses to influenza and pneumonia infection.[110–113] These data must be

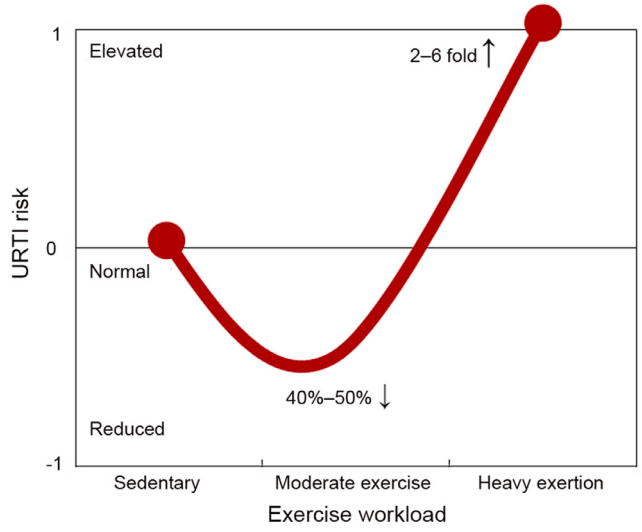

Fig. 5. J-curve model of the relationship between the exercise workload continuum and risk for upper respiratory tract infection (URTI). Other factors such as travel, pathogen exposure, sleep disruption, mental stress, and dietary patterns may influence this relationship. This figure was adapted from Nieman.[95]

carefully balanced with published reports of increased infectious disease severity when vigorous exercise was engaged in during active influenza or other viral infections.[114–116] There is also increasing support for improved antibody responses to influenza immunization in elderly adults who engage in regular exercise training regimens.[117–119]

3.2. Reduced systemic inflammation in physically active and lean individuals

Each exercise bout causes transient increases in total white blood cells, granulocyte-related proteins, and a variety of plasma cytokines including interleukin-6 (IL-6), IL-8, IL-10, IL-18, IL-1 receptor antagonist (IL-1ra), granulocyte colony stimulating factor, and monocyte chemoattractant protein 1.[30,40,52] The magnitude of change in these inflammation-related biomarkers depends on the overall exercise workload. Acute phase proteins including C-reactive protein (CRP) are also increased after heavy exertion, but increases are delayed in comparison with most cytokines.[30,52] Despite regular increases in these inflammation biomarkers during each intense exercise

Table 2.
Research on the relationship between moderate exercise and illness.

Investigator	Study population	Research design	Key finding
Randomized controlled trials			
Nieman et al.[96]	36 mildly obese sedentary women (aged 34.4 ± 1.1 years)	Randomized to 15 weeks of moderate intensity (45 min/day × 5 days/week) walking program or observational control	Fewer days with illness symptoms reported in walkers *vs.* controls (5.1 ± 1.2 days *vs.* 10.8 ± 2.3 days).
Nieman et al.[21]	32 sedentary women (aged 73.4 ± 1.2 years); 12 highly conditioned women (aged 72.5 ± 1.8 years)	Sedentary women randomized to a 12-week moderate intensity (30- to 40-min/day × 5 days/week) walking program or stretching (45 min/day × 5 days/week) in fall season	Illness incidence 8% in highly conditioned, 21% in walkers, and 50% in controls.
Nieman et al.[97]	91 obese women (aged 45.6 ± 1.1 years)	Randomized to a 12-week moderate intensity (45 min/day × 5 days/week) walking program or stretching 45 min/day × 4 days/week	Fewer days with illness symptoms reported in walkers *vs.* controls (5.6 ± 0.9 days *vs.* 9.4 ± 1.1 days).
Chubak et al.[98]	115 postmenopausal women (aged 60.7 ± 6.9 years)	Randomized to 1 year of moderate intensity exercise (45 min/day × 5 days/week) or stretching control (45 min/day × 1 day/week)	Illness incidence 30% in exercise *vs.* 48% in controls. Three-fold decreased risk of illness in exercise group *vs.* control in final 3 months.
Barrett et al.[99,100]	373 male and female older adults (aged 59.3 ± 6.6 years (2012); 49.9 ± 11.8 years (2018))	Randomized to 8 week moderate-intensity sustained exercise (group sessions; home practice) or observational control	Pooled datasets: proportional reductions of incidence, days-of-illness, and global severity were 14%, 23%, and 31% for exercise compared with controls.
Epidemiologic studies			
Mathews et al.[101]	547 male and female adults (aged 48.0 ± 12.4 years)	Participants followed for 1 year; interviewed for physical activity and illness symptoms every 90 days	29% decreased illness risk in upper *vs.* lower quartile of activity.
Fondell et al.[102]	1509 male and female adults (aged 20–60 years)	Participants followed for 4 months; baseline questionnaire on physical activity; illness symptoms assessed every 3 weeks	18% decreased illness risk in high *vs.* low physical activity.
Nieman et al.[103]	1002 male and female adults (aged 18–85 years)	Participants followed for 12 weeks in winter and autumn seasons; baseline questionnaire on physical fitness levels; daily illness symptoms checklist	46% decrease in total day with illness in high *vs.* low physical fitness tertile. 43% decrease in those who reported ≥5 days/week aerobic activity *vs.* <1 day/week.
Zhou et al.[104]	1413 male and female adults (aged 38.9 ± 9.0 years)	Participants retrospectively reported frequency of illness and physical activity over the past year	26% decreased illness risk in high *vs.* low physical activity.

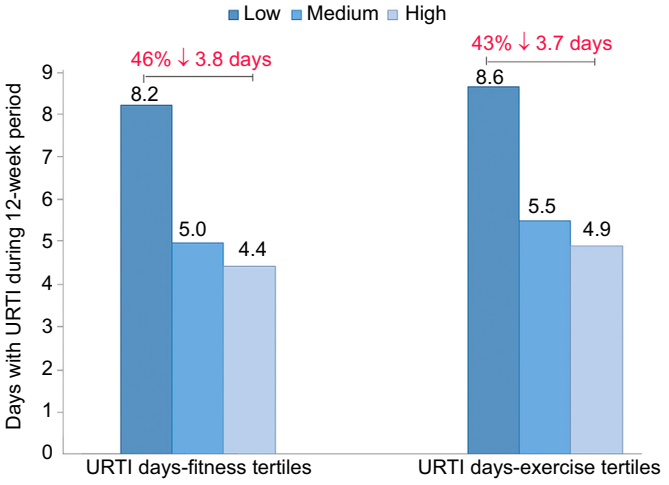

Fig. 6. The upper tertiles of fitness and exercise frequency are associated with reduced numbers of days with upper respiratory tract infections (URTI). Data from Nieman et al.[103]

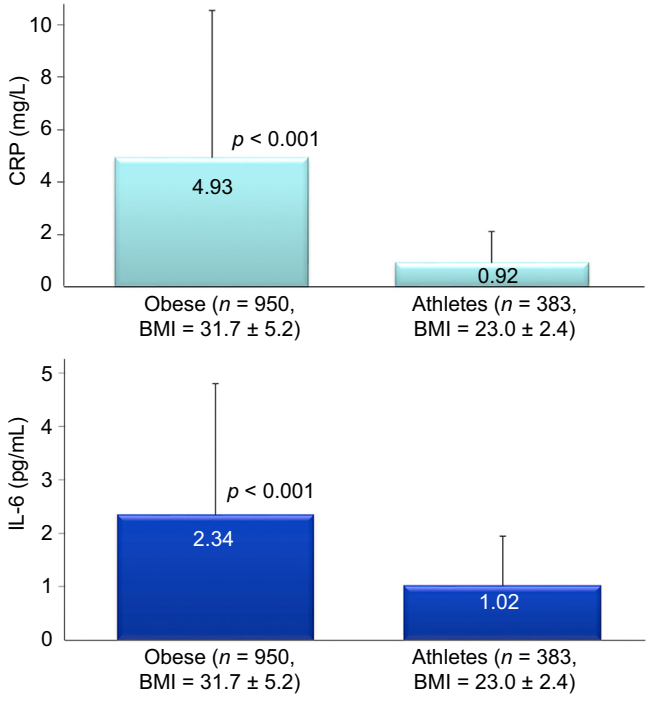

Fig. 7. C-reactive protein (CRP) and interleukin-6 (IL-6) values for obese and athletic groups (data expressed as mean ± SD). Data are from ongoing studies in the first author's lab during the past 2 decades. BMI = body mass index.

bout, physically fit individuals have lower resting levels in contrast with those who are overweight and unfit. Fig. 7 compares serum CRP (4.4-fold difference) and plasma IL-6 (1.3-fold) in large groups of obese individuals ($n = 950$; mean BMI = 31.7 kg/m^2) and endurance athletes ($n = 383$; mean BMI = 23.0 kg/m^2) studied over the course of the past 2 decades in the author's laboratory. There is increasing evidence that regular exercise training has an overall anti-inflammatory influence mediated through multiple pathways including improved control of inflammatory signaling pathways, release of muscle myokines that stimulate production of IL-1ra and IL-10 (perhaps by blood mononuclear immune cells), a decrease in dysfunctional adipose tissue and improved oxygenation, enhanced innate immune function, and an improved balance of oxylipins.[7,33,50,55,120]

The persistent increase in inflammation biomarkers is defined as chronic or systemic inflammation, and is linked with multiple disorders and diseases including obesity, arthritis, atherosclerosis and cardiovascular disease, chronic kidney disease, liver disease, metabolic syndrome, insulin resistance and type 2 diabetes mellitus, sarcopenia, arthritis, bone resorption and osteoporosis, chronic obstructive pulmonary disease, dementia, depression, and various types of cancers.[121–127] Obesity induces a constant state of low-grade inflammation characterized by activation and infiltration of proinflammatory immune cells such as macrophages and granulocytes, and a dysregulated production of acute-phase proteins, reactive oxygen species, metalloproteinases, oxylipins, adipokines, and proinflammatory cytokines.[124,128] Many of the inflammation biomarkers increased transiently after intense and prolonged exercise bouts are chronically expressed at lower levels in obese individuals (resting state).

Epidemiologic studies consistently show reduced white blood cell count, CRP, IL-6, IL-18, tumor necrosis factor alpha, and other inflammatory biomarkers in adults with higher levels of physical activity and fitness, even after adjustment for potential confounders such as BMI.[129–131] For example, in a study of 1002 community-dwelling adults (aged 18–85 years), a general linear model analysis showed that BMI had the strongest effect on CRP followed by gender (greater in females), exercise frequency, age, and smoking status.[129] Another study of 1293 middle-aged Danes showed that cardiorespiratory fitness was inversely associated with CRP, IL-6, and IL-18, and was only partly explained by lower levels of abdominal obesity.[130]

Most randomized, controlled trials, however, have failed to demonstrate that inflammation is decreased by a clinically significant level with exercise training in the absence of weight loss.[132–136] There are several potential explanations for these null findings when compared with epidemiologic studies, including the small reported changes in aerobic fitness and activity levels, the short duration of the intervention trials, and issues with compliance. In general, moderate exercise training is unlikely to lower chronic inflammation at the individual level unless the exercise workload is increased to more than 300 min per week and significant weight loss is experienced.

3.3. *Exercise–immune linkages to reduced chronic disease*

Do exercise-induced perturbations in immunity help to explain altered risks of cancer, heart disease, type 2 diabetes, arthritis, nonalcoholic fatty liver disease, and other chronic conditions? Research in this area is still emergent, but there is increasing evidence that the circulation surge in cells of the innate immune system with each exercise bout and the anti-inflammatory and antioxidant effect of exercise training have a summation effect over time in modulating tumorigenesis, atherosclerosis, and other disease processes.[36,137–139]

Obesity, the metabolic syndrome, and most common chronic diseases such as atherosclerosis, specific types of cancer, and type 2 diabetes are characterized in part by high inflammation, oxidative stress, and immune dysfunction.[137] Exercise training counters these elements of the disease process, stimulating many cellular and molecular changes throughout body tissues that promote anti-inflammatory and antioxidant responses, and augment immunosurveillance. For example, IL-1β is a proinflammatory cytokine that is involved in disease pathogenesis, and the release of IL-6 from the exercising muscle induces high levels of plasma IL-1ra during recovery that competitively inhibits IL-1β signaling.[137] Exercise training also downregulates Toll-like receptor 4 expression, a key transmembrane receptor that is activated by numerous ligands including oxidized low-density lipoproteins and involved in obesity-induced insulin resistance and type 2 diabetes, and atherosclerosis.[137]

Inflammation involves several types of immune cells, including macrophages and neutrophils, and is an important mediator of oxidative stress. Reactive oxygen species (ROS) or reactive nitrogen species (RNS), are double-edged molecules. ROS/RNS can function as important inflammatory effectors in supporting immune system clearance of pathogens and repair of damaged muscle tissue, or they can amplify chronic inflammation (e.g., during obesity) and induce tissue damage. Oxinflammation is a term used to describe the complex interactions between oxidative stress and inflammation.[138] Exercise training decreases oxidative stress by augmenting antioxidant defenses consisting of enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, and nonenzymatic antioxidants including glutathione.[137,138]

Exercise training has immunomodulating effects that may alter the cross-talk between the immune system and tumorigenesis. For example, exercise may increase intra-tumoral cytotoxic T-cell infiltration and reduce regulatory T-cell infiltration, enhance the recirculation and function of tumor-specific NK cells, and decrease inflammatory influences that support cancer cell growth.[139]

In general, exercise promotes the recirculation of key immune cells and mediates an anti-inflammatory and antioxidant state through multiple mechanisms. Although many information gaps exist, these exercise-induced effects may help to counter the development of chronic metabolic diseases and are likely multiplied when body fat mass is reduced.

3.4. Exercise, gut immune function, and the microbiome

The gastrointestinal tract is colonized by trillions of microorganisms that include a gene set 150 times larger than that of the human genome.[140] The most abundant bacterial phyla are the Firmicutes (~60%) and Bacteriodetes (~20%), with low proportions of Actinobacteria, Proteobacteria, and Verrucomicrobia. One-third of the adult gut microbiota is similar between most individuals, but diversity is associated with a healthier status. The gut bacteria composition and diversity is influenced by a variety of factors, including dietary and exercise habits, age, gender, genetics, ethnicity, antibiotics, health, and disease.

The gut microbiota influences human health and immune function, in part through the fermentation of indigestible food components in the large intestine. The microbiome and derived metabolites including short chain fatty acids and biotransformed bile acids have been shown to influence immune function both within the gut and systematically.[141] Although research in this area is emerging, recent studies indicate that exercise and physical fitness diversifies the gut microbiota, enhancing the number of benign microbial communities.[142,143] The underlying mechanisms are still being explored, with no clear consensus, in part owing to confounding from diet, exercise workload and intensity, and body composition. More human research is needed to establish whether the positive linkage between long-term exercise training and a diverse microbiome translates to improved immune function in physically fit individuals and athletes.[144,145]

4. Nutritional interactions on exercise-induced immune changes

Several comprehensive reviews have been published on the value of nutritional support as countermeasures to exercise-induced immune dysfunction, inflammation, and oxidative stress.[4,6,7,33] The most effective nutritional strategies for athletes, especially when evaluated from a multiomics perspective, include increased intake of carbohydrates and polyphenols.

4.1. Carbohydrates attenuate postexercise inflammation

During the 1990s, several studies reported that carbohydrate ingestion (30−60 g/h) during prolonged endurance exercise (90 min and longer) was linked with lower postexercise plasma stress hormone levels and inflammation.[20,146−150] These results have been confirmed by many subsequent studies (Table 3).[31,151−165] A consistent finding is that carbohydrate intake during prolonged and intense exercise, whether from 6%−8% beverages or sugar-dense fruits such as bananas (with water), is associated with higher plasma glucose and insulin levels; lower plasma stress hormones (epinephrine and cortisol), adrenocorticotropic hormone, and growth hormone; diminished fatty acid mobilization and oxidation; and reduced inflammation as measured by a variety of biomarkers including skeletal muscle IL-6 and IL-8 messenger ribonucleic acid (mRNA), blood neutrophil and monocyte cell counts, cytokines such as IL-6, IL-1ra, and IL-10, and granulocyte phagocytosis (Table 3 and Fig. 8). The effect of carbohydrate ingestion in attenuating postexercise inflammation is strong (about 30%−40%), especially when contrasted with water-only intake in overnight fasted athletes.[7,27,31−33,164,166]

4.2. Polyphenols counter exercise-induced immune changes

Fruits contain a mixture of sugars and a wide variety of biologically active polyphenols. Polyphenols, in particular flavonoids, have attracted much attention owing to their bioactivity and related health benefits, and new evidence using metabolomics supports their value as potential countermeasures to exercise-induced immune changes.[6,7,31,33]

Table 3.
Research showing the effect of carbohydrates on inflammation and immune biomarkers after >90 min of endurance exercise.

Investigator	Study population	Exercise protocol	Carbohydrate intervention	Postexercise immune response
Nieman et al.,[146] Nehlsen-Cannarella et al.,[20] Henson et al.[147]	30 male and female marathon runners (aged 41.5 ± 2.0 years) randomized to CHO or placebo	2.5-h run at 75%−80%VO_{2max}	6% CHO or placebo beverage consumed before, during, and after exercise	CHO ↑ glucose; ↓ cortisol; ↓ total leukocytes, neutrophils, monocytes, and lymphocytes; ↓ IL-6, IL-1ra *vs.* placebo group. Placebo ↑ T cells and NK cells immediately after running; ↓ 3-h recovery *vs.* the CHO group.
Nieman et al.,[148] Nieman et al.,[149] Henson et al.[150]	10 male and female triathletes (aged 34.0 ± 2.1 years) in cross-over design	2.5-h cycle and run at 75%VO_{2max}	6% CHO or placebo beverage consumed before, during, and after exercise	CHO ↑ glucose, insulin; ↓ cortisol, growth hormone; ↓ neutrophils, monocytes, lymphocytes; ↓ granulocyte, monocyte phagocytosis and oxidative burst activity; ↓ neutrophil/lymphocyte ratio; ↓ NK cell cytotoxicity; ↓ IL-6, IL-1ra *vs.* placebo trial.
Henson et al.[151]	15 Olympic female rowers (aged 22.4 ± 0.5 years) in a cross-over design	2-h rowing session	6% CHO or placebo beverage consumed before, during, and after exercise	CHO ↑ glucose; ↓ total leukocytes, neutrophils, and monocytes; ↓ phagocytosis; ↓ IL-1ra *vs.* placebo trial.
Nieman et al.[152]	16 marathon runners (aged 50.1 ± 1.5 years) in a cross-over design	3-h run at 70%VO_{2max}	6% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose, insulin; ↓ cortisol; ↓ total leukocytes, monocytes, lymphocytes, and granulocytes; ↓ plasma IL-6, IL-10, IL-1ra; ↓ skeletal muscle IL-6, IL-8 mRNA *vs.* placebo trial.
Bishop et al.[153]	9 trained male cyclists (aged 25.0 ± 2.0 years) in a cross-over design	2-h cycle at 75%VO_{2max}	6.4% CHO or placebo beverage consumed before, during, and after exercise	CHO ↑ glucose; ↓ cortisol; ↓ neutrophils *vs.* placebo trial.
Keller et al.[154]	8 untrained men (aged 24.0 ± 1.0 years) in a cross-over design	3-h cycle at 60% maximal workload	6% CHO or placebo beverage consumed during exercise	CHO ↑ glucose; ↓ free fatty acids; ↓ plasma IL-6, ↓ adipose tissue IL-6 mRNA *vs.* placebo trial.
Febbraio et al.[155]	7 men (aged 22.1 ± 3.8 years) in cross-over design	2-h cycle at 65%VO_{2max}	6.4% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose; ↓ free fatty acids; ↓ IL-6 *vs.* placebo trial.
Henson et al.[156]	48 male and female marathon runners (aged 42.5 ± 2.4 years) randomized to CHO or placebo	42-km marathon	6% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose, insulin; ↓ cortisol; ↓ total leukocytes, neutrophils, and monocytes *vs.* placebo group.
Davison and Gleeson[157]	6 moderately trained men (aged 25.0 ± 2.0 years) in a cross-over design	2.5-h cycle at 60%VO_{2max}	6% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose; ↓ cortisol; ↓ ACTH; ↓ total leukocytes, neutrophils; ↑ bacterial-stimulated neutrophil degranulation *vs.* placebo trial.
Lancaster et al.[158]	7 moderately trained men (aged 25.0 ± 1.0 years) in a cross-over design	2.5-h cycle at 65%VO_{2max}	6.4%, 12.8% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose; ↓ cortisol; ↓ growth hormone; ↓ total leukocytes, neutrophils, monocytes; ↓ $CD4^+$ T cell IFN-γ and $CD8^+$ T cell IFN-γ lymphocytes. No significant difference between CHO concentrations.
Li and Gleeson[159]	9 men (aged 28.7 ± 1.6 years) in a cross-over design	90-min cycle at 60%VO_{2max}	10% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose; ↓ cortisol, epinephrine, ACTH, growth hormone; ↓ total leukocytes, monocytes, lymphocytes; ↓ IL-6 *vs.* placebo trial.
Nieman et al.[160]	15 trained male cyclists (aged 29.2 ± 6.0 years) in a cross-over design	2.5-h cycle at 75%VO_{2max}	6% CHO or placebo beverage consumed before, during, and after exercise	CHO ↑ glucose, insulin; ↓ cortisol, epinephrine; ↓ total leukocytes, neutrophils; ↓ IL-6, IL-10, IL-1ra *vs.* placebo trial.
Nieman et al.[161]	12 trained male cyclists (aged 21.0 ± 1.0 years) in a cross-over design	2-h cycle at 75%VO_{2max}	6% CHO or placebo beverage consumed before and during exercise	CHO ↑ glucose, insulin; ↓ cortisol; ↓ total leukocytes, neutrophils, and monocytes *vs.* placebo trial.
Scharhag et al.[162]	14 trained male cyclists/triathletes (aged 25.0 ± 5.0 years) in a cross-over design	4-h cycle at 70% anaerobic threshold	6%, 12% CHO, or placebo beverage consumed before and during exercise	6% and 12% CHO ↑ glucose; ↓ cortisol; ↓ total leukocytes, neutrophils, and monocytes *vs.* placebo trial. 12% CHO ↓ CRP and NK cells *vs.* placebo trial.
Nieman et al.[163]	14 trained male cyclists (aged 37.0 ± 7.1 years) in a cross-over design	75-km time trial	6% CHO beverage or matched CHO banana	No difference in immune and inflammation measures (e.g., IL-6, granulocyte and monocyte phagocytosis)

(*continued on next page*)

Table 3. (Continued)

Investigator	Study population	Exercise protocol	Carbohydrate intervention	Postexercise immune response
			consumed before and during exercise	between banana and CHO beverage; higher FRAP and plasma dopamine with banana.
Nieman et al.[164]	20 trained male cyclists (aged 39.2 ± 1.9 years) in a cross-over design	75-km time trial	Banana, pear, or water consumed before and during exercise	Banana and pear ↑ glucose, RER; ↓ cortisol, IL-10; ↓ neutrophil/ lymphocyte ratio; ↑ antioxidant capacity (sulfated phenolics, FRAP), ↓ fatty acid mobilization and oxidation metabolites *vs.* water trial. ↑ in fruit-specific metabolites.
Shanely et al.[165]	20 trained male cyclists (aged 48.5 ± 2.3 years) in a cross-over design	75-km time trial	6% CHO beverage or matched CHO watermelon consumed before and during exercise	No difference in inflammation measures (e.g., cytokines and immune cell counts) between watermelon and CHO beverage; watermelon ↑ antioxidant capacity (FRAP, ORAC); ↑ citrulline, arginine, nitrate *vs.* CHO beverage.
Nieman et al.[31]	20 trained male and female cyclists (aged 39.1 ± 2.4 years) in a cross-over design	75-km time trial	6% CHO beverage, 2 types of banana, or water consumed before and during exercise	Bananas and CHO beverage ↑ glucose, fructose; ↓ cortisol; ↓ IL-6, IL-10, IL-1ra; ↓ total leukocytes; ↓ 9+13 HODES; ↓ fatty acid mobilization and oxidation metabolites *vs.* water trial. Both banana trials ↓ COX2 mRNA expression; ↑ amino acid and xenobiotics metabolites.

Abbreviations: ACTH = adrenocorticotropic hormone; CHO = carbohydrate; COX2 = cyclo-oxygenase 2; CRP = C-reactive protein; FRAP = ferric reducing ability of plasma; HODES = hydroxyoctadecadienoic acid; IFN-γ = interferon gamma; IL-1ra = interleukin-1 receptor antagonist; mRNA = messenger ribonucleic acid; NK = natural killer; ORAC = oxygen radical absorbance capacity; RER = respiratory exchange ratio; VO_{2max} = maximal oxygen uptake.

Fig. 8. Carbohydrate ingestion before and during exercise attenuates postexercise inflammation.

Many of the earlier studies reported few discernable immune-related influences of increased polyphenol intake for athletes, but research design deficiencies portrayed a misunderstanding of polyphenol bioavailability and metabolism, and the appropriate outcome measures. Polyphenol absorption, disposition, metabolism, and excretion is complex and requires both untargeted and targeted metabolomics procedures to measure small molecule shifts in humans after increased intake.[167] A high proportion of ingested polyphenols from fruits, vegetables, and other plant foods pass through the small intestine unabsorbed and reach the colon, where bacterial degradation produces smaller phenolics that can reabsorbed into the circulation after undergoing phase 2 conjugation in the liver.[33] The biotransformed, gut-derived phenolics circulate throughout the body, exerting a variety of bioactive effects that are important to athletes including anti-inflammatory, antiviral, antioxidative, and immune cell signaling effects.[167–172]

Several studies using metabolomics and *ex vivo* cell cultures comparing ingestion of bananas with intake of water only or a 6% sugar beverage during prolonged and intensive cycling have shown large-fold increases in at least 18 banana-related metabolites.[31,163,164] Banana flesh contains many unique molecules including serotonin, dopamine, phenolics, and xenobiotics. Soon after ingestion, plasma levels of metabolites derived from banana flesh molecules increase, and may confer anti-inflammatory effects by countering cyclooxygenase-2 (COX-2) mRNA expression the morning after heavy exertion.[31]

In general, evolving data support the intake of fruits such as dates, raisins, and bananas by athletes during training to provide the sugars and polyphenols that exert anti-inflammatory influences that may enhance metabolic recovery. Future studies using system-wide approaches such as metabolomics, lipidomics, and proteomics will improve scientific understanding regarding the complex and multilevel interactions between exercise, nutrition, and the immune and metabolic systems.

5. Exercise influences immunosenescence

Immunosenescence is defined as immune dysregulation with aging and is related to an increased susceptibility to infections, autoimmune diseases, neoplasias, metabolic diseases, osteoporosis, and neurologic disorders. Recent evidence supports that immunity can be remodeled during the aging process as a result of interactions with the environment and lifestyle and is instrumental in shaping immune status in later life.[173–175] Immune system interactions with pathogens, the host microbiome, nutritional and exercise influences, mental stress, and many other extrinsic factors are considered as crucial modulators of the immunosenescence process.

Early cross-sectional studies compared immune function in highly conditioned and sedentary elderly men and women.[31,176] One study contrasted immune function in 30 sedentary elderly women and 12 age-matched, highly conditioned elderly women who were active in state and national senior game and road race endurance events.[31] The highly conditioned elderly women had significantly higher levels of NK cells and T-lymphocyte function and reduced illness rates compared with the 30 sedentary elderly women. Another study compared immune function in 17 elderly runners who had trained for about 17 years and 19 elderly controls, and reported significantly higher T lymphocyte function in the elderly runners.[176]

These studies stimulated many additional studies on the effects of exercise training on immunosenescence. Data support that habitual exercise is capable of regulating the immune system and delaying the onset of immunosenescence, and has been associated with the following:[31,175,177–179]

- Enhanced vaccination responses,
- Lower numbers of exhausted/senescent T cells,
- Increased T-cell proliferative capacity,
- Lower circulatory levels of inflammatory cytokines (i.e., decreased “inflamm-aging”),
- Increased neutrophil phagocytic activity,
- Lowered inflammatory response to bacterial challenge,
- Greater NK cell cytotoxic activity, and
- Longer leukocyte telomere lengths.

6. Conclusion

This review summarized research discoveries within 4 areas of exercise immunology: acute and chronic effects of exercise on the immune system, clinical benefits of the exercise–immune relationship, nutritional influences on the immune response to exercise, and the exercise effect on immunosenescence. The immune system is very responsive to exercise, with the extent and duration reflecting the degree of physiological stress imposed by the workload. Key exercise immunology discoveries since 1980 include the following.

- Acute exercise (moderate-to-vigorous intensity, less than 60 min) is now viewed as an important immune system adjuvant to stimulate the ongoing exchange of distinct and highly active immune cell subtypes between the circulation and tissues. In particular, each exercise bout improves the antipathogen activity of tissue macrophages in parallel with an enhanced recirculation of immunoglobulins, anti-inflammatory cytokines, neutrophils, NK cells, cytotoxic T cells, and immature B cells. With near daily exercise, these acute changes operate through a summation effect to enhance immune defense activity and metabolic health.
- In contrast, high exercise training workloads, competition events, and the associated physiological, metabolic, and psychological stress are linked with transient immune perturbations, inflammation, oxidative stress, muscle damage, and increased illness risk. Metabolomics, proteomics, and lipidomics have revealed that metabolism and immunity are inextricably interwoven, providing new insights on how intense and prolonged exercise can cause transient immune dysfunction by decreasing immune cell metabolic capacity.
- Illness risk may be increased when an athlete competes, goes through repeated cycles of unusually heavy exertion, and experiences other stressors to the immune system. The wealth of acute illness epidemiologic data collected during international competition events has revealed that 2%–18% of elite athletes experience illness episodes, with higher proportions for females and those engaging in endurance events. Other illness risk factors include high levels of depression or anxiety, participation in unusually intensive training periods with large fluctuations, international travel across several time zones, participation in competitive events especially during the winter, lack of sleep, and low diet energy intake.
- The IOC has also focused on load management of both internal (e.g., psychological responses) and external factors (e.g., training and competition workloads), and lifestyle strategies (e.g., hygiene, nutritional support, vaccination, regular sleep) to reduce illness incidence and associated downturns in exercise performance, interruptions in training, missed competitive events, and risk of serious medical complications.
- Randomized clinical trials and epidemiologic studies consistently support the inverse relationship between moderate exercise training and incidence of URTI. These data led to the development of the J-curve model that links URTI risk with the exercise workload continuum. Several epidemiologic studies also suggest that regular physical activity is associated with decreased mortality and incidence rates for influenza and pneumonia.
- Regular exercise training has an overall anti-inflammatory influence mediated through multiple pathways. Epidemiologic studies consistently show decreased levels of inflammatory biomarkers in adults with higher levels of physical activity and fitness, even after adjustment for potential confounders such as BMI.
- There is increasing evidence that the circulation surge in cells of the innate immune system with each exercise bout and the anti-inflammatory and antioxidant effect of exercise training have a summation effect over time in modulating tumorigenesis, atherosclerosis, and other disease processes.

- Recent studies indicate that exercise and physical fitness diversifies the gut microbiota, but more human research is needed to determine potential linkages to immune function in physically fit individuals and athletes.
- The most effective nutritional strategies for athletes, especially when evaluated from a multiomics perspective, include increased intake of carbohydrates and polyphenols. A consistent finding is that carbohydrate intake during prolonged and intense exercise, whether from 6%−8% beverages or sugar-dense fruits such as bananas is associated with reduced stress hormones, diminished blood levels of neutrophils and monocytes, and dampened inflammation. Gut-derived phenolics circulate throughout the body after increased polyphenol intake, exerting a variety of bioactive effects that are important to athletes including anti-inflammatory, antiviral, antioxidative, and immune cell signaling effects.
- Immunosenescence is defined as immune dysregulation with aging. Emergent data support that habitual exercise is capable of improving regulation of the immune system and delaying the onset of immunosenescence.

The future of exercise immunology will take advantage of advances in mass spectrometry and genetic testing technology, with increased utilization of metabolomics, proteomics, lipidomics, microbiome characterization, and genomics. Use of these system-wide approaches will provide new insights on the interactions between exercise, nutrition, and immune function, with application down to the personalized level. Additionally, these methodologies will improve mechanistic understanding of how exercise-induced immune changes reduce risk for common chronic diseases.

Authors' contributions

DCN and LMW conducted the literature review and wrote the manuscript. Both authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

Both authors declare that they have no competing interests.

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