ARTICLE

Exercise and Respiratory Tract Viral Infections

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MARTIN, S.A., B.D. PENCE, and J.A. WOODS. Exercise and respiratory tract viral infections. *Exerc. Sport Sci. Rev.*, Vol. 37, No. 4, pp. 157–164, 2009. *Prolonged intense exercise causes immunosuppression, whereas moderate-intensity exercise improves immune function and potentially reduces risk and severity of respiratory viral infections. Here, based on available evidence, we present a model whereby moderate exercise–induced increases in stress hormones reduce excessive local inflammation and skew the immune response away from a T_H1 and toward a T_H2 phenotype, thus improving outcomes after respiratory viral infections.* **Key Words:** physical activity, URTI, virus, influenza, inflammation

INTRODUCTION

Respiratory viral infections represent the most prevalent and pathogenic form of infectious disease, accounting for more than 7% of all deaths in both men and women in 2004 (17). Infection occurs when a host comes in contact with infected aerosolized droplets or contaminated surfaces, following which the virus invades and infects the host's upper and/or lower respiratory mucosal tissues. Illness duration typically lasts 7–14 d, and the usual symptoms include cough, nasal congestion, fever, body aches, malaise, and in severe cases, death. Deaths associated with respiratory viral infection occur most often in children, elderly, and other immune-compromised individuals because their immune systems are incapable of handling the elevated viral load.

Respiratory viruses encompass a broad spectrum of virulence, ranging from rhinovirus (*i.e.*, the *common cold*) to significantly more pathogenic viruses such as influenza (*i.e.*, the *flu*). Every year, a seasonal flu epidemic occurs, beginning in October and peaking in January. These yearly epidemics pose a significant health burden in the United States, ultimately being responsible for 200,000 hospitalizations and 36,000 deaths (9). In addition to the yearly epidemic, a pandemic influenza outbreak arises every 10–50 yr, culminating in the death of millions of people; a classic example is the *Spanish flu* pandemic of 1918, which killed an estimated 40 million individuals. Influenza vaccination is the primary method of disease prevention, but often, the vaccine is in short supply, and even when available, a large percentage of the population fails to receive vaccination. To further compound vaccination problems, research suggests that vaccination efficacy in preventing hospitalization is roughly 75% and plummets to 45% and 30% for individuals older than 65 and 75 yr, respectively (32). Understanding how behaviors such as physical activity or exercise affect viral infection outcomes is of public health importance.

Cross-sectional and longitudinal data suggest that persons who engage in regular moderate-intensity exercise maintain a reduced risk of self-reported respiratory symptoms (14,18,23,34). In addition, work from our laboratory and others demonstrates that moderate-intensity exercise performed before infection (6) or infectious symptoms (15) reduces respiratory virus–associated mortality in animals. In contrast, intense exercise before or during viral infection has been associated with greater morbidity and mortality (8,11,24). These findings have given rise to the *J-shaped* hypothesis (Fig. 1) relating exercise dose with infection risk (adapted from Nieman [22]). The primary purpose of this brief article is to summarize current literature regarding exercise and viral respiratory infections and provide a platform for further investigation into the mechanisms mediating the protective effect of exercise against respiratory viral infections. It includes human epidemiological studies, human experimental trials, and animal models, and highlights research from our laboratory providing insight into potential mechanisms through which regular exercise may be protective. Although there is evidence that exercise can beneficially affect bacterial infection outcomes, viral infections through other portals, and responses to vaccinations, we are limiting the scope of this article to specifically focus

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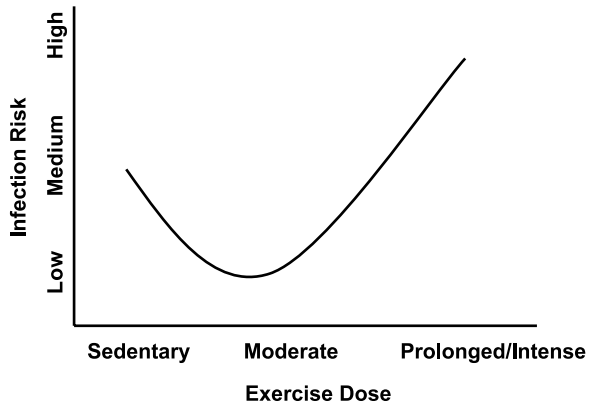

Figure 1. The J-shaped model depicting dose-dependent effect of exercise on risk and severity of respiratory tract infections (RTI). Sedentary persons are considered to be at normal risk of upper RTI (URTI). Exercise of low-to-moderate intensity or frequency is associated with reduced risk of URTI (3,18,23,25,34), whereas high-intensity exercise is associated with an increased risk of infection (8,11,24). [Adapted from Nieman DC, Johanssen LM, Lee JW. Infectious episodes in runners before and after a roadrace. *J. Sports Med. Phys. Fitness.* 1989; 29(3):289–96. Copyright © 1989 BMJ Publishing Group Ltd. Used with permission.]

on exercise and respiratory viral infections because there seems to be sufficient evidence to warrant conclusions.

IMMUNE DEFENSE AGAINST RESPIRATORY VIRAL INFECTIONS

Respiratory viruses such as influenza and rhinovirus are submicroscopic noncellular infectious agents that invade respiratory mucosal tissue and replicate inside the host's living cells. Unlike bacterial infections, viruses are metabolically insufficient, relying completely on the host's cellular metabolism for replication and viral protein synthesis. Because viruses use host machinery, they often evade host immune surveillance, allowing rapid replication and increased viral load. The complexity of viral escape mechanisms selectively pressured the immune system to develop a broad spectrum of antiviral responses that coordinate the recognition and clearance of viruses. Later, we will briefly highlight the major antiviral defenses.

Respiratory viruses bind glycoproteins on the surface of mucosal epithelial cells, inducing receptor-mediated endocytosis and ensuing infection of the host cell. In immunized individuals, salivary and mucosal immunoglobulins, primarily IgA, recognize and bind viral epitopes, blocking their entry into mucosal cells and reducing susceptibility to secondary infection. Virus invasion of the respiratory mucosa evokes an innate immune response through binding of pathogen-associated molecular patterns to toll-like receptor (TLR) molecules on lung macrophages (Mφ), myeloid dendritic cells (mDC), and plasmacytoid dendritic cells (pDC). Specifically, TLR 3, 7, and 9 recognize single- and double-stranded mRNA characteristic of the viral genome and initiate signal transduction, leading to nuclear factor-κ light-chain enhancer of activated B cell (NF-κB) transcriptional activity, which promotes the synthesis of Type I interferons (IFN) α/β. Secretion of IFN-α and IFN-β by alveolar pDC and Mφ induces host cell upregulation of two critical antiviral mechanisms: double-stranded RNA–activated inhibitor of translation (DAI) and Mx proteins. DAI phosphorylates and inhibits eukaryotic initiation factor 2, a protein required for initiation of viral mRNA translation, whereas Mx proteins prevent nucleocapsid assembly and inhibit viral polymerase activity. Together, these antiviral mediators prevent viral replication and further infection of host cells, transiently halting viral activity until the adaptive cellular immune response eliminates the virus.

In addition to inducing antiviral activity in host cells, activated innate immune cells also secrete numerous proinflammatory cytokines, including interleukin 1 (IL-1), IL-6, IL-12, and tumor necrosis factor-α (TNF-α), which induce a local and systemic inflammatory response characterized by increased production of acute-phase opsonizing complement proteins, enhanced extravasation of leukocytes to infected tissues, and increased antigen presentation and cytotoxic capacity. These same cytokines communicate with the brain and are responsible for sickness behaviors associated with infection (4).

Of particular importance is IL-12, which bridges the gap between innate and adaptive immunity by driving the differentiation of naive T helper cells (T_H0) toward a T_H1 phenotype characterized by the production of proinflammatory cytokines IL-2 and IFN-γ. T_H1-secreted IL-2 promotes the maturation of antigen-specific cytotoxic T lymphocytes ($CD8^+$ T cells), which recognize viral antigens on infected cells through the association of major histocompatibility complex I (MHC I) interactions with T-cell receptors (TCR). Activation of $CD8^+$ TCR induces cytotoxic killing of virally infected cells, $CD8^+$ cell proliferation, production of antiviral cytokines such as IFN-γ and activation-induced cell death. IFN-γ has multiple wide-ranging effects, including synthesis of antiviral proteins, upregulation of MHC I receptors, and stimulation of natural killer (NK) cells. NK cells induce apoptosis of infected cells, following which the dead cells are phagocytosed by macrophages, mDC, and pDCs, and the intracellular antigens cross presented to CD4+ and CD8+ cells.

A strong T_H1 response is necessary in the early stages of viral infection because it promotes rapid clearance of the virus. Prolonged T_H1 activity, however, may lead to respiratory tissue pathology through increased cell damage and necrosis (31). Immune counterregulatory mechanisms attempt to prevent T_H1-induced pathology by shifting the Th cell phenotype toward T_H2, characterized by the secretion of anti-inflammatory proteins IL-4 and IL-10. IL-10 acts to inhibit the effect of proinflammatory cytokines, whereas IL-4 stimulates naive B cells to enlarge in size and upregulate synthesis of MHC II molecules important for antigen presentation. Circulating naive B cells recognize viral proteins and glycoproteins on the surface of infected cells. Antigen activation of the B-cell receptor, along with coactivation by T_H2 cells, causes the B cell to differentiate into plasma and memory B cells. Plasma cells secrete large amounts of antiviral antibodies, particularly IgA, which bind viral epitopes to prevent viral entry into uninfected cells. Antibody binding of infected cells also induces NK cell antibody-dependent cell-mediated cytotoxicity (ADCC) and complement protein activation, both of which lead to

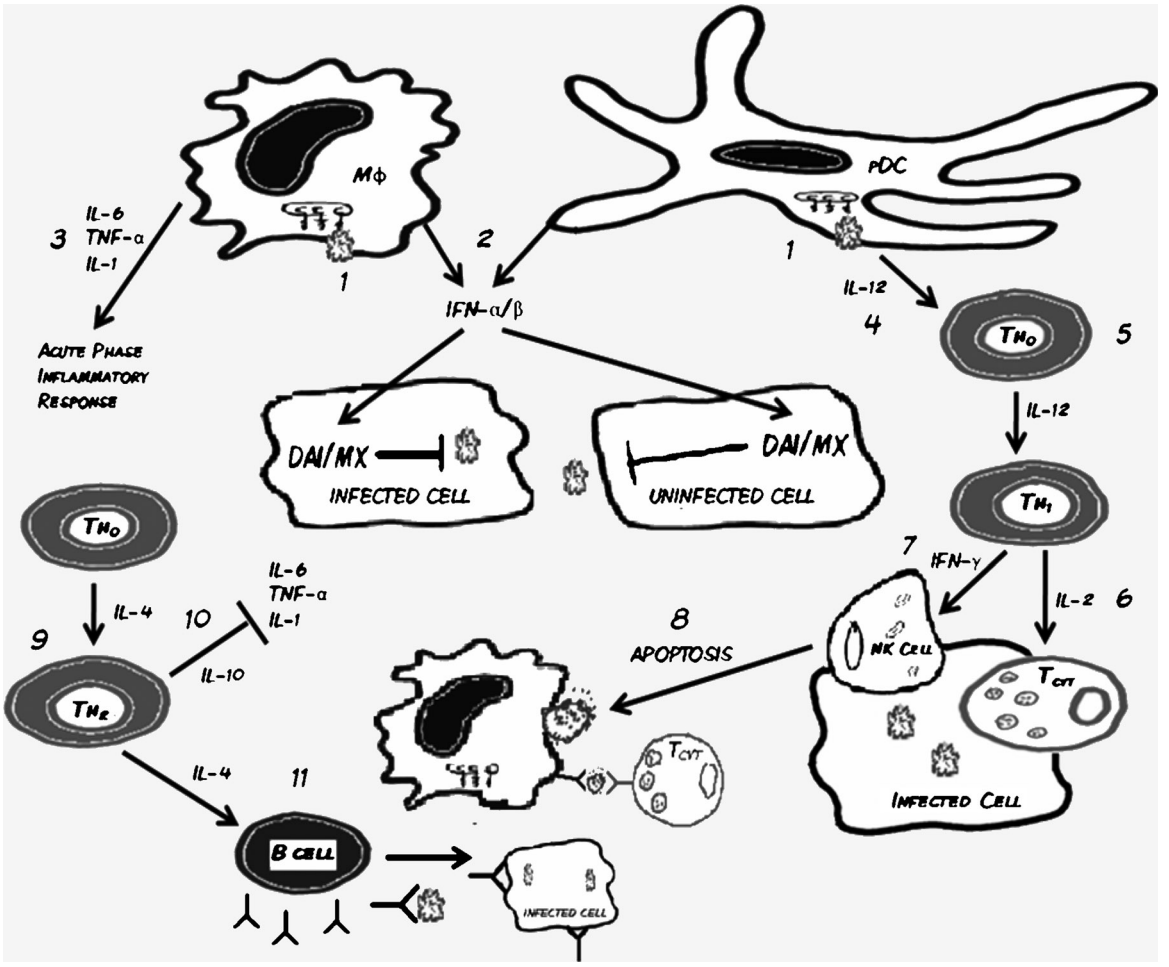

Figure 2. 1) Respiratory viruses invade respiratory mucosal epithelial cells and residential innate immune cells, where they activate Toll-like receptors and induce the innate immune response. 2) Activated macrophages (Mφ) and plasmacytoid dendritic cells (pDC) produce interferon-α/β (IFN-α/β), which prevents viral replication in host cells. 3) In addition, macrophages secrete proinflammatory cytokines (interleukin 6 [IL-6], tumor necrosis factor-α [TNF-α], and IL-1) that stimulate the acute-phase inflammatory response. 4) Secretion of IL-12 by pDC differentiates naive T_{helper} (T_H0) cells into T_H1 cells 5), which secrete IL-2 and IFN-γ. 6) IL-2 promotes maturation of $T_{cytotoxic}$ cells, which recognize antigen presented through major histocompatibility complex (MHC) 1 on infected cells, and promote apoptosis. 7) IFN-γ stimulates natural killer (NK) cells activity, also leading to increased apoptosis. 8) Apoptotic cells are phagocytized by Mφ, pDCs, and myeloid dendritic cells, and the intracellular antigen is cross presented to $T_{cytotoxic}$ cells. To counterregulate the inflammatory T_H1 response, naive T_H0 cells differentiate into 9) T_H2 cells that secrete anti-inflammatory cytokines IL-10 and IL-4. 10) IL-10 down-regulates the acute-phase response, whereas IL-4 promotes differentiation of B cells into plasma and memory B lymphocytes. 11) Plasma B cells secrete antibodies, particularly IgA, which block viral entry and opsonize infected cells for antibody-dependent cellular cytotoxicity. DAI indicates double-stranded RNA–activated inhibitor of translation.

infected cell apoptosis. In summary, innate immune mechanisms (*e.g.*, IFN) hold viral replication and spread in check until adaptive immune responses (primarily cytotoxic $CD8^+$ T cells) clear the infection; a process that takes place within 7–14 d. Primary infection leads to the development of adaptive immune responses characterized by specific antibodies that prevent subsequent viral attachment and memory T cells that respond with greater vigor upon secondary exposure. A summary of immune defense mechanisms against respiratory viruses is presented in Figure 2.

EXERCISE AND VIRAL INFECTION IN HUMANS

Observational Evidence

A large body of epidemiological literature has examined the effects of differing amounts and intensities of physical activity/exercise on a wide variety of respiratory symptoms. An early study published by Heath *et al.* (11) found runners in the upper two quartiles of yearly mileage (>866 miles run during the 12-month follow-up period) had a significantly higher risk of self-reported upper respiratory tract infection (URTI) symptoms compared with runners in the lowest quartile (<486 miles). A recent study found that low-to-moderate frequency of exercise reduced the risk of influenza-associated mortality in adults living in Hong Kong during 1998, whereas a high frequency of exercise (>4 d per wk) failed to reduce the risk of mortality when compared with the sedentary referent group (34). A retrospective study by Kostka *et al.* (14) found no relation between fitness level and self-reported weeks with URTI symptoms, although energy expenditure during leisure-time sports was significantly negatively correlated with total weeks of URTI symptoms as well as with number of episodes of URTI

during a 1-yr period. Matthews *et al.* (18) found a 29% decrease in incidence rate of URTI symptoms in adult men and women who engaged in moderate-to-vigorous physical activity of at least 11.96 METs·h·d^{-1} when compared with those individuals who were less physically active.

These studies support the hypothesis that moderate exercise is protective against URTI symptoms and that there may be a differential dose-response effect such that intense prolonged exercise or overtraining increases disease risk or symptom severity. Unfortunately, epidemiological and retrospective studies such as those previously mentioned rely on subject recall of symptoms and self-reporting of a variety of important variables including training status and exercise intensity. In addition, because of the large subject numbers in such epidemiological studies and the often heterogeneous subject populations, it is difficult to control for potential confounders such as nutritional status or other environmental factors. Because of these restrictions, in-depth investigation of the effects of exercise on URTI has necessitated the undertaking of human and animal experiments that restrict subject populations and conditions to allow for better control of these potential confounding factors.

A number of longitudinal studies have sought to determine the effects of specific intensities and durations of exercise training on the incidence of various URTI symptoms including rhinovirus and influenza. Several early studies examined the effects of intense bouts of exercise in competitive athletes on the risk for later development of URTI symptoms. A pair of studies from the laboratory of David Nieman examined the incidence of URTI in athletes who participated in a variety of running races. A comparison of runners competing in a 5-km, 10-km, or 21.1-km race (23) found athletes who ran more than 15 miles per wk had reduced incidence of respiratory symptoms when compared with athletes training at a lesser volume, and that runners training for the 21.1-km race had fewer infections than their shorter-distance counterparts in the 2 months before the race. In addition, there was no increased reporting rate of URTI symptoms in the 7 d after the races when compared with the 7 d before the races. A second study examined more than 2000 athletes competing in the Los Angeles Marathon (24). Runners who trained more than 97 km per wk had twice the risk of the development of URTI symptoms when compared with the referent group that trained less than 32 km per wk. Furthermore, runners who completed the marathon increased their risk for URTI nearly 6-fold during the week after the race when compared with similarly trained controls that registered but did not participate in the marathon. In a more recent study, Ekblom *et al.* (8) found that 19% of marathon finishers experienced URTI symptoms during a 3-wk period after race completion. However, when compared with the 16% of marathoners who experienced URTI symptoms in the 3-wk period before the race, the investigators concluded that a single strenuous bout of activity does not increase risk of respiratory infections. However, 33% of runners who experienced an infectious episode before the race had a recurrence of URTI symptoms after the race, suggesting that a strenuous bout of exercise potentially increases the risk of subsequent infection if the exercise is performed soon after an initial infection.

Nieman *et al.* (25) also examined the effect of 15 wk of moderate-intensity exercise training on symptoms of URTI. Exercising subjects demonstrated shorter infectious episodes compared with their sedentary controls as measured by the number of symptom days per infectious episode. In addition, URTI symptom days were negatively correlated with increases in fitness. A recent 12-month study examined the effects of moderate-intensity exercise on the development of cold symptoms in obese sedentary postmenopausal women (3), a subject population known to have reduced immune function. Exercising subjects were found to have a significantly reduced number of incidences of self-reported cold symptoms compared with their stretching controls, with the largest differences between groups coming during months 6–12 of the study. The results of these studies support the hypothesis of the J-shaped curve (Fig. 1), in which moderate-intensity exercise is protective against respiratory viral infection, whereas high-intensity exercise increases the risk of infection.

Concentrations of salivary IgA (s-IgA) have been examined as a means of explaining the incidence rates of URTI in athletes because s-IgA binds to and opsonizes foreign organisms including respiratory viruses. Salivary IgA is considered a first line of defense in subjects who have been previously exposed to specific pathogens. It seems that long-duration and high-intensity exercise, in both an acute and chronic fashion, decreases s-IgA and is associated with increased respiratory symptoms (9). In contrast, limited research suggests both acute and chronic moderate-intensity exercise increases s-IgA levels, providing protection against respiratory symptoms. Klentrou *et al.* (12) found that 12 wk of moderate exercise training reduced self-reported infections and decreased URTI symptoms, which were correlated with increased s-IgA. Additional research by Shimizu *et al.* (27) demonstrated a similar s-IgA response in elderly subjects, further supporting exercise training as an adjunct method to protect against respiratory virus infections. A definitive role for s-IgA in explaining exercise-induced changes in RTI symptoms has not yet been provided and necessitates further research.

Experimental Evidence

Some researchers have questioned the validity of the J-shaped model describing the effects of exercise on viral infection risk (28) because most of the studies on which the model is based examined only the symptoms associated with URTI and not clinically diagnosed infection with a particular pathogen. Because of these deficiencies, several studies have attempted to more closely examine the effects of exercise on the pathogenesis and clinical outcomes attributed to specific respiratory viruses or bacteria using both human and animal models.

An important study by Spence *et al.* (28) tested elite athletes, recreational athletes, and sedentary individuals during a 5-month surveillance period. Individuals who reported symptoms of URTI were tested for several common viral and bacterial pathogens by nasopharyngeal and throat swabs. Nine sedentary, seven recreational athletes, and 21 elite athletes developed URTI symptoms during the course of the study, a result which supports the J-shaped curve hypothesis. The subjects showing URTI symptoms were

tested for most of the major pathogens responsible for URTI in humans, including adenovirus, influenza viruses A and B, several types of parainfluenza virus, respiratory syncytial virus, and others. Actual pathogens, however, were detected in only 30% of all cases, with the percentages of positive findings distributed approximately equally between the three groups. This finding suggested that although the symptoms were consistent with URTI, the underlying cause of the symptoms seen with different intensities of exercise training may not be caused by common respiratory pathogens, but instead to other phenomena such as allergic reactions or idiopathic causes such as airway hypersensitivity and asthma-associated symptoms.

Because of ethical considerations, there are very few experimental studies examining the effects of exercise on viral infection in people, with one notable exception. Weidner *et al.* (33) inoculated college-aged subjects with rhinovirus, after which half of the subjects performed six exercise bouts at 70% heart rate reserve during a 10-d period, whereas the other half remained sedentary. There were no significant differences in symptom severity or mucous weights between the exercising and nonexercising groups at any time point during the course of the study. Thus, this experimental study refutes epidemiological and longitudinal evidence reporting beneficial effects of moderate exercise on URTI. The reason for the discrepancy between this study and the others is unknown. However, most of the subjects in the Weidner study engaged in regular physical activity before the study began, baseline fitness is likely to have blunted any potential beneficial effects of moderate exercise on immune function that might have been expected based on the epidemiological and observational data that have already been discussed. In addition, the restriction in human experiments such as the Weidner study to viruses that cause only mild symptoms precludes investigation of other common but more serious respiratory infections such as the influenza virus as well as less common respiratory symptom–associated adenoviruses and enteroviruses. Clearly, within the confines of ethical considerations, more human experimentation is warranted to definitively test whether exercise dose affects the course of respiratory viral infection.

EXERCISE AND VIRAL INFECTION IN ANIMAL MODELS

Because of the difficulties in experimentally establishing the effects of exercise on specific viral pathogens in humans, studies in mice, including work performed in our laboratory, have been undertaken. One limitation of all these animal studies is that they have all examined primary, and not secondary (after immunologic memory has been obtained), responses to infection. Clearly, the effects of exercise on responses to secondary respiratory pathogen exposure need to be performed.

Davis *et al.* (5) inoculated mice with herpes simplex virus 1 (HSV-1) 15 min after either a single bout of 30 min of moderate-intensity (18 $m \cdot min^{-1}$) or high-intensity (gradually increasing from 18 $m \cdot min^{-1}$ to 36 $m \cdot min^{-1}$) treadmill running to volitional fatigue. Sedentary mice served as controls, and all mice remained in their home cages for 21 d postinfection. At the 21-d time point, 41% of the mice that exercised to fatigue had died; significantly higher than the 16% mortality rate experienced by the control group. There was no statistical difference in mortality rate between the control and moderately exercised group (9% mortality at 21 d). These results demonstrated that a single bout of intense exercise can cause serious deficiencies in immune defense when a potentially lethal viral infection is contracted. Follow-up studies have confirmed this finding (2), although one study has also indicated that short-term moderate exercise before infection in mice can be protective against viral infection–associated mortality (6). Unfortunately, HSV-1 is not a true respiratory pathogen, thus, this model is limited in the amount of information it can provide regarding the effects of exercise on common RTI pathogenesis in people.

As a result of this limitation, our laboratory conducted a study (15) that tested the effects of exercise on influenza virus infection. We used the common laboratory influenza strain A/Puerto Rico/8/34 at a dose designed to induce approximately 50% mortality in sedentary control Balb/cByJ mice. Four hours after infection, mice began a 4-d exercise program of either 30 (moderate) or 150 (prolonged) min of exercise daily. We reasoned that by applying exercise after infection but before symptom onset, we would impart exercise effects on the developing immune response better than if exercise was applied at some point before infection. Moreover, because no one knows exactly when they become infected, we thought this paradigm was more realistic than a single bout of exercise followed by infection. The exercise program was terminated after day 4 when mice began exhibiting symptoms (*e.g.*, lethargy, reduced nest building) of infection. We found that mice assigned to moderate exercise had significantly lower mortality rates than did the

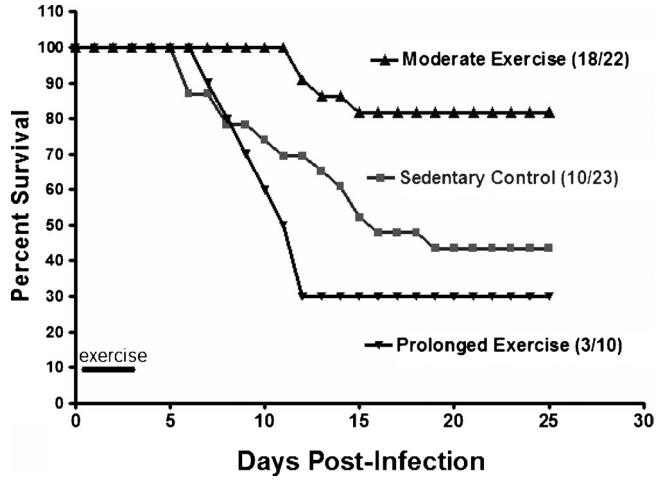

Figure 3. Influence of exercise on mortality caused by influenza (H1N1 Puerto Rico A/8/34) in male 20- to 24-wk-old Balb/c mice. Mean survival was 14 ± 1, 17 ± 2, and 16 ± 3 d for control, moderate, and prolonged exercise, respectively (results shown as (survivors/controls) in figure). There was a statistically significant difference between control and moderate exercise (log-rank = 7.3; $P = 0.007$), but not between control and prolonged exercise (log-rank = 1.1; $P = 0.29$). (Reprinted from Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. *Brain Behav. Immun.* 2005; 19(5):377–80. Copyright © 2005 Elsevier. Used with permission.)

control nonexercising group (18% vs 56% mortality, respectively) after 25 d (Fig. 3). Mice in the prolonged exercise group did not have a statistically different mortality rate than controls, although prolonged exercise did result in a greater percentage of mortality than controls (70% vs 56% mortality, respectively). Indeed, the detrimental effect of intense prolonged exercise on mortality caused by influenza virus has recently been established (21). Mice in the prolonged exercise group also had greater influenza-associated composite morbidity score (as measured by observed physical activity, response to handling, and physical appearance) before death than did their control and moderate exercise counterparts, although morbidity scores were not different at any time point between the latter two groups. This study was the first to indicate that moderate exercise initiated after infection but before symptom onset can have a beneficial effect on susceptibility to a true human respiratory pathogen. It is important to note that the dose at which the influenza virus was given induced a lower RTI, thus the results of this study may have implications on viral infections that are considerably more serious than normal infections to which athletes and exercisers are routinely exposed.

We conducted a further experiment to define potential mechanisms through which exercise improves survival in this influenza virus model (16). Using the identical exercise and influenza infection model previously described, we analyzed cellular infiltration in lungs, spleen, and draining mediastinal lymph nodes, and cytokine gene and protein expression at several time points postinfection. We hypothesized that exercise training would promote an anti-inflammatory shift from a T_H1-dominated phenotype toward a T_H2-type immune response while not totally abrogating T_H1-mediated immunity. T_H1 inflammatory immune responses induce upregulation of proinflammatory cytokines, particularly IFN-γ, which initiates improved Mφ antigen presentation and enhanced phagocytotic/cytotoxic activity. A sufficient T_H1 response is essential for early antiviral activity and promotes elevated immune surveillance, enhanced viral clearance, and memory responses. Evidence suggests, however, that a prolonged or exaggerated T_H1 inflammatory response triggers tissue damage causing lung pathology ultimately reducing survival rates (31).

We found that the same moderate exercise that improved survival also resulted in significantly lower cell infiltration into the lungs and draining lymph nodes and reduced (but not absent) IFN-γ mRNA and protein expression 3 and 5 d after influenza infection. Qualitative protein expression analysis (*e.g.*, antibody array) revealed a twofold reduction in T_H1-type cytokines and chemokines including IFN-γ, IL-17, IL-13, IFN-inducible T-cell alpha chemoattractant, leptin, stromal cell–derived factor 1, and lipopolysaccharide-inducible CXC chemokine. Contradicting our hypothesis, however, was an observed increase in IL-12 and no change in IL-2, both hallmark cytokines of a T_H1 response. In regard to IL-12, our data revealed that the protein was expressed at extremely low levels in the lung tissue. IL-2 plays a critical role in the differentiation and maturation of T regulatory (Treg) cells ($CD4^+CD25^+$), which are anti-inflammatory immune cells that play a crucial role in controlling T_H1-type inflammatory responses. A possible explanation is that exercise may not reduce IL-2, but instead improve Treg maturation, promoting an anti-inflammatory environment in the lungs. This hypothesis has yet to be tested.

In parallel with the reduction in many (but not all) T_H1 cytokines, we observed a shift toward T_H2-type anti-inflammatory cytokine profile. IL-4 lung protein levels were 2-fold higher for the exercising mice compared with sedentary mice 3 d postinfection. IL-4 promotes the differentiation of naive T_H cells to a T_H2 phenotype, which then costimulate B cells, initiating the production of virus-neutralizing antibodies. Viral antibodies reduce viral load by inhibiting infection of uninfected cells and opsonizing virus-infected cells for ADCC. Further supporting the anti-inflammatory hypothesis, exercise increased soluble TNF-α receptor (sTNFrII), which binds circulating TNF-α, preventing membrane binding and the subsequent activation of NF-κB signaling pathways. In addition to elevated expression of T_H2-type cytokines, exercise increased expression of eosinophil chemoattractants, which induce extravasation of eosinophils into virus-infected tissue, where their ribonucleases can degrade viral single-stranded RNA, inhibiting virus replication. In summary, we found that moderate-intensity exercise after influenza infection reduced lung inflammation by inducing a shift from T_H1-type inflammatory response to an anti-inflammatory T_H2-type response, and this was associated with a reduction in morbidity and mortality. Our findings are consistent with a study by Kohut *et al.* (13) who demonstrated that intense prolonged exercise resulted in reduced IFN-γ and proinflammatory cytokines in splenocytes stimulated *ex vivo* with HSV-1. In contrast, they also reported reduced IL-2 production. Comprehensive quantitative analysis of the T_H1 and T_H2 response in the lungs and respiratory tract of infected mice is needed to definitively determine whether exercise skews cytokine balance.

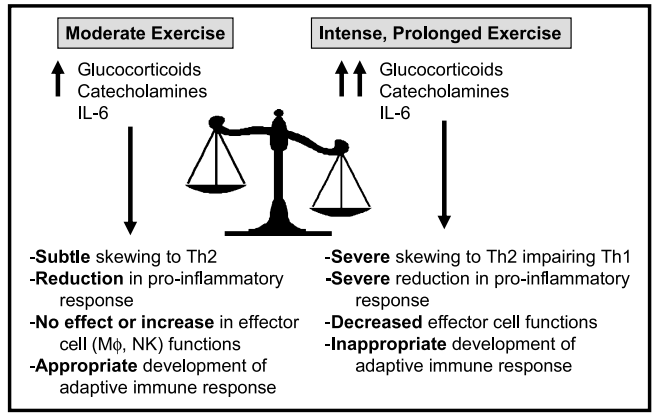

Figure 4. Hypothetical model describing the exercise dose-response effect on T_H1 and T_H2 immune responses to respiratory viral infection. Moderate exercise transiently increases glucocorticoids, catecholamines, and interleukin 6 (IL-6) to moderate levels resulting in a subtle skewing away from T_H1 and toward T_H2 while either not affecting or increasing key effector cell functions and allowing for development of an appropriate adaptive immune response. Conversely, intense prolonged exercise results in a greater longer-lasting increase in glucocorticoids, catecholamines, and IL-6 resulting in severe skewing away from T_H1 toward T_H2, decreased effector cell function, and failure to develop appropriate adaptive immune responses. Mφ indicates macrophages; NK, natural killer.

Explanation of the hormetic effect (*e.g.*, favorable biological responses at low doses, unfavorable responses at higher doses) of exercise on survival in response to a primary viral infection is a difficult task. Although speculative, it may be that intense prolonged exercise affects the cytokine balance and immune cell function more dramatically than moderate exercise. Based on our data, our current hypothesis (Fig. 4) maintains that moderate exercise causes a subtle shift away from T_H1 and toward a T_H2 response, enhancing recovery and improving survival rates in cases where viral load and morbidity/mortality risk are high. Under these conditions, an exaggerated inflammatory response to the high viral load contributes to the pathology seen in the lung and, ultimately, increased morbidity and mortality. There seems to be a point of diminishing return, however, as intense prolonged exercise leads to a suppression of inflammation and reduction in critical antiviral effector functions, including those of alveolar Mφ (5) and perhaps NK cells (22) resulting in increased morbidity and mortality. Indeed, a role for exercise-induced modulation of alveolar Mφ function in response to HSV-1 infection has been elegantly described by Murphy *et al.* (20). In that study, intranasal treatment with clodronate liposomes (which depleted alveolar Mφ) completely inhibited the protective effect of exercise on HSV-1 mortality and morbidity, suggesting a critical role of lung Mφ in the initial recognition and clearance of that virus. This contrast between moderate-intensity exercise and prolonged or high-intensity exercise is supported by numerous studies (1,10,19) that demonstrate that a highly polarized T_H2 response, as observed during prolonged intense exercise (29,30), may be detrimental to influenza recovery. Together, these findings suggest that influenza outcomes are primarily mediated by the T_H1/T_H2 balance, and a moderate exercise–induced counterregulatory shift toward T_H2 response, without profound suppression of T_H1 response, may reduce mortality and morbidity in high-risk individuals or in response to inocula that are quite large (as were the ones used in the previous animal studies). It is important to note, however, that our hypothesized model of exercise and respiratory viral infection may not hold true for lower inocula of virus or secondary exposures.

As for the direct modulators responsible for a skewing of the immune response, exercise and other physical/physiological stressors promote upregulation of stress hormones, particularly catecholamines and glucocorticoids, which are capable of binding immune cells and influencing antiviral immune functions. Dhabhar (7) suggests that stress hormones exert a bidirectional effect on immune function, with the slightly elevated concentrations of glucocorticoids and catecholamines observed during acute stress providing crucial immunoenhancing and anti-inflammatory effects during proinflammatory reactions. In contrast, chronic stress, which affects circadian rhythms and significantly elevates stress hormone concentration for prolonged periods, exerts immunosuppressive effects and increases susceptibility to infection. Indeed, adrenalectomy and glucocorticoid/catecholamine blockade exacerbate inflammatory diseases and eliminate stress-induced enhancement of skin delayed-type hypersensitivity reactions (7). In addition to stress hormones, exercise increases IL-6 locally in muscle and systemically in blood (26), which subsequently induces IL1-ra, sTNF receptor, and IL-10 that may limit excessive inflammation induced by respiratory virus infection (Fig. 4). It seems that the balance between inadequate and excessive stress responses is the result of evolutionary selective pressure. Acute stressors of limited duration, such as moderate-intensity exercise or being chased by a predator, stimulate fight-or-flight responses priming the immune system for potential challenges imposed by the stressor. Chronic stressors, on the other hand, may be evolutionarily adaptive in that immunosuppression conserves energy potentially used for coping with the stressor, albeit at the cost of increased risk for infection (7). Moderate-intensity exercise may provide an appropriate stress response that leads to immunopotentiation and anti-inflammatory actions resulting in improved recovery and survival after respiratory viral infection.

CONCLUSIONS

This article has provided evidence to support the hypothesis that moderate-intensity exercise reduces inflammation and improves the immune response to respiratory viral infections. We hypothesize that acute and chronic moderate exercise induces a level of stress hormones that downregulates excessive inflammation within the respiratory tract and aids in activating innate antiviral immunity, shifting the immune response toward a T_H2 profile (Fig. 4), thereby balancing the T_H1/T_H2 responses to prevent an excessive T_H1 immune reaction to these pathogens. Prolonged intense exercise may do this as well but may shift the balance too much toward T_H2 and away from T_H1, actually allowing the virus to gain a better foothold and cause greater pathology. Further research is necessary to examine cellular and molecular mechanisms through which exercise modulates immune function. In addition, human studies should attempt to elucidate the most common respiratory pathogens responsible for infections associated with high-intensity exercise training and athletic competitions and the methods they use to evade immune response, as well as attempt to translate mechanistic studies to a human experimental model. Based on the available evidence, moderate-intensity exercise training should be used as an adjunct to other preventive measures against respiratory tract viral infection.

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