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Review Article **Open Access**

Exercise during the coronavirus pandemic, two sides of the same coin: the intensity-specific effect of physical training on the innate and acquired immune systems of humans

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Abstract

In recent years, the global spread of the novel coronavirus responsible for COVID-19 has posed an unprecedented public health threat. Fortunately, research has shown that regular, moderate-intensity aerobic exercise can have a positive impact on the immune system when it comes to upper respiratory tract infections (URTI). Numerous studies have demonstrated that moderate aerobic exercise at 65–80% VO2max can boost antibody production, lymphocyte proliferation, gamma interferon levels, immunoglobulin M and G levels, natural killer cell counts, and Toll-like receptor activity. This suggests that exercise is beneficial for immune function in both recreational and elite athletes, with a J-shaped curve for recreational athletes and an S-shaped curve for elite athletes. Therefore, it's important for individuals of all ages to engage in regular exercise to enhance their immune response. Some helpful recommendations may include: During this time, it's wise to avoid heavy exercise, as it could potentially increase susceptibility to infection through the open window hypothesis. However, healthy individuals who don't exhibit symptoms can still benefit from moderate exercise while following proper hygiene protocols. This aligns with the J-shaped model, which suggests that moderate exercise can enhance immune system function. If you're experiencing mild upper respiratory symptoms, such as a runny nose or sinus congestion, it's safe to engage in light exercise for no more than 60 minutes with precautions. However, it's important to limit the intensity and duration to no more than 60% VO_2max in one hour. If you're exhibiting lower-neck symptoms, such as fever, cough, severe sore throat, myalgia, shortness of breath, or general fatigue, it's best to avoid exercise altogether if you suspect you may have COVID-19.

Keywords: Innate immune, Adaptive immune, Coronavirus, Exercise.

Introduction

Acute respiratory infections (ARIs) are the most infectious diseases in humans, caused by respiratory viruses and bacteria.[1,2] Rhinovirus is the most common culprit, but over 200 different viruses can cause ARIs.[3,4] In December 2019, a new coronavirus outbreak was reported in China. This virus, known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), spread rapidly and has since infected over 14 million people. It was declared a health emergency by the International Public Service on January 30, 2020.[5,6] The resulting pandemic, COVID-19, has had a significant impact on global morbidity and mortality.[1]

To mitigate the spread of COVID-19, key strategies include social and physical distancing, hygiene measures, contact tracing, isolation, testing, monitoring, and boosting immunity in individuals and the public. However, developing a vaccine is still in its early stages.[2] The clinical pattern of COVID-19 generally involves three stages. Stage I is an asymptomatic incubation period with or without the presence of a detectable virus. Stage II is a non-severe symptomatic period with the presence of the virus. Finally, Stage III is a severe respiratory-symptomatic stage with a high viral load and inflammation.[2] Individuals in Stage I, also known as stealth carriers, are the most challenging to manage because they may spread the virus unknowingly within the community, contributing to its highly contagious nature.[4]

Up to April 2020, statistics showed that around 15% of confirmed COVID-19 cases progressed to the severe phase. Patients over 65 years old with preexisting comorbidities such as diabetes, heart disease, lung disease, and compromised immune systems have a higher chance of fatality.[5] During the incubation and non-severe stages (Stages I and II), a specific adaptive immune response is necessary to eliminate the virus and prevent the disease from progressing to the severe stages. For this response to occur, the host needs to be in good pre-existing health. Therefore, improving preexisting fitness levels, getting appropriate nutrition and adequate sleep, and maintaining mental health can be significant public health interventions to boost an individual's immune status, even before getting infected (i.e., before Stage I).[6]

Physical activity (PA) has consistently been shown to reduce the risk of systemic inflammation, excess body weight, and non-communicable diseases. These benefits are known to boost immune function. Recently, in the context of the novel coronavirus outbreak, there have been questions about the potential role of physical activity in immune function. This newly formed field is called exercise immunology, which examines the immune system's responses and adaptations to sports activities. Exercise has been shown to be beneficial to health as a part of a healthy lifestyle, reducing the risk of disease and mortality. Niemann and Nehlsen-Cannarella (1994) described the relationship between the risk of upper respiratory tract infections (URTIs) and regular exercise as a "J-shaped curve" [Figure 1].[7,8]

Increasing the amount of exercise can initially decrease the risk of infection. However, in some cases, increasing the level of exercise can also increase the risk of infection.[8] Animal studies have shown that moderate-intensity exercise can protect against infection, while strenuous exercise before infection leads to increased mortality. In humans, epidemiological studies have found that strenuous, competitive exercise, such as marathon running, increases susceptibility to upper respiratory tract infections (URTI). Conversely, physical activity or light exercise have been found to reduce the number of URTI symptoms. However, it is still unclear how exercise and infectious diseases such as the flu interact in human societies.

Physical activity, sports and Flu

Recent research has shown that both animal and human studies have been conducted to understand how exercise affects influenza and influenza vaccination. In animal studies, Lowder et al. found that moderate-intensity endurance exercise (95 minutes per day) had a protective effect on mice against death due to the flu. However, mice that exercised for longer periods of time (5.5 hours per day) experienced an increase in some symptoms. While there was no statistically significant difference in mortality compared to sedentary mice, they concluded that prolonged exercise could be detrimental to influenza-infected mice. Overall, the study suggested that moderate exercise could be beneficial for combating the flu.[6] Wood et al. conducted a large study to determine the effect of 10 months of regular endurance exercise on improving the flu vaccination response in older adults, who are at higher risk for infectious diseases due to their weakened immune systems. The study found that regular, moderate-intensity aerobic exercise could have a protective effect.[9] While emphasizing the importance of receiving the annual flu vaccine, the researchers also concluded that moderate-intensity, regular endurance exercise might enhance the protective effect of the vaccination. To maintain antibody protection throughout the flu season, flu vaccination should be performed annually. Table 1 summarizes some of the research on the interaction effects of physical activity and exercise on infectious diseases, particularly the flu. Wood et al.,[9] emphasized that both influenza and the coronavirus can cause respiratory tract infections that may lead to complications and death, especially in those with weakened immune systems or inadequate immunity to the virus. Despite COVID-19 being a serious condition, flu is a much bigger problem due to its commonality and longevity, yet it may not receive as much attention as new viruses that spread.[9]

Table 1. Research on the interactions of physical activity about infectious diseases, especially the Flu

Researcher	Study population	Study Design	Results
Williams [10]	2160 patients with diabetes	Subjects participated in a long-term course (mean 8.9 years) in 1.5-km brisk walk (1 MET · h ~1-km run) programs.	Significantly reduced mortality from sepsis, pneumonia and influenza associated with exercise
Williams [11]	Homogenized groups of runners (109352 people) and walker (40798 people)	Dose-response relationship between mortality from respiratory disease, pneumonia and aspiration pneumonia with energy expenditure running and walking (MET-hours / d, 1 MET = 3.5 ml O2 / kg / min)	Higher doses of running and walking are associated with a lower risk of respiratory disease, pneumonia, and aspiration pneumonia mortality.
Wong et al., [8]	Death profile of 24656 adult	Investigating the relationship between exercise habits, other lifestyles and the main cause of death from influenza A (H3N1 and H1N1) with different levels of exercise including: never / rarely (less than once a month), low / moderate (once a month to three times in Weekly) and frequent (four or more times a week)	Low to moderate-frequency exercise has rarely and never been associated with fewer flu-related deaths than no-exercise.
Kohut et al.,[12]	Wistar rats	Mice were divided into three groups: without exercise, acute exercise (40 minutes running on a treadmill at a speed) of 18 m/min and chronic exercise (5.3 months, 40-45 minute running at a speed of 8-18 m/min). The acute group became infected with the influenza virus (A/PR/8/34) 15 minutes and the chronic group 24 hours after exercise. Infection of the inactive group was similar to the two sports groups.	Chronic exercise has reduced symptoms, viral load, and levels of inflammatory cytokines and chemokines. Acute exercise also showed benefits such as limiting the early phase of the infection
Warren et al.,[13]	Wistar rats	Mice were divided into four groups: non-obese without exercise, non-obese with exercise, obese without exercise and obese with exercise. Exercise activities included: 8 weeks, 45 minutes of daily treadmill running (intensity) 80-65% VO_2 max and feeding obese mice with a high fat diet. Mice became infected with the A/PR/8/34 virus 24 hours after the last training session.	Exercise restores the immune response of obese mice to a phenotype similar to that of non-obese mice by improving the delay in immune activation. In contrast, in non-obese mice, exercise therapy reduces the premature viral load of the lung and limits the inflammatory response.
Folsom et al.,[14]	Pony horses	Horses infected with the equine influenza virus were divided into rest and strenuous exercise groups. The exercise program included a 5-day period of strenuous exercise. Horses of all groups were also vaccinated against the virus	Exercise significantly suppresses the T cell-mediated immune response to the virus by reducing lymphocyte proliferation and interferon-gamma production. But infected and vaccinated resting horses were completely protected from the disease. In general, suppression of immunity due to strenuous exercise to the influenza virus can be associated with increased susceptibility to the disease.
Kohut et al.,[15]	24 Adults (64±3 years old)	Subjects were divided into two groups: control and moderate-intensity exercise (30-30 minutes, 3 days a week for 10 months). People were vaccinated with the triple flu vaccine before and after exercise intervention	Moderate-intensity exercise may increase antibody titers in response to influenza immunization if influenza antigen is present from last year's vaccine.
de Araújo et al.,[16]	61 men (65-85 years old)	Subjects were evaluated for long-term (up to 29 years) in 3 groups: moderate exercise lifestyle (less than 6 km per week), intense exercise lifestyle (more than 50 km per week) and non-exercise group for poor response to influenza vaccination. The strains used were H3N2, B and H1N1	First, in both exercise groups, older men had significantly higher antibody titers than those without exercise. Second, there was a higher titer against B and H1N1 strains in both exercise groups before vaccination. Third, both moderate and vigorous exercise were associated with stronger and longer antibody responses to the flu vaccine.

The SARS-CoV-2 is concerning due to its novelty and lack of information. New viruses pose a risk because there is no protection against them, and there is no vaccine yet developed. However, efforts are being made to understand and develop preventive strategies to counter the COVID-19 threat. The most crucial action currently is to take global precautions to limit the spread of the disease until a vaccine or other treatment is available. The general public is advised to follow WHO/ACSM recommendations of at least 150 minutes per week of moderate-intensity aerobic activity or at least 75 minutes of vigorous-intensity aerobic activity throughout the week, in addition to 2 muscle strength training sessions per week.[24,25] Given that the behavior of the virulent SARS-CoV-2 is still not fully understood and many individuals are facing nutritionally and psychologically challenging environments, it may be unwise to engage in exercise sessions that are excessively intense or lengthy.[17]

Exercise considerations during the outbreak of COVID-19

While coronavirus outbreaks are ongoing, it is generally safe for healthy individuals to exercise. Daily exercise has numerous health benefits that should not be underestimated, even in the presence of a new virus. However, it is important to take precautions to minimize the risk of infection. As the virus is transmitted through airborne droplets and direct contact with infected individuals, particularly through coughing and sneezing from an infected person at close range (3 to 6 feet or 90 to 180 cm from someone without protection), it is best to avoid exercising in crowded environments where asymptomatic individuals may be present. In some cases, wearing a mask while exercising may be a way to reduce exposure.[17,18]

When using sports equipment in gyms, it is crucial to disinfect the equipment both before and after use. For cleaning hands during exercise, the most effective method is to wash hands with soap and water for a minimum of 20 seconds, and then dry hands using a clean towel.[2,5] Manual disinfectants containing at least 60% alcohol can also be used, although the US Centers for Disease Control and Prevention (CDC) caution that they may not be effective against all germs. Additionally, it is important to avoid touching the face and neck if it is not possible to disinfect hands right away.[19]

Exercise for people with the Flu, severe acute respiratory syndrome (SARS) and COVID-19

Individuals who experience mild upper respiratory symptoms such as a runny nose, sinus congestion, or a mild sore throat may still engage in exercise. However, if symptoms such as a severe sore throat, body aches, shortness of breath, general fatigue, dry cough, or fever develop, it is advisable to avoid exercise and seek medical attention. Resting for 2–9 weeks is typically necessary for recovery from respiratory viral infections, during which time the immune system produces the cytotoxic T cells required to eliminate the virus from infected cells. Once symptoms have fully resolved, individuals can gradually start regular exercise with low intensity.[17,18]

Short-term or long-term physical activity

Exercise immunologists have discovered that even one exercise session can help enhance immune function, although regular, long-term exercise provides more advantages for the immune system. It has been demonstrated that cellular and molecular changes begin shortly after the onset of exercise or physical activity. There is a conventional belief that exercise causes a stress response in the body, triggering immune cells to handle potential infectious and non-infectious challenges related to physical activity. Due to evolutionary physical activity, injuries such as micro-injuries to skeletal muscles may occur, leading to inflammatory reactions.[18,19]

Physical activity intensity

Ethical considerations make it challenging for individuals with infectious diseases to be exposed to intense exercise. Generally, elite athletes who engage in high-level competition and training are capable of handling significant pressure without compromising their safety.[20] Research on animal models has demonstrated that prolonged and strenuous exercise, particularly if not previously experienced, can exacerbate the signs and symptoms of infectious diseases. It is worth noting that animal research has its limitations, including species differences, exercise-related stress, pathogen type, and timing of exercise in relation to infection, among other factors that must be taken into account.

Exercise at an intensity of 60% or more of maximum oxygen consumption (≥60% VO_2max) can have negative effects on the immune system, including a reduction in the respiratory explosion of neutrophils. Furthermore, hard exercise can cause cortisol-induced lymphocytopenia by recruiting pro-inflammatory and inflammatory factors, resulting in decreased phagocytic activity.[17]

Excessive training syndrome (OTS), also known as unexplained underperformance syndrome (UPS), can have severe effects on the immune system. These effects include: 1) an increase in neutrophil to lymphocyte ratio; 2) a decrease in bone marrow neutrophil reserves; 3) a drop in salivary immunoglobulin A (s-IgA); 4) a decrease in plasma glutamine; and 5) HPA axis problems. Moderate-intensity exercise (60% VO2max) can, on the other hand, cause a re-distribution of newly released lymphocytes (lymphocytosis) and neutrophils (neutrophilia), resulting in an increase in leukocytosis.[18] Moderate physical activities can increase immune indexes through a possible mechanism that involves increased shear pressure and adrenal secretion. Adrenaline has several effects on the body, such as attaching to alpha 1 receptor and causing blood recruitment from the viscera to the lungs; attaching to beta 1 receptors and increasing cardiac output; and attaching to beta 2 receptors and increasing blood flow in skeletal muscle. Through the messaging role of CAMP, adrenaline can also enhance the degradation of immunological factors (lymphocytes), resulting in improved immune system defenses during moderate physical exercise.[19,20]

Type of physical activity

While there have been recent studies examining the impact of resistance exercise and high-intensity intermittent exercise (HIIT) on safety parameters, their small number makes it challenging to draw definitive conclusions. One study by Yang et al. looked at the effect of 5 months of Chinese Tai-Chi exercise on the immune response to influenza vaccination in older adults. Individuals participating in these traditional activities had a significant increase in the amount and duration of antibody responses to the H1N1 and H3N2 strains as compared to sedentary individuals.[21,22] In a systematic review study, Falkenberg et al.[22] investigated the impact of mental yoga exercises on immune function. They found that yoga was effective in reducing levels of IL-6, IL-1β, and TNF-α and improving cellular and mucosal immunity in individuals with inflammatory diseases. Therefore, low-intensity physical activities like aerobics, strength, stretching, balance, and even mental exercises can be utilized during the COVID-19 outbreak.[22]

Conclusions

Research suggests that intense and prolonged exercise during viral infections can hinder immune parameters. In contrast, moderate-intensity exercise can help reduce inflammation and improve the immune response to respiratory viral infections. There are several epidemiological studies that indicate regular physical activity is linked to reduced mortality and the incidence of influenza and pneumonia.[18] Moreover, animal studies have demonstrated a positive association between chronic exercise and an improved host response to influenza and pneumonia.[12] In seniors, physical activity and exercise, along with a healthy lifestyle, have been reported to produce more durable and robust antibody responses after receiving seasonal flu vaccinations.[13] In general, moderate-intensity exercise boosts glucocorticoids, catecholamines, and IL-6 levels, moving Th1 toward Th2 without impairing critical cell function or increasing the optimal adaptive immune response.[15]

Based on an analysis of current research and the similarities between COVID-19 and other respiratory infections like H1N1, the following exercise recommendations are suggested amidst the COVID-19 outbreak:

1. Due to the possibility of asymptomatic carriers and the Open Window Hypothesis [Figure 1],[7] it is advisable to limit strenuous exercise as it increases the risk of infection in non-adolescents.
2. Asymptomatic and healthy individuals can safely continue moderate-intensity exercise while adhering to health guidelines and benefiting from improved immune function, as per the J-shaped curve.
3. The most important hygiene considerations for exercise during the COVID-19 outbreak include regular hand washing, disinfecting equipment and

surfaces, exercising at home or in isolated places, and maintaining a 1-2-meter distance from others while wearing a mask.

4. Individuals with mild upper respiratory symptoms such as a runny nose or sore throat can incorporate low-intensity exercise (e.g., aerobics, strength, stretching, balance, and even mental exercise) with appropriate consideration and caution.
5. The recommended intensity and duration of exercise to boost the immune system should not exceed 60% VO_2max for a maximum of one hour.

Individuals experiencing significant COVID-19 symptoms such as a severe sore throat, body aches, shortness of breath, general fatigue, dry cough, or fever (lower-neck symptoms) should refrain from exercise until they have fully recovered.

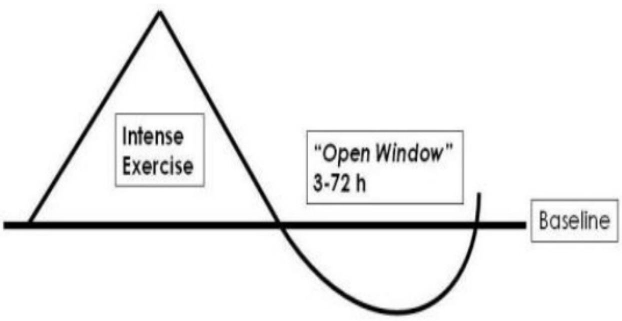

Figure 1. The Open Window Hypothesis states that 9–72 hours post-exercise, the immune system's "open window" creates an opportunity for infectious agents, like viruses, to penetrate the body and cause infection.[7]

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

Coronavirus disease 2019: COVID-19; Severe acute respiratory syndrome coronavirus 2: SARS-CoV-2; World Health Organization: WHO; Acute respiratory infections: ARIs; Upper Respiratory Trunk Infections: URTI; Physical activity: PA; Centers for Disease Control and Prevention: CDC; Severe acute respiratory syndrome: SARS; Over training syndrome: OTS; Unexplained underperformance syndrome: UPS; High-intensity intermittent exercise: HIIT.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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