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# Effect of physical activity on COVID-19 and underlying mechanisms

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## Abstract

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly transmitted globally since December 2019. As COVID-19 was caused by a novel coronavirus, people only counted on their innate immune system in the early COVID-19 pandemic. However, given that the defense against viral infection depends upon a competent adaptive response, understanding adaptive immunity in SARS-CoV-2 immune responses is critical. This review paper discussed the effect of physical activity on COVID-19 and plausible underlying mechanisms. Therefore, promoting regular physical activity has the potential to mitigate the impact of the pandemic at a personal and societal level. Also, it is important for policymakers to make public health policies concentrating on measures for encouraging physical activities to enhance an individual's immune system during the pandemic.

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## 1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly transmitted globally since December 2019.[1] Considering that SARS-CoV-2 is highly contagious, it has contaminated people of all ages with respiratory droplets and direct contact transmission.[2] Most confirmed cases are asymptomatic or mild symptoms like fever, cough, and shortness of breath, but the others can be severe or critical and lead to death.[1] Consequently, the pandemic has escalated to more than 500 million confirmed cases of COVID-19, including over 6.5 million deaths globally.[2] Adults with comorbid medical conditions, cardiovascular diseases (CVD), and asthma are at high risk of developing severe illnesses from COVID-19.[2, 3] Few children and adolescents have become infected with the COVID-19 virus compared to adults. The severity of COVID-19 in children varied among different ages.[4] This might be because those aged 4 to 13 have higher angiotensin-converting enzyme 2 (ACE2) and differential CD4+ and CD8+ T cell populations.[5]

## 2. Pathogenesis of COVID-19

### *2.1 SARS-CoV-2 Entry*

The infection of the cytopathic virus, like SARS-CoV-2, initiates with viral entry, in which

the virion recognizes a host cell receptor and fuses its membrane with the host cell membrane.[6] Several studies identified that cells with high ACE2 and transmembrane protease serine 2 (TMPRSS2) have strong SARS-CoV-2 binding capacity and are vulnerable to infection.[7] ACE regulates the renin-angiotensin-aldosterone system (RAS), which contains renin, angiotensinogen (ANG), angiotensin I (Ang I), Ang II, and ACE10. Hence, it has been proven that the spike glycoprotein (S) of SARS-CoV-2 binds to ACE2 expressed in epithelial cells of the lung and small intestine.[8] Such that ACE2 serves as a receptor for the virus causing COVID-19.[9] The coronavirus S protein is constituted of S1 and S2 functional subunits with the S1/S2 cleavage site.[9] The viral S glycoprotein interacts with the ectodomain of ACE2 and the complex is endocytosed, leading to decreased surface ACE2 expression.[9] The N-terminal S1 subunit interacts with the ACE2 receptor for initial docking, while the carboxyl-terminal S2 subunit induces the proteolytic fusion between the viral envelope and the cellular membrane by conformational reconfiguration.[10] Subsequently, TMPRSS2 cleaved the multibasic S1/S2 site of the S glycoprotein protein.[10] The association between ACE2 downregulation with the systemic RAS imbalance stimulates the development of multiorgan impairment from SARS-CoV-2 infections.[11]

### *2.2 Cellular immunity*

As COVID-19 was caused by a novel coronavirus, people only counted on their innate immune system in the early COVID-19 pandemic.[12] However, given that the defense against viral infection depends upon a competent adaptive response, understanding adaptive immunity in SARS-CoV-2 immune responses is critical. The immune systems contain the innate immunity activation and memory of three adaptive response compartments; B cells (antibodies synthesis), CD8+ (killer T cells), and CD4+ (helper T cells) lymphocytes.[12] Those CD8+ and CD4+ T lymphocytes recognize viral peptides attached to human leukocyte antigen (HLA) class I and II molecules, respectively.[13] CD8+ T cells directly attack and kill infected cells, whereas CD4+ T lymphocytes help B cells and CD8+ T cells and differentiate into helper and effector cells. CD4+ T cells also take charge of cytokine production to drive immune cell recruitment and migration through cytokine secretion. Dysregulation of innate immune response with excessive inflammatory cytokine production causes severe COVID-19 disease.[11] For SARS-CoV-2 infection, TNF-α, interleukin (IL)-6, and IFN-α/-γ pro-inflammatory cytokines are secreted. As COVID-19 deteriorates, CD4+ T lymphocytes and CD8+ T lymphocytes gradually decline.[14] Indeed, lymphopenia and reduced CD4+ and CD8+ cell counts are significant manifestations of SARS-CoV-2 infection.[14]

### *2.3 Impacts of COVID-19*

In the first months of the epidemic, it was confined to China, and its impact on the Chinese economy caused production disruptions and declines. Consequently, the global supply chain was disrupted. A few months later, the outbreak spread worldwide, and eventually, the COVID-19 pandemic became a severe threat to the world and negatively affected most aspects of our lives. Especially measures to prevent the spread of COVID-19, such as social distancing and

home confinement, changed lifestyle behavior for children and adolescents.[15] Children could not access school-based physical activities (PAs), including physical education, recess, and commuting to and from school. Besides, classes for youth physical education and activities such as gymnastics, dance, and martial arts have also been canceled or postponed. Several studies confirmed that the COVID-19 outbreak reduced PA and increased prolonged sedentary behavior.[16] Those radical changes in lifestyle behaviors make the loss of muscular and cardiorespiratory fitness, weight gain, poor sleep quality, and poor academic achievements.[16]

## 3. PA

Technically, PA is not just about sport nor just exercise. It is defined as any bodily movement produced by skeletal muscle that requires energy expenditure according to the 2018 Global Action Plan on Physical Activity from World Health Organization (WHO).[17] The health benefits of PA are well verified and have a lower risk of CVD, diabetes, hypertension, strokes, breast cancer, colon cancer, and all causes of death.[18] PA can also positively affect mental health and dementia and help maintain a healthy weight.[19] For school children, it has been found that sufficient PA plays a significant role in physical growth, cognitive functions, and lifelong health. To reap the benefits, WHO and several national governments around the world issued guidelines encouraging the engagement of PA.[20] Guidelines recommend that children aged 5 to 17 should do moderate-to-vigorous intensity PA for more than 60 minutes per day and engage in vigorous-intensity PA at least three days a week. Aerobic PA can improve aerobic capacity and is categorized into vigorous PA and moderate PA.[21] Moderate PA is classified as an activity that causes mild shortness of breath or a slight increase in heart rate; Vigorous PA is an activity that causes shortness of breath, such as fast cycling, fast swimming, jogging, soccer, basketball, and taekwondo.

In addition, as part of their 60 minutes or more of daily PA, they should also do muscle-strengthening PA at least three days a week.[22] Muscle-strengthening exercises include sit-ups, push-ups, and weight lifting. Adults should engage longer time (≥150 min/week of moderate-intensity PA or ≥75 min/week of vigorous-intensity PA) in aerobic activity.

However, previous studies reported that the prevalence of insufficient PA in adolescents and adults is 23% and 81%, respectively.[23] Although global trends in PA engagement in leisure time, occupational PA, and transportation-related PA have decreased because of behavioral and environmental factors like rapid urbanization and increased demand for vehicles.[24] The passive attitude towards the inactivity of PA as considered a personal choice is mistaken. Most people are only aware of the benefits of being physically active, but they seem unaware of the consequences of being physically inactive. The main reason that getting the public to exercise becomes a public health priority is that physical inactivity significantly contributes to deaths from non-communicable diseases such as coronary heart disease, breast and colon cancers, and type 2 diabetes.[25] Among the 36 million deaths yearly from non-communicable diseases, physical inactivity contributes to about 5 million.[25]

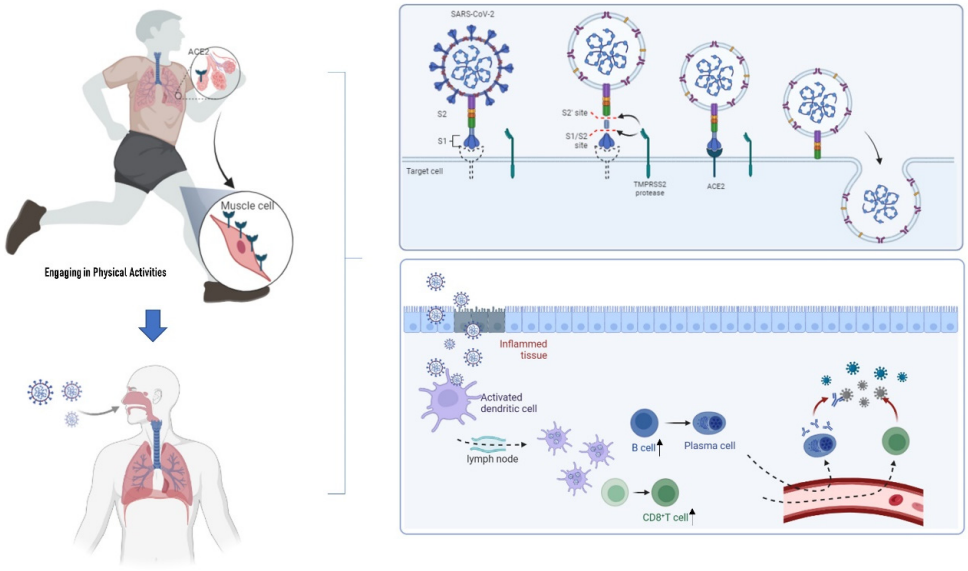


**Fig. 1. Effect of physical activity on COVID-19 and underlying mechanisms**

## 4. Effect of PA on COVID-19 pathogenesis

The pathogenesis of acute respiratory viral infections and the severity of the disease are regulated by the virus and/or dysregulated immune responses.[25] Likewise, as the progression of COVID-19 depends on one's possessed immune system, the development of the immune system against the virus is critical during the pandemic.[26] Engaging in regular PA has been established to enhance physical and mental health. It has been presented to reduce the risk of adverse health conditions (i.e., obesity, CVD, and diabetes)[27] that increase the adverse effects of COVID-19. Besides the fact that it can improve the immune system, which is likely to have a positive impact on COVID-19 progression.[27]

### *4.1 PA and ACE2*

Indeed, the ACE2 protein mediates the SARS-CoV-2 entry and regulation of angiotensin II. Still, the mechanism underlying that PA positively influences the progression of COVID-19 is unknown. One of the studies reported that PA causes chronic alteration in the concentration of ACE2 serum.[28] The result of the study showed that PA makes higher skeletal muscle ACE2 expression and lower flowing ACE2 levels.[28] Thereupon, ACE2 proteins expressed in skeletal muscle would not be bound to SARS-CoV-2 inhaled through the nasal or lung. Therefore, decreased concentration of ACE2 on the epithelial cell of the lung and small intestine would reduce the risk of COVID-19 infection.

### *4.2 PA and Cellular Immune System*

According to the studies, the most prominent characteristic of confirmed cases of COVID-19 in China was lymphocytopenia (83.2%).[29] Because the white blood cell (WBC) counts in

peripheral blood decreased.[29] Also, SARS-CoV-2 attacks the respiratory system, causing pneumonia and lymphopenia in infected individuals. Among the WBC, neutrophils and lymphocytes are critical components of the immune response to coordinate inflammation. It is known that the concentration of neutrophils, leukocytes, and all lymphocyte subsets increases, but the magnitude varies based on the PA intensity and duration throughout the workout period.[30] Moderate-intensity PA facilitates cellular immunity, while prolonged and vigorous-intensity PA without proper rest can activate decreased cellular immunity, increasing the propensity for diseases[30]. Both the number of CD4+ T and CD8+ T lymphocytes increase during PA, protecting against SARS-CoV-2 by attacking the virus and memorizing it. A relatively more significant increase in CD8+ T lymphocytes than CD4+ T resulted in depressed CD4/CD8 ratios. For cytokines, PA induces the release of a cascade of inflammatory cytokines such as IL-6, IL-1 receptor antagonists, TNF receptors, and IL-10.[30] With these increased lymphocyte populations throughout the PA, the immune system would be improved to help to fight against COVID-19.

## 5. Post-COVID-19 syndrome and PA

After the first COVID-19 cases, it has been seen that patients showed persistence of symptoms after the initial COVID-19 related symptoms.[31] These symptoms includes fatigue, muscle pain, low grade fever, cough, shortness of breath, chest pain, headache, and cognitive dysfunction.[32] Prevalence of post-COVID-19 symptoms depends on its definition. Some studies reported symptoms like cough or shortness of breath lasting 6 weeks while some studies reported symptoms like cognitive impairment lasting 6 months after the initial COVID-19 period.[32] As mentioned above physical inactivity has been linked to severe COVID-19 outcomes. Recent studies emphasized the potential benefit of proper and tailored PA on post-COVID-19 syndrome via regulating the immune system, healing functional impairment in cardiopulmonary system, recovering the neurological and biopsychological disturbances.[33]

## 6. Conclusion

Therefore, promoting regular PA can potentially mitigate the pandemic's impact at a personal and societal level. Also, it is important for policymakers to make public health policies concentrating on measures for encouraging PAs to enhance an individual's immune system during the pandemic.

### Capsule Summary

This review paper discussed the effect of physical activity on COVID-19 and plausible underlying mechanisms. Therefore, promoting regular physical activity has the potential to mitigate the impact of the pandemic at a personal and societal level.

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## Author Contribution

Dr RK, AÖY, and SHC contributed to the preparation of this review.

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## Conflicts of Interest

The authors have no conflicts of interest to declare for this study.

## Provenance and peer review

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