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# Physical Exercise and CoViD-19: A Brief Narrative Review on Immunology, Prevention and Recovery

## *Exercício físico e CoViD-19: imunologia, prevenção e recuperação: uma breve revisão narrativa*

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### *Abstract*

**Introduction:** The new coronavirus, the etiological agent of CoViD-19, causes damage to several systems in the human body, particularly the lungs, heart, brain, kidneys, and vascular system. Spread to the world in early 2020, little was known about the disease. More recently, evidence has begun to emerge that physical exercise (PE) can help prevent it.

**Objective:** To present a brief review of the literature about the relationship between PE and health promotion of the immune system and its relationship with CoViD-19.

**Methods:** This study was a narrative review. The search was carried out using the PubMed and Google Scholar databases. The language used was English and the following terms were used: "*exercise and CoViD-19*".

**Results and Discussion:** PE improves endothelial function, improving the immune system, contributes to reducing obesity, as well as contributing to mental health, providing additional benefits, as both negative affective states and obesity increase inflammation and decrease function immunological. In addition, the literature shows that higher levels of physical activity were associated with lower prevalence of CoViD-19 symptoms and physical inactivity had a 32% higher relative risk for hospitalization for CoViD-19.

***Key Points***
*- The recommended exercise intensity to improve endothelial and immune systems functioning, as well as to better mental health is moderate intensity.*
*- Higher levels of physical activity were associated with lower prevalence of CoViD-19 symptoms.*
*- Physical inactivity Physical inactivity had a 32% higher relative risk for hospitalization for CoViD-19.*

**Conclusion:** PE promotes mitochondrial health, contributing to the maintenance of the immune system. The intensity of PE is important to improve endothelial function, immunity and mental health and must be moderate, in addition to maintaining the regularity of the practice so the organic benefits can be achieved.

***Keywords:*** physical activity, immunology, coronavirus, pandemic, preventive medicine.

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## Resumo

**Introdução:** O novo coronavírus, agente etiológico da CoViD-19, causa danos a diversos sistemas do corpo humano, particularmente, aos pulmões, coração, cérebro, rins e sistema vascular. Tendo sido espalhada para o mundo no início de 2020, pouco se sabia sobre a doença. Mais recentemente, começaram a surgir evidências de que o exercício físico (EF) pode ajudar na sua prevenção.

**Objetivo:** Apresentar uma breve revisão da literatura acerca da relação de EF com promoção da saúde do sistema imunológica e sua relação com a CoViD-19.

**Métodos:** Este estudo foi do tipo revisão narrativa. A busca foi realizada na base da dados do PubMed e o Google Scholar. A linguagem utilizada foi o inglês e foram utilizados os seguintes termos: *"exercise and CoViD-19"*.

**Resultados e Discussão:** O EF melhora a função endotelial, aprimorando o sistema imunológico, contribui para reduzir a obesidade, bem como contribui para melhorar a saúde mental, proporcionando benefícios adicionais, pois, tanto estados afetivos negativos quanto obesidade aumentam a inflamação e diminuem a função imunológica. Além disso, a literatura exibe dados que mostraram que maiores níveis de atividade física se associaram a menor prevalência de sintomas de CoViD-19 e inatividade física teve o risco relativo 32% maior para internação hospitalar por CoViD-19.

**Conclusão:** O EF promove a saúde mitocondrial, contribuindo para a manutenção do sistema imunológico. A intensidade do EF é importante para melhorar a função endotelial, a imunidade e a saúde mental. Assim o exercício deve ser de intensidade moderada, além de ser mantida a regularidade da prática para que os benefícios orgânicos sejam alcançados.


***Pontos Chave***

*- A intensidade do exercício físico para promover o funcionamento dos sistemas endotelial e imunológico, bem como promover a saúde mental é a intensidade moderada.*

*- Maiores níveis de atividade física associaram-se a menos sintomas de COViD-19.*

*- Inatividade física inatividade física teve o risco relativo 32% maior para internação hospitalar por CoViD-19.*

***Palavras-chave:*** atividade física, imunologia, coronavírus, pandemia, medicina preventiva.

# Physical Exercise and CoViD-19: A Brief Narrative Review on Immunology, Prevention and Recovery

## Introduction

In the years of 2002-2003 there was a severe acute respiratory syndrome (SARS) pandemic caused by a coronavirus named SARS-CoV, originated from China**(1)**. Almost two decades after that, at the beginning of 2020, a new pandemic emerged from a new coronavirus that also caused SARS having its origin in China as well. In that context, the new coronavirus was called SARS-CoV2, and the new disease was named CoViD-19 (disease cause by SARS-CoV2 in 2019). Besides SARS, CoViD-19 leads to deleterious inflammatory**(2,3)** and neurological**(4–8)** symptoms. On its severe phase, there is triggered a cytokine storm**(9)** – a phenomenon phlogistic[1] characterized by an inflammatory and febrile condition, which is fed back by the production of cytokines, a process that overloads the counter-regulation mechanisms**(9,11)**.

As physical activity is closely linked to health promotion and preventive medicine, this study aimed to present a brief literature review about the relationship of physical exercise with immunology, prevention and recovery aspects of CoViD-19.

## Methods

This was narrative review, and the research was conducted in the database of

[1]Phlogistic: of or relating to inflammations and fevers(10)

PubMed, that includes MedLine and other scientific bases, and in Scholar Google. The English language was used to track the publications, using the search terms "*exercise and CoViD-19*".

## Results and Discussion

### *CoViD-19 a disease of the endothelial system*

SARS-CoV2, etiological agent of CoViD-19, causes damage to several systems of the human body, particularly the lungs, heart, brain, kidneys and vascular system**(11)**. This can be explained because SARS-CoV2 receptors are ACE2[2] protein**(13)**, which is predominantly present in pulmonary alveoli, respiratory epithelial cells, ilium, esophagus, myocardium, and olfactory neuroepithelium**(14)**. Nunn et al.**(14)** explained that the increased risk for aggravation of CoViD-19 in obese individuals is due to the fact that ACE2 receptors are found in adipose tissue: both in visceral and subcutaneous tissues. Likewise, other agents – CD26[3] and CD147[4], may also act as receptors for SARS-CoV2, which are altered with age and relates to comorbidities such as obesity and hypertension. ACE2 and CD147 are increased in case of lung disease, which activates the *renin-angiotensin aldosterone system* (RAAS) accelerating the damage to the body, which explains the cytokine storm**(14)**. Therefore, the severity degree of CoViD-19 is linked to previous existence of other age-related diseases such as diabetes, hypertension and other cardiovascular diseases**(17,18)**, all of which compromise endothelial function. Complications of the disease are more frequent in the elderly because with advancing age, there is a reduction in pulmonary function, which causes impairment of pulmonary epithelial integrity, greatly compromising the elderly's ability to fight against respiratory infections, resulting in greater susceptibility to lung diseases**(19)**. The respiratory function decline related to age is independent of physical exercise**(20)**.

Libby and Lüscher**(11)** investigated the mechanisms of CoViD-19 examining the stages of later complications and concluded that it is an endothelial disease. The authors explain:

> *"The vascular endothelium provides the crucial interface between the blood compartment and tissues, and displays a series of remarkable properties that normally maintain homeostasis. This tightly regulated palette of functions includes control of haemostasis, fibrinolysis, vasomotion, inflammation, oxidative stress, vascular permeability, and structure.*
>
> *While these functions participate in the moment-to-moment regulation of the circulation and coordinate many host defense mechanisms, they can also contribute to disease when their usually homeostatic and defensive functions over-reach and turn against the host.*
>
> *SARS-CoV-2, the aetiological agent of COVID-19, causes the current pandemic. It produces protean manifestations ranging from head to toe, wreaking seemingly indiscriminate havoc on multiple organ systems including the lungs, heart, brain, kidney, and vasculature (...)*
>
> *Cytokines, protein pro-inflammatory mediators, serve as key danger signals that shift endothelial functions from the homeostatic into the defensive mode. The endgame of COVID-19 usually involves a*

[2]ACE2: The angiotensin converting enzyme-2 (ACE2) is an enzyme attached to the membrane of cells in the kidney, testis, heart, and the intestinal tract, gallbladder and lung(12).

[3]CD26: The dipeptidyl peptidase IV/DPP IV/adenosine deaminase binding protein/ADAbp (CD26) is a multifunctional membrane, type II cell surface glycoprotein widely expressed on T cells, B cells and natural killer cells(15).

[4]CD147: Cluster of differentiation 147 (CD147) is a transmembrane glycoprotein belonging to the immunoglobulin superfamily. Its overexpression relates to immunologic disorders(16).

*cytokine storm, a phlogistic phenomenon fed by well-understood positive feedback loops that govern cytokine production and overwhelm counter-regulatory mechanisms.*

*The concept of COVID-19 as an endothelial disease provides a unifying pathophysiological picture of this raging infection, and provides a framework for a rational treatment strategy at a time when we possess an indeed modest evidence base to guide our therapeutic attempts to confront this novel pandemic."*

## *Physical exercise and immunity*

Physical exercise promotes health of several human organism systems: cardio-vascular**(21–23)**, endocrine**(17,24)**, psycho-logical**(25,26)**, immunological**(14,25,27)**, respiratory**(28)**. Such comprehensive benefits may explain the association of physical exercise with prevention of several cancer types**(29)**.

The effects of physical exercise that achieve all human body tissues are those that occur into the vascular endothelium – which is the crucial interface between the blood compartment and the tissues**(11)**. Libby and Lüscher**(11)** explained that the endothelium is the only surface on which, under physiological conditions, blood does not clot. The practice of physical exercise, with increased oxygen consumption, causes the blood to circulate with an increase in the tangential force of the blood flowing on the endothelial surface of the blood vessel phenomenon named "*shear stress*"**(30–33)**. The shear stress occurs during exercise promoting vascular adaptation, and even leads to a vessel remodeling**(34,35)**, due to those hemodynamic stimuli. Such beneficial changes induce functional and structural changes in the arterial wall through endothelial cell signal transduction**(36)**. Shear stress on endothelial cells is a potent stimulus for the nitric oxide (NO) production, and physical training involving repetitive physical exercise sessions, for weeks or months, regulates NO increasing in the endothelial bioactivity**(30)**. In the words of Green and Smith**(37)**: "*exercise is vascular medicine*".

Recently, scientists discovered that the mitochondrial system is a key component of an effective immune system**(14,38)**. Mitochondria are highly mobile organelles due to fission[5], fusion, transport and mitophagy – processes that together are called mitochondrial dynamics. That dynamic plays an important role in energy production, cell division, cell differentiation and cell death**(38)**. Xie et al.**(38)**, in a systematic review study, explained that by the last decade, many studies demonstrated the importance of mitochondrial metabolism for the immune system, with mitochondrial dynamics playing an essential role in immune responses, which are mediated by various types of cells, such as T, B, and other immune cells involved in the innate immune response. The control of the inflammation depends on the control of reactive oxygen species (ROS) in the mitochondria. The health of the mitochondrial system depends on hormesis, keeping the metabolism alert**(14)**. The factors that promote mitochondrial hormesis are physical exercise (in adequate doses), vegetable components in the diet and caloric restriction**(14,40,41)**. Physical exercise promotes the effect of hormesis, especially of the aerobic type, favoring the mitochondrial function, both in young and in the elderly**(14)**. Nunn et al.**(14)** explained that, on the one hand, the active muscle usually presents in an inflamed state, which, on the other hand, promotes compensation to the body, inducing powerful anti-inflammatory and antioxidant mechanisms. The authors**(14)** point out that physical exercise, as long as it's not done excessively, especially allowing enough time for recovery, is highly beneficial increasing the anti-inflammatory and antioxidant responses. Furthermore, scientists have shown that muscle has important immunological functions,

[5]Fission: the splitting of an atomic nucleus resulting in the release of large amounts of energy(39).

harboring and supplying antiviral stem cells, preventing T cell depletion and protecting the proliferative potential during inflammation**(14,42)**.

The literature indicates that moderate-intensity exercises stimulate cell immunity, while high-intensity exercises without adequate recovery time trigger a decrease in immunity**(43)**.

### *Physical activity, mental health and inflammation*

According to longitudinal epidemiological studies conducted population samples, people with increased inflammation are at higher risk for developing cardiovascular diseases**(44)**, type 2 diabetes**(45)** in addition to psychiatric disorders**(46)**. The literature shows that chronic mental stress and mood are psychosocial factors important predictors of longevity and well-being**(47)**. Studies showed that depression is independently associated with cardiovascular diseases, mortality from all causes and as comorbidity to chronic diseases and may worsen their prognoses**(47)**. Neuropsychiatric symptoms and mental illnesses are commonly present in patients with chronic systemic diseases**(48)**. Anxiety and depression are present in up to 50% of those patients, resulting in impaired physical recovery and a more complex treatment regimen**(48)**. Furthermore, stress associates with the physical and emotional aspects of systemic disease presenting harmful effects that can lead to comorbid mental disorders. According to Duric et al.**(48)**, psychological distress resulting from negative affective states increases inflammation and decreases immune function. Clinical reports indicated that the relationship between systemic and psychiatric diseases is bidirectional**(48)** – both chronic diseases affect mental health and mental health may be associated with chronic diseases development.

The literature shows that regular physical exercise is associated with reduced psychological stress and better mood and, consequently, can potentially mediate associations of depression and stress with health outcomes**(47,49–51)**. In that context, physical exercise plays an important role in reducing inflammation. Nevertheless, intensity should be carefully observed. Paolucci et al.**(52)** in an experimental longitudinal study (six weeks) showed that the optimal physical exercise for the mental health promotion together with decreased inflammation was continuous and moderate intensity exercise.

### *The relationship between physical activity and CoViD-19*

Science advances brings knowledge on CoViD-19 mechanisms while new evidence that physical activity can contribute to the prevention of CoViD-19 emerge. Silveira et al.**(43)** discussed in depth how physical exercise can be a tool to help the immune system to fight against CoViD-19. Zadow et al.**(53)** contributed to the analysis regarding coagulation interactions with the protective effect of physical exercise for CoViD-19. Nunn et al.**(14)** brought a deep and comprehensive analysis of the relationship of lifestyle – which deals with the level of physical activity and other habits in health, with CoViD-19. The immune function is dependent of mitochondrial function, which declines with aging process, but the decline rate can be modified by lifestyle**(14)**.

Hamer et al.**(54)**, conducted a longitudinal study of a prospective cohort in a population sample (n=387,109), in the United Kingdom. Lifestyle variables in relation to hospitalization by CoViD-19 were examined. The results exhibited showed that the relative risk (RR) of being hospitalized for the disease was higher among physically inactive (32%) and smokers (42%). Among obese individuals, the relative risk for hospitalization by CoViD-19 was higher than double compared to non-obese individuals (RR=2.05)**(54)**.

In Brazil, the study by Vancini et al.**(55)** found association of level of physical activity with the prevalence of symptoms of CoViD-19 ($p$= 0.0012), as shown in Table 1.

Considering the levels of physical activity, categories used in the study were:

**Tabela 1 –** Prevalência de sintomas de CoViD-19 segundo nível de atividade física (n=1.726), estudo de Vancini et al. (51), conduzido no Brasil

| **Level of physical activity** | ***n*** | **Freq. (%)** | **Prevalence of symptoms of CoViD-19 (%)** |
|---|---|---|---|
| Insufficient | 620 | 35.9 | 30.6 |
| Very low | 391 | 22.7 | 36.1 |
| Low | 425 | 24.6 | 19.4 |
| Intermediate | 187 | 10.8 | 13.9 |
| High | 103 | 6.0 | - |
| | *1.276* | *100.0* | - |

Prevalence of CoViD-19 symptoms according to level of physical activity. **Freq.:** Relative frequency. Likelihood ratio test $p$=0.0012.

Very Low; Low; Intermediate; and High**(55)**. In the sample studied (n=1,726), most had insufficient activity level (35.9%). As observed at Table 1, the lowest levels of physical activity were the ones with the highest prevalence of CoViD-19 symptoms. As the level of physical activity increased, the prevalence decreased, and the group with a high level of physical activity (n=103) did not present any case.

Yanuck et al.**(56)** presented a study outlining an evidence-based strategy to improve clinical outcomes in CoViD-19 using a phased immuno-physiological approach to the disease from prevention to recovery.

The four phases of CoViD-19**(56)** are:

1) Prevention – the focus lies on the efficiency of immunological surveillance and in the reduction of basal levels of inflammation, with the purpose of improving the prognosis if the individual is infected;

2) Infection – the focus is immune activity against infection;

3) In-creasing inflammation – the focus is on anti-inflammatory measures; and

4) Recovery – the focus is on resolving inflammation, inhibiting fibrosis and other forms of tissue damage, reducing losses in immune function by restoring and reoptimizing it. As it has been observed, to prevent patients to fall into the phase of increasing inflammation, it is essential that clinical surveillance continue in the recovery phase.

Physical exercise should be present in the prevention phase keeping the immune system alert, improving endothelial function, reducing oxidative stress and decreasing inflammation. The authors proposed that the exercise should follow the recommendations regarding moderate intensity to favor and improve the immune system**(43,53)**.

In brief, the literature indicates that:

1. The mitochondrial system is a key component of an effective immune system**(14,38)**.
2. The lifestyle to promote mitochondrial health, contributing to the maintenance of the immune system, includes Practice of physical exercise, diet that includes vegetables and caloric reduction**(14)**.
3. Physical exercise promotes the effect of hormesis, especially of the aerobic type**(14)**.
4. Physical exercise favors the mitochondrial function, both in young and in the elderly**(14)**.
5. Regularity and intensity of physical exercise to improve endothelial function, immunity and mental health need to be observed**(43,53)**.
6. Physical exercise promotes *shear stress***(34,35)**.

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7. Shear stress promotes vascular adaptation, and even leads to a vessel remodeling, and is a potent stimulus for the nitric oxide (NO) production (anti-oxidative effect) **(34,35)**.
8. Muscle has important immunological functions: harboring and supplying antiviral stem cells, preventing T cell depletion and protecting the proliferative potential during inflammation**(14,42)**.
9. Physical exercise intensity to improve immunity and mental health should be moderate**(43,53)**.
10. "*Exercise is vascular medicine*" - Green and Smith**(37)**.

### *Strengths and limitations of the study*

The strong point was to gather knowledge about the relationship between physical exercise and a new disease that affects the world in a pandemic: CoViD-19.

One limitation of the study is that this is not a systematic review with the broad and well-defined scope and delimitations. However, most of the studies that were part of the present study were composed of review studies, in addition to clinical trials and epidemiological studies with population sample, which confers high reliability to the report.

## Conclusion

This study was a brief review of the literature about the relationship of physical exercise with immunity, prevention and recovery of CoViD-19.

The main findings were that exercise promotes mitochondrial health, contributing to the maintenance of the immune system. In addition, the intensity of physical exercise is an important factor to improve endothelial function, immunity and mental health, and the recommendation is that and should be performed at moderate intensity. Another fundamental factor for the organic benefits to be achieved is that the regularity of physical exercise is maintained.

In this sense, the literature has, to date, two studies showing an inverse association with CoViD-19:

1. The higher the level of physical activity there were fewer symptoms of the disease, and at the higher level there were no cases of CoViD-19 symptoms; and
2. Physically inactive people have a 32% higher risk of being hospitalized for CoViD-19.

Considering that obesity increases the risk of worsening of the disease and that higher levels of physical activity have shown a protective effect for symptoms and hospitalization by CoViD-19, it is recommended to practice regular exercises both for health promotion and for the prevention of CoViD-19.

### *Declaração de conflito de interesses*

Não há conflito de interesses em relação ao presente estudo.

### *Declaração de financiamento*

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