

# Effect of physical activity on COVID-19 symptoms: A narrative review

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## ABSTRACT

In 2019, a new condition caused by the COVID-19, became a global pandemic, presenting a disparate symptomatological picture. The immune response to the virus depends on multiple factors, making the practice of physical exercise an important enhancer of the immune system, but it is unknown what effects it could have on the very different symptoms. In order to achieve and summarize the most outstanding information on the influence of the different types and parameters of physical exercise on the immune system and symptoms presented by COVID-19, it was decided to carry out a review of the literature in the databases PubMed and Medline until August 2020. The results showed that while high intensity and prolonged volume exercise produces counterproductive alterations in the immune system, increasing the possibility of contracting infections; low and moderate intensity exercise reverses these effects, increasing the benefits, providing the body with better protection against viruses. For the symptoms of COVID-19 related to cough, dyspnea, pulmonary obstruction, hypoxia, muscle pain and neuromuscular conditions, exercise at low and moderate intensity is recommended, while those people who present gastrointestinal symptoms and fatigue are recommended to exercise at low intensity. Exercise is completely contraindicated in case of fever and myocarditis.

**Keywords:** Physical activity; Immune system; Coronavirus; Symptomatology.

### Cite this article as:

Fritz, N.B., Gene-Morales, J., Saez-Berlanga, A., Babiloni-López, C., Jueas, A., & Colado, J.C. (2021). Effect of physical activity on COVID-19 symptoms: A narrative review. *Journal of Human Sport and Exercise*, 16(4proc), S2042-S2056. <https://doi.org/10.14198/jhse.2021.16.Proc4.51>

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Abstract submitted to: Spring Conferences of Sports Science. [Costa Blanca Sports Science Events](#), 21-22 June 2021. Alicante, Spain.

JOURNAL OF HUMAN SPORT & EXERCISE ISSN 1988-5202.

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doi:10.14198/jhse.2021.16.Proc4.51

## INTRODUCTION

The world we know has changed due to the spread of the new coronavirus SARS-CoV-2, which causes the COVID-19 disease, which has infected more than 38.9 million people, while the world number of deaths is found above one million (World Health Organization, 2020).

The planet first suffered from the coronavirus in 2002-2003 due to Severe Acute Respiratory Syndrome (SARS) and in 2011 due to Middle East Respiratory Syndrome (MERS) (Chowdhury et al., 2020). These causative agents of both cases (SARS-CoV and MERS-CoV) were recognized with origin in an animal species, while the current coronavirus emerged for the first time in Wuhan (China), at the end of 2019.

People infected by COVID-19 suffer from serious respiratory conditions, being the population with comorbidities and the elderly the most prone to developing this infection. Currently there is no treatment or vaccine with proven effectiveness, however, there are more than 200 experimental vaccines in development, of which more than 60 are in the clinical phase in many countries. (World Health Organization, 2020).

Regardless of the hope placed on vaccination, we must not forget the importance of physical exercise as the simplest and most economical tool to optimize the life quality of the population, in addition to foreseeing and improving the health status of patients infected with SARS-CoV-2.

### ***Impact of COVID-19 on the human body***

According to the studies by Guo et al. (2020) and Guan et al. (2020) the current coronavirus is transmitted thanks to the respiratory droplets of coughs, sneezes or speech. Penetrating through the nasal system by inhalation, beginning to spread until reaching the respiratory tract. There it faces a stronger congenital immune response. Throughout this contagion stage, the disease is exposed clinically, presenting symptoms such as fever, cough, dyspnea, muscle aches and fatigue, headaches, gastrointestinal disorders, cardiovascular problems, etc. It has been shown that the ailment will be mild for 80% of infected patients and in general it will stick to the upper respiratory tract and through conservative symptomatic therapy, patients could be monitored at home. On the contrary, approximately 20% of infected patients will suffer from pulmonary infiltrates and some of them will develop a very severe pulmonary infection picture, which will even require ventilatory assistance in intensive care units.

The mortality rate of patients with the current severely diagnosed coronavirus can reach 50% (Chen et al., 2020; Huang et al., 2020; Wang et al., 2020) and age is the main risk factor in the most serious cases, this is also compounded by the presence of severe underlying diagnoses and comorbidities such as obstructive pulmonary disease, coronary heart disease, chronic kidney disease, malignant tumour, high blood pressure, among others.

### ***Human immune system against COVID-19***

Around the entire human body are numerous immune organs (angina and adenoids; lymph nodes and lymphatic vessels; thymus; spleen; appendix; Peyer's patches; bone marrow) that have the function of protecting the organism from infections (Chowdhury et al., 2020). Now, following the works of Elgert (2009), Guyton & Hall (2011) and Mitchell et al. (2017), the human immune system can be classified into three levels: 1) innate immunity, which is the rapid response; 2) adaptive immunity, which is the slow response; 3) and passive immunity. The latter is classified into two subtypes, and they are the artificial immunity that we receive from medicine and the natural immunity that we receive from the mother. When the body encounters any

virus or germ for the first time, the immune system does not have the ability to operate effectively and we become ill, this situation is what has occurred in the case of SARS-CoV-2.

New research (Mohammadi et al., 2020; Wang et al., 2020; Wu et al., 2020) suggests that, in mild diagnoses, macrophages in lung tissue are able to withstand COVID-19, thus natural and adaptive immune responses are optimally fired against viral replication. Although, serious coronavirus diagnoses are related to an imbalance in antiviral immunity, determined by two primary circumstances: 1) a storm of pro-inflammatory cytokines (a defensive immune reaction that is potentially fatal); and 2) a state of lymphopenia in the blood. The cytokine storm and the degree of lymphopenia is linked to the severity of the coronavirus. This is due to the activation of the complement system, which has a powerful capacity to recruit inflammatory cells and stimulate neutrophils, which can cause tissue damage (da Silveira et al., 2020; Liu et al., 2020).

An earlier study by Lu et al. (2020) talks about the existence of similar circumstances in other respiratory viral diseases, such as SARS-CoV, MERS-CoV and the flu. Both of the aforementioned situations, together with circulatory alterations and viral spread (spread to other tissues through the blood or the lymphatic system) to various organs, are the causes of viral sepsis (Prompetchara et al., 2020).

### ***Influence of physical exercise on the immune response***

Physical practice is considered one of the most important components for a healthy life. The regular practice of physical activity stimulates improvements in the quality of life. In addition to fulfilling functions related to the prevention of excess body weight, chronic non-transmittable diseases and systemic inflammation (da Silveira et al., 2020). For all these reasons, physical exercise is considered a beneficial tool to reduce transmittable diseases, including viruses. Now, the practice of physical exercise, both in its moderate form and in its high intensity form, significantly alters the immune system (Peake et al., 2015, Peake et al., 2017). Nieman & Wentz's (2019) research indicates that the modulation of the immune response associated with physical activity depends on elements such as duration, intensity, regularity, and the type of effort made. Moderate intensity physical exercises stimulate cellular immunity, while high intensity or prolonged exercise without an adequate break can cause a decrease in cellular immunity, increasing the predisposition to infectious diseases. Therefore, according to the International Society for Exercise and Immunology (ISEI), the loss of the immune system occurs just after prolonged physical exercise, that is, after 90 minutes of moderate to high intensity physical exercise.

Therefore, the present work aims to carry out a narrative bibliographic review related to the effect of physical activity on the symptomatology of SARS-CoV-2, and how physical activity can also modify the immune system. We consider that physical activity is the simplest and cheapest tool not only to improve people's lives, but also to prevent and improve the health of those affected by the coronavirus.

## **METHODS**

The methodology used to carry out the bibliographic research and the steps carried out to achieve it are presented below.

### ***Sources and research in literature***

In order to carry out this search, the PUBMED and MEDLINE databases were used, obtaining from both of them original articles, primary and secondary documents, and systematic reviews. To delimit the tracking, it was stipulated to segment the criteria for the search. First, articles on the specific topic of SARS-CoV-2 symptomatology, its influence on the human body's immune system, as well as the beneficial role that

physical exercise can have on the virus, were recovered with a time limit (August 2020). While for questions of the influence of physical activity on symptoms presented by the coronavirus, the research published from the year 2010 to August 2020 was accepted as a limit. No language restriction was used.

### **Search methodology**

For the article search in the different databases, different algorithms formulated with the keywords linked by Boolean operators were used. The different algorithms treated are listed below: 1) The first algorithm tested was: ("*physical activity*" OR "*exercise*" OR "*training*" OR "*sport*") AND ("*immune system*"); 2) The second algorithm tested was: ("*physical activity*" OR "*exercise*" OR "*training*" OR "*sport*") AND ("*Coronavirus*" OR "*SARS-CoV-2*" OR "*COVID-19*"); 3) The third algorithm tested was: ("*physical activity*" OR "*exercise*" OR "*training*" OR "*sport*") AND ("*cough*" OR "*fever*" OR "*dyspnea*" OR "*fatigue*" OR "*muscle pain*" OR "*gastro intestinal tract*" OR "*myocarditis*" OR "*COPD*"). By virtue of the documents obtained, an attempt was made to obtain a superior bibliography of the subject through two ways: 1) Through the recommendations made automatically by the database server; 2) Obtaining the articles that are remarkable to us from the bibliography.

In order to materialize the bibliographic search, the items described by Aranda (2006) were continued for the preparation of bibliographic reviews. First, we began by determining the keywords to begin the search and to be able to recognize the references that could be useful thanks to the computerized search. While this step was being elaborated, the suitability of the texts was examined according to the variables specified in our selection criteria and our algorithms, established subsequently, through a first filter according to the title and a second according to its abstract. After this, the document is studied and the appropriate notes are written down, compiling them by the variables that it dealt with, and the references collected in the same article were examined to carry out the indicated screen and observe their value for our study. To conclude, these notes were compiled and organized in order to write the review.

### **Selection criteria**

The search for relevant articles to develop the objective of this study was carried out by 3 reviewers. If there was uncertainty regarding the eligibility of a study, the summary was obtained and added to the next phase of the review for further clarification. Then, the summaries were selected to determine their eligibility considering 3 key points: 1) The study provides information on the different effects that physical activity has on people's immune systems; 2) The study provides information on the impact of COVID-19 on physical activity and vice versa; and 3) The study provides information on the different effects that physical activity has on cough, fever, chronic lung disease, dyspnea, alterations in the gastrointestinal tract, fatigue, muscle aches and / or myocarditis.

Eligible summaries were included in the full-text recovery stage only if they fulfilled the 3 criteria described above. In case that the clarification about any of these criteria was needed, the reviewers consulted an external collaborator.

### **Methodological quality**

All the selected works had to be indexed in databases that use blind peer reviews for approval with the editorial committee.

Table 1. Effect of exercise on the symptoms present in the coronavirus.

Author	Type of study	Population	Variable Symptom Covid	Physical Exercise Intervention	Evaluation	Effects of the exercise/Recommendation *
Dick & Diehl (2013)	Clinical review	Athletes	Fever	Mild-moderate intensity + Shorter duration = ↑ immunity Prolonged high intensity = ↓ immunity	-	↓ muscle power ↓ muscle endurance ↑ muscle catabolism ↓ exercise tolerance ↑ fatigue <b>* Exercise NOT recommended</b>
Demoulin-Alexicova et al. (2017)	Experimental	30 non-asthmatic children (average age: 10 years; 17 men) and 29 non-asthmatic adults (average age: 10 years; 12 men)	Cough	Continuous running on a motorized treadmill at a HR ≥ 80% predicted for the age. Exercise duration: 3-4 minutes	Cough reflex sensitivity	Adults and children: ↑↑ bronchodilation ↑↑ pulmonary blood flow ↓↓ cough <b>*Recommended exercise</b>
Katajisto et al (2012)	Descriptive	719 people with COPD (average age: 63.4 years)	Dyspnea Pulmonary obstruction	Physical activity level record. The active group performed sports such as skiing, golf, yoga, rowing, bowling, swimming, etc.	Self-reported questionnaire: level of physical activity, dyspnea, and barriers to exercise. Spirometries	Active people ↓↓ subjective perception of dyspnea ↓↓ bronchial obstruction <b>*Recommended exercise</b>
Svensden et al. (2016)	Experimental	12 active and healthy men (average age 28 ± 4 years)	Hypoxia	Cycling for 75 minutes in hypoxic and normoxic conditions	Markers of systemic immunity: before, during, after exercise and 2 hours after finishing it.	Hypoxia does not influence post-exercise cytokine production Hypoxia does not impair the immune system <b>*Recommended exercise</b>
Soogard, and Siogaard (2017)	Systematic revision	Active working population (17 randomized controlled trial)	Muscle pain	Tasks where the target muscle affected by pain is worked	EMG measurements Biopsy and microdialysis techniques	Strength exercise: ↓↓ pain ↑↑ maximum muscle activation ↑↑ muscle power ↑↑ cross sectional area ↑↑ number of satellite cells.  Aerobic exercise: ↑↑ blood flow ↑↑ oxygenation ↓↓ pain <b>*Aerobic and muscular strength exercise recommended</b>
Halle et al. (2020)	Clinical review	Recreational and elite athletes with acute myocarditis	Myocarditis	Moderate intensity, after 1 to 3 months of the event with normal reassessment. High intensity or competition not recommended until 6 months after the event, with normal reassessment.	Echocardiography at rest. Cardiac magnetic resonance 24 h Holter. Maximum exercise tests. Cardio-pulmonary exercise tests with spirometry	↑ risk of myocarditis on overtraining. <b>* Exercise not recommended: in acute disease phases.</b> <b>* Low / moderate intensity exercise recommended in recovered patients (regenerative intensity &lt;50% VO<sub>2max</sub>.)</b>

Table 1 (Cont.). Effect of exercise on the symptoms present in the coronavirus.

Author	Type of study	Population	Variable Symptom Covid	Physical Exercise Intervention	Evaluation	Effects of the exercise/Recommendation *
Ament & Verkerke (2009)	Clinical review	General population	Fatigue	Prolonged exercise in time (45-60 min.) To moderate-high intensity (60 - 80% HRmax.)	-	↑↑ energy consumption ↑↑ metabolites and heat: affect homeostasis of the internal environment ↑↑CNS fatigue ↑↑ blood concentration of cytokines, which ↑↑ feeling fatigued <b>*Moderate-high intensity exercise NOT recommended</b>
Egerton et al. (2015)	Cohort	980 seniors between 70 - 77 years (471 women)	Fatigue	Physical daily activity level record.	Self-reported fatigue (Fatigue Severity Scale) Physical Activity: steps per day, minutes of moderate and vigorous physical activity, minutes of physical activity per day and average energy expenditure Physical condition: sit-to-stand (speed) and cardiorespiratory fitness test on a treadmill (↑ VO <sub>2peak</sub> )	↓↓ obesity ↑↑ speed getting up from a chair ↑↑ VO <sub>2peak</sub> ↓↓ comorbidity and health problems ↓↓ number of prescription drugs ↑↑ physical activity level ↑↑ quality of life <b>* Recommended practice of regular exercise</b>
Puetz et al (2006)	Systematic review and meta-analysis	Adults with fatigue (Average age: 49 ± 10 years; 88% women)	Fatigue	Walk of at least 20-30 minutes, 3 times or more per week	Vitality scale of the SF-36 questionnaire	↓↓ risk of fatigue <b>* Low intensity exercise recommended</b>
Narici et al. (2020)	Clinical review	Sedentary people sick with coronavirus	Neuromuscular conditions	Regular, high-volume and low-intensity exercise Combine aerobic exercise and muscle strength training. Meet > 5,000 daily steps (range 4500-6000 steps/day)	-	↓↓neuromuscular degeneration ↓↓muscular atrophy ↑↑protein synthesis ↑↑cardiorespiratory fitness ↑↑glucose homeostasis <b>*Recommended high volume and low intensity exercise</b>
Peters et al. (2001)	Clinical review	Active people and athletes with gastrointestinal problems	Gastrointestinal tract problems	Prolonged physical exercise for months (light continuous running, walking, cycling, etc.)	-	Vigorous exercise (temporary effects) ↑↑nausea ↑↑ acidity ↑↑ diarrhea Low intensity exercise: ↑↑ protection of the gastrointestinal tract ↑↑ gastrointestinal motilities ↑↑ gastrointestinal blood flow <b>*Low intensity exercise recommended</b>

(↓) Reduction; (↓↓) Statistically significant reduction; (↑) Increase; (↑↑) Statistically significant increase; (HR) Heart Rate; (COPD) Chronic Obstructive Pulmonary Disease; (EMG) Electromyography; (ECG) Electrocardiogram; (VO<sub>2 peak</sub>) Volume of oxygen peak; (MR) Maximum Repetition.

## RESULTS

### **Features of the studies**

Once the search was carried out, complying with the steps previously explained, a total of 64 articles were retrieved, of which 40 were original scientific articles and 24 were reviews (clinical, systematic or meta-analysis). And after applying the filters, 11 articles were selected, corresponding to studies that analysed the possible interaction that physical exercise could generate in the different symptoms that are present today in COVID-19. In the Table 1 the main characteristics of the studies, study population, symptom related to COVID-19, as well as the intervention carried out and its results are summarized.

## DISCUSSION

The objective of this bibliographic review was to describe the effect of physical activity on the symptomatology presented by the SARS-CoV-2, and how physical activity can also modify the immune system. Under this premise and after the analysis of the data obtained, it was observed that the practice of physical exercise at low and moderate intensity is recommended for most of the symptoms related to COVID-19 such as: cough, dyspnea, pulmonary obstruction, hypoxia, muscle pain, and neuromuscular conditions, while regular low-intensity exercise is recommended for those with gastrointestinal symptoms and fatigue. However, exercise is totally contraindicated in case of fever and symptomatic acute myocarditis.

In addition, it is recognized that having an active lifestyle is a protective factor when the severity of these symptoms does not increase, so it is essential to avoid a sedentary lifestyle and change in eating habits that generate weight gain, growth of adipose tissue, among other damage to health (Andersen et al., 2016; Ayres, 2020; Sanchis-Gomar et al., 2020), due to its significant relationship with the reduction of physical condition, functional loss and increase comorbidities (Nieman & Wentz, 2019). In addition, being physically active is associated with lower risks of reactivation of latent viral infections in situations of isolation and confinement, which entails having a favoured immune system compared to subjects with less physical fitness (Damiot et al., 2020).

For all these reasons, physical activity has been, is and will be the best and cheapest non-pharmacological tool for the prevention and treatment of diseases of psychological, physical and / or metabolic origin (Raiol, 2020). Entities of great global impact such as the World Health Organization (WHO) and the American College of Sports Medicine (ACSM) recommend that physical exercise be maintained on a regular basis and at appropriate intensity levels, prescribed by exercise and health professionals, both in situations of normality and social isolation, since it helps to reinforce the immune system against SARS-CoV-2 (Denay et al., 2020). Among the exercises that the ACSM recommends are: aerobic exercises and strength training, both at moderate intensities and with the possibility of being able to perform them both at home and outdoors when permitted by government authorities (ACSM, 2020).

Regular physical activity at moderate intensity carries numerous benefits at the immune level, such as: improvement in the body's immune protective function against pathogens; increased exchange of white blood cells between tissues and the circulatory system; and the decrease in comorbidities (Cornish et al., 2020; da Silveira et al., 2020; Kohut et al., 2009; Nieman & Wentz, 2019; Pedersen & Hoffman-Goetz, 2000). However, there is clear evidence that high workloads and high intensity physical activities, along with the associated metabolic, psychological and physiological stress, cause immune system dysfunction, oxidative stress, muscle damage and inflammation (Nieman & Wentz, 2019; Peake et al., 2015, 2017; Simpson et al., 2020).

But is it known the effects that physical activity has on the current coronavirus? There is no clear evidence, but despite the few concrete data on the way in which physical exercise increases the immune response against the current virus, there is evidence that the number of acute respiratory infections, the intensity and duration of symptoms, as well as the risk of mortality due to infectious respiratory diseases is lower in subjects who exercise adequately and regularly (Nieman & Wentz, 2019). All of the above is caused by the fact that during regular physical activity, stress hormones and inflammatory responses decrease. While lymphocytes, monocytes and natural killer (NK) cells are found in high proportions (Nieman & Wentz, 2019). In this way, there is an improvement in immunity, as well as a decrease in the systemic inflammatory process, aspects that certify that regular physical exercise leads to the improvement of the immune system, at the same time that it helps to prevent respiratory conditions and, consequently, to be preserved against viruses such as coronavirus (Hammami et al., 2020; Nieman, 2020; Nyenhuis et al., 2020; Steinacker et al., 2020; Timpka, 2020). In contrast, strenuous physical activity before or throughout an infectious situation, such as the coronavirus or the flu, can cause significant health conditions due to changes in the immune system (Gleeson et al., 2012). This happens due to the production of anti-inflammatory cytokines to reduce the damage of muscle tissue, although in strenuous activities this effect can give levels of immunosuppression, thus causing the occasion of suffering an infection (Gleeson et al., 2012; Nieman & Wentz, 2019). Therefore, more consideration should be given to the importance of promoting physical activity at appropriate performance levels. All this is more important if we pay attention to the elderly population, as physical exercise is even more essential, since these subjects normally have more comorbidities and, in correspondence with the current coronavirus, are more vulnerable to suffering from the condition (Damiot et al., 2020; Ferreira et al., 2020).

### ***Effects of physical activity on the symptomatology presented by COVID-19***

#### *Fever*

In the case of infections that cause fever, such as the current virus, they can be harmful to any type of population, including physically active people (Broom, 2007). According to Dick & Diehl (2013), fever affects the body's ability to regulate body temperature and increases fluid loss. These effects can be aggravated if the person exercises in a hot climate, causing a greater risk of suffering dehydration and heat injuries (heat stroke, heat exhaustion, etc.) if they exercise with a fever. Additionally, febrile injuries have been shown to reduce muscular endurance and strength, exercise tolerance, and increase fatigue, so any benefit from exercising during fever is questionable (Dick & Diehl, 2013; Harris, 2011). Ultimately, if the subject has systemic symptoms, such as fever, myalgia, among others, they should abstain from sports practice until the symptoms have resolved for a period of approximately 7 to 14 days (Dick & Diehl, 2013).

#### *Cough*

There is clear evidence that exercise appears to modulate the cough reflex response (Demoulin-Alexikova et al., 2017). Clinical studies in normal and asthmatic subjects have shown airway dilation and/or cough suppression during exercise. Therefore, the ventilatory response to exercise has a strong potential to modulate cough, since voluntary hyperventilation, as well as that induced by exercise in adults, suppresses cough (Eckert et al., 2006). Likewise, exercise-induced bronchodilation together with increased pulmonary blood flow facilitate cough inhibition (Demoulin-Alexikova et al., 2017).

#### *Pulmonary obstruction and Dyspnea*

It has been shown that physically active patients suffering from COPD reduced the subjective perception of dyspnea (Katajisto et al., 2012), despite the fact that the perception of dyspnea was the most significant explanatory factor for inactivity when exercising (Katajisto et al., 2012; Troosters et al., 2010). Physical activity is significantly correlated with subjective dyspnea reported by patients, health-related quality of life, mobility,



and bronchial obstruction. Consequently, numerous studies call for the creation of rehabilitation programs adapted to the needs of the person and that recognize the exercise history of patients, thus supporting the subject's own exercise preferences (Bossenbroek et al., 2011; Kantorowski et al., 2018; Katajisto et al., 2012; Shin, 2018).

### *Hypoxia*

Regarding the symptom of hypoxia, the study by Svendsen et al. (2016) shows that the effect of hypoxia is not large enough to influence cytokine production in post-exercise, so it is unlikely to significantly impair the subject's defences. The main conclusion of the previous study was that, despite offering a somewhat greater response to stress, as indicated by the presence of hormones in the plasma after exercise (e.g., cortisol), physical activity in a hypoxic state does not seem to pose any significant additional threat to immune function. However, despite the above data, numerous studies recommend a little more caution during the 2-hour window immediately after exercise, in order to minimize exposure to pathogens (Lancaster et al., 2004; Lancaster et al., 2005; Svendsen et al., 2016).

### *Muscle pain*

Throughout the scientific community it is recognized the beneficial effects of aerobic strength and resistance training to reduce muscle pain and problems in the neuromuscular system. In the work of Sogaard & Sjogaard (2017), strength training was applied to the muscles affected by pain and initially, the pain increased after an exercise session, but after a training period of 10 weeks, a significant decrease was found. Additionally, maximal muscle activation, muscle cross-sectional area (in type II fibres), satellite cell number, and strength also increased. While aerobic training caused a temporary reduction of pain after the end of each exercise session. Also, during a standardized repetitive work stage, improved blood flow and oxygenation were observed, as well as a reduction in sensitivity to both peripheral and central pain.

Now, thinking of bedridden patients, they may see their muscles affected due to high periods of inactivity. Despite this, an important fact to comment is that there are equally valid alternatives in order to prevent the neuromuscular system from worsening, as is the case with exercises using one's own body weight or elastic resistance bands. The work of Narici et al. (2020) has shown that strength training with low loads and high volume (30% 1 RM; around 24 repetitions) leads to a greater increase in protein synthesis in order to battle neuromuscular degeneration and muscle atrophy (Bellar et al., 2011; Martins et al., 2013). Ultimately, regardless of whether the patient is bedridden or not, daily exercise is essential to counteract the effects of inactivity.

### *Fatigue*

Prolonged exercise has been shown to consume a lot of energy affecting long-term fuel reserves and the central nervous system (Ament & Verkerke, 2009). Likewise, physical activity increases the blood concentration of cytokines released by the muscles, which leads to an increase in the feeling of fatigue during exercise (Ament & Verkerke, 2009). In short, the perception of fatigue is equivalent to less exercise, which implies a worsening of the quality of life and an increase in health problems and comorbidities, especially in the elderly population (Egerton et al., 2015; Puetz, 2006).

### *Myocarditis*

Halle et al. (2020) in their study showed that factors such as an impaired immune system, sleep deprivation or exhausting efforts can cause myocarditis. In addition, continuous physical training coupled with symptoms of common cold infection can be an additional factor that, when combined, can cause different pathogens to break through physical barriers, spread systemically, and affect the myocardium (Halle et al., 2020).

Anyone with impaired cardiovascular function due to myocarditis during its acute phase, even with full recovery, should be advised to refrain from high-intensity physical activity for at least 6 months (Pelliccia et al., 2019). Once the results are normal, they are advised to start with a regenerative intensity resistance exercise ( $<50\% \text{VO}_{2\text{max.}}$ ), which will then gradually increase in duration and intensity (moderate  $50\text{-}70\% \text{VO}_{2\text{max.}}$ ) for 4 -6 weeks before resuming higher intensity exercise (Eichhorn et al., 2020; Maron et al., 2015; Pelliccia et al., 2019).

#### *Gastrointestinal tract problems*

Finally, in the case of gastrointestinal tract problems, science confirms that vigorous exercise can cause gastrointestinal symptoms such as nausea, heartburn, or diarrhea (ter Steege et al., 2008). Despite the above, these symptoms are temporary in effect, so that in the long term the health of the subject is not in danger (Peters, 2001). However, periods of relatively low intensity repetitive exercise, such as continuous running, walking or cycling, can have protective effects on the gastrointestinal tract, since physical activity decreases gastrointestinal blood flow and increases gastrointestinal motility (Peters, 2001).

Finally, the main limitation of this review is found in the reviewed papers, which refer to studies with a type of sample and under conditions that are very different from those of the current situation. However, to our knowledge, there are not enough studies that have related these variables under the current context of pandemic in which the world finds itself. That is why it is essential that future research, study different exercise programs, with different intensities and volumes, in which the different symptoms in patients affected by the virus are measured pre and post intervention, it would be much more representative, and can also study the effects on the immune system.

## **CONCLUSION**

After the reading of the articles retrieved for the review, it has been seen that with regard to exercise/physical activity and the different symptoms that the current coronavirus presents, there is still much to discover. Based on the available evidence reviewed, it has been shown that exercise at high intensity and prolonged volume produces counterproductive alterations in the immune system, increasing the possibility of contracting infections; on the contrary, low and moderate intensity exercise reverses these effects, increasing the benefits in the immune system and providing the body with better protection against viruses such as the current coronavirus.

Regarding the practice of physical exercise specifically for the symptoms of the current coronavirus, it is possible to recommend low and moderate intensity physical exercise in people who present as symptoms of COVID-19: cough, dyspnea, pulmonary obstruction, hypoxia, muscle pain and neuromuscular conditions. While in those people who present gastrointestinal symptoms and fatigue, exercise at low intensity is recommended. In addition, exercise is totally contraindicated in case of fever and symptomatic acute myocarditis. Unfortunately, it is not possible to make a recommendation on the recommended training modality, although it is recognized that having an active lifestyle is a protective factor for the development of the severity of symptoms, which is why future research should address the potential effects of different training modalities on the immune system and COVID-19 symptoms.

## **REFERENCES**

- Ament, W., & Verkerke, G. J. (2009). Exercise and Fatigue. *Sports Medicine*, 39(5), 389-422. <https://doi.org/10.2165/00007256-200939050-00005>

- Andersen, C. J., Murphy, K. E., & Fernandez, M. L. (2016). Impact of Obesity and Metabolic Syndrome on Immunity. *Advances in Nutrition*, 7(1), 66-75. <https://doi.org/10.3945/an.115.010207>
- Aranda, F. (2006). Presentación por escrito de la revisión bibliográfica. Buenos Aires. Universidad Adventista del Plata. Secretaría de Ciencia y Técnica. Available at: <http://paveca3.blogspot.com/2010/11/presentacion-por-escrito-dela-revision.html>
- Ayres, J. S. (2020). A metabolic handbook for the COVID-19 pandemic. *Nature Metabolism*, 2(7), 572-585. <https://doi.org/10.1038/s42255-020-0237-2>
- Bellar, D. M., Muller, M. D., Barkley, J. E., Kim, C. H., Ida, K., Ryan, E. J., Bliss, M. V., & Glickman, E. L. (2011). The Effects of Combined Elastic- and Free-Weight Tension vs. Free-Weight Tension on One-Repetition Maximum Strength in the Bench Press. *Journal of Strength and Conditioning Research*, 25(2), 459-463. <https://doi.org/10.1519/jsc.0b013e3181c1f8b6>
- Bossenbroek, L., de Greef, M. H., Wempe, J. B., Krijnen, W. P., & ten Hacken, N. H. (2011). Daily Physical Activity in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, 8(4), 306-319. <https://doi.org/10.3109/15412555.2011.578601>
- Broom, M. (2007). Physiology of fever. *Paediatric Nursing*, 19(6), 40-44. <https://doi.org/10.7748/paed.19.6.40.s32>
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., & Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, 395(10223), 507-513. [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7)
- Chowdhury, M. A., Hossain, N., Kashem, M. A., Shahid, M. A., & Alam, A. (2020). Immune response in COVID-19: A review. *Journal of Infection and Public Health*, 13(11), 1619-1629. <https://doi.org/10.1016/j.jiph.2020.07.001>
- da Silveira, M. P., da Silva Fagundes, K. K., Bizuti, M. R., Starck, D., Rossi, R. C., & de Resende e Silva, D. T. (2020). Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. *Clinical and Experimental Medicine*, 21(1), 15-28. <https://doi.org/10.1007/s10238-020-00650-3>
- Damiot, A., Pinto, A., Turner, J., & Gualano, B. (2020). Immunological Implications of Physical Inactivity among Older Adults during the COVID-19 Pandemic. *Gerontology*, 66(5), 431-438. <https://doi.org/10.1159/000509216>
- Demoulin-Alexikova, S., Marchal, F., Bonabel, C., Demoulin, B., Foucaud, L., Coutier-Marie, L., Schweitzer, C. E., & Ioan, I. (2017). Down-Regulation of Cough during Exercise Is Less Frequent in Healthy Children than Adults. Role of the Development and/or Atopy? *Frontiers in Physiology*, 8. <https://doi.org/10.3389/fphys.2017.00304>
- Denay, K. L., Breslow, R. G., Turner, M. N., Nieman, D. C., Roberts, W. O., & Best, T. M. (2020). ACSM Call to Action Statement: COVID-19 Considerations for Sports and Physical Activity. *Current Sports Medicine Reports*, 19(8), 326-328. <https://doi.org/10.1249/jsr.0000000000000739>
- Dick, N. A., & Diehl, J. J. (2013). Febrile Illness in the Athlete. *Sports Health: A Multidisciplinary Approach*, 6(3), 225-231. <https://doi.org/10.1177/1941738113508373>
- Egerton, T., Chastin, S. F. M., Stensvold, D., & Helbostad, J. L. (2015). Fatigue May Contribute to Reduced Physical Activity Among Older People: An Observational Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 71(5), 670-676. <https://doi.org/10.1093/gerona/glv150>
- Elgert, K. D. (2009). *Immunology: understanding the immune system*. John Wiley & Sons.

- Eichhorn, C., Bière, L., Schnell, F., Schmied, C., Wilhelm, M., Kwong, R. Y., & Gräni, C. (2020). Myocarditis in Athletes Is a Challenge. *JACC: Cardiovascular Imaging*, 13(2), 494-507. <https://doi.org/10.1016/j.jcmg.2019.01.039>
- Eckert, D. J., Catcheside, P. G., Stadler, D. L., McDonald, R., Hlavac, M. C., & McEvoy, R. D. (2006). Acute sustained hypoxia suppresses the cough reflex in healthy subjects. *American journal of respiratory and critical care medicine*, 173(5), 506-511. <https://doi.org/10.1164/rccm.200509-1455OC>
- Ferreira, M. J., Irigoyen, M. C., Consolim-Colombo, F., Saraiva, J. F. K., & De Angelis, K. (2020). Vida Fisicamente Ativa como Medida de Enfrentamento ao COVID-19. *Arquivos Brasileiros de Cardiologia*. Published. <https://doi.org/10.36660/abc.20200235>
- Gleeson, M., Bishop, N., Oliveira, M., McCauley, T., Tauler, P., & Muhamad, A. S. (2011). Respiratory infection risk in athletes: association with antigen-stimulated IL-10 production and salivary IgA secretion. *Scandinavian Journal of Medicine & Science in Sports*, 22(3), 410-417. <https://doi.org/10.1111/j.1600-0838.2010.01272.x>
- Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D. S., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., . . . Zhong, N. S. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*, 382(18), 1708-1720. <https://doi.org/10.1056/nejmoa2002032>
- Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., Tan, K. S., Wang, D. Y., & Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Military Medical Research*, 7(1). <https://doi.org/10.1186/s40779-020-00240-0>
- Guyton, A. C., & Hall, J. E. (2011). *Fisiologia Medica* (11.a ed.). Elsevier Science Health Science Div.
- Halle, M., Binzenhöfer, L., Mahrholdt, H., Johannes Schindler, M., Esefeld, K., & Tschöpe, C. (2020). Myocarditis in athletes: A clinical perspective. *European Journal of Preventive Cardiology*. Published. <https://doi.org/10.1177/2047487320909670>
- Hammami, A., Harrabi, B., Mohr, M., & Krustup, P. (2020). Physical activity and coronavirus disease 2019 (COVID-19): specific recommendations for home-based physical training. *Managing Sport and Leisure*, 1-6. <https://doi.org/10.1080/23750472.2020.1757494>
- Harris, M. D. (2011). Infectious Disease in Athletes. *Current Sports Medicine Reports*, 10(2), 84-89. <https://doi.org/10.1249/jsr.0b013e3182142381>
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., . . . Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497-506. [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5)
- Kantorowski, A., Wan, E. S., Homsy, D., Kadri, R., Richardson, C. R., & Moy, M. L. (2018). Determinants and outcomes of change in physical activity in COPD. *ERJ Open Research*, 4(3), 00054-02018. <https://doi.org/10.1183/23120541.00054-2018>
- Katajisto, M., Kupiainen, H., Rantanen, Kilpeläinen, Lindqvist, A., Tikkanen, & Laitinen, T. (2012). Physical inactivity in COPD and increased patient perception of dyspnea. *International Journal of Chronic Obstructive Pulmonary Disease*, 743. <https://doi.org/10.2147/copd.s35497>
- Lancaster, G. I., Halson, S. L., Khan, Q., Drysdale, P., Wallace, F., Jeukendrup, A. E., Drayson, M. T., & Gleeson, M. (2004). Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2 T lymphocytes. *Exercise immunology review*, 10, 91-106.
- Lancaster, G. I., Khan, Q., Drysdale, P. T., Wallace, F., Jeukendrup, A. E., Drayson, M. T., & Gleeson, M. (2005). Effect of prolonged exercise and carbohydrate ingestion on type 1 and type 2 T

- lymphocyte distribution and intracellular cytokine production in humans. *Journal of Applied Physiology*, 98(2), 565-571. <https://doi.org/10.1152/jappphysiol.00754.2004>
- Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., Li, W., Tong, Q., Yi, J., Zhao, L., Xiong, L., Guo, C., Tian, J., Luo, J., Yao, J., Pang, R., Shen, H., Peng, C., Liu, T., . . . Zheng, X. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*, 55, 102763. <https://doi.org/10.1016/j.ebiom.2020.102763>
- Maron, B. J., Levine, B. D., Washington, R. L., Baggish, A. L., Kovacs, R. J., & Maron, M. S. (2015). Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 2: Preparticipation Screening for Cardiovascular Disease in Competitive Athletes. *Circulation*, 132(22). <https://doi.org/10.1161/cir.0000000000000238>
- Martins, W. R., de Oliveira, R. J., Carvalho, R. S., de Oliveira Damasceno, V., da Silva, V. Z. M., & Silva, M. S. (2013). Elastic resistance training to increase muscle strength in elderly: A systematic review with meta-analysis. *Archives of Gerontology and Geriatrics*, 57(1), 8-15. <https://doi.org/10.1016/j.archger.2013.03.002>
- Mitchell, R. N., Kumar, V., Abbas, A. K., & Aster, J. C. (Eds.). (2017). *Compendio de Robbins y Cotran. Patología estructural y funcional*. Elsevier Health Sciences.
- Mohammadi, S., Moosaie, F., & Aarabi, M. H. (2020). Understanding the Immunologic Characteristics of Neurologic Manifestations of SARS-CoV-2 and Potential Immunological Mechanisms. *Molecular Neurobiology*, 57(12), 5263-5275. <https://doi.org/10.1007/s12035-020-02094-y>
- Narici, M., Vito, G. D., Franchi, M., Paoli, A., Moro, T., Marcolin, G., Grassi, B., Baldassarre, G., Zuccarelli, L., Biolo, G., di Girolamo, F. G., Fiotti, N., Dela, F., Greenhaff, P., & Maganaris, C. (2020). Impact of sedentarism due to the COVID-19 home confinement on neuromuscular, cardiovascular and metabolic health: Physiological and pathophysiological implications and recommendations for physical and nutritional countermeasures. *European Journal of Sport Science*, 21(4), 614-635. <https://doi.org/10.1080/17461391.2020.1761076>
- Nieman, D. C., & Wentz, L. M. (2019). The compelling link between physical activity and the body's defense system. *Journal of sport and health science*, 8(3), 201-217. <https://doi.org/10.1016/j.jshs.2018.09.009>
- Nyenhuis, S. M., Greiwe, J., Zeiger, J. S., Nanda, A., & Cooke, A. (2020). Exercise and Fitness in the Age of Social Distancing During the COVID-19 Pandemic. *The Journal of Allergy and Clinical Immunology: In Practice*, 8(7), 2152-2155. <https://doi.org/10.1016/j.jaip.2020.04.039>
- Peake, J. M., Della Gatta, P., Suzuki, K., & Nieman, D. C. (2015). Cytokine expression and secretion by skeletal muscle cells: regulatory mechanisms and exercise effects. *Exercise immunology review*, 21, 8-25.
- Peake, J. M., Neubauer, O., Walsh, N. P., & Simpson, R. J. (2017). Recovery of the immune system after exercise. *Journal of Applied Physiology*, 122(5), 1077-1087. <https://doi.org/10.1152/jappphysiol.00622.2016>
- Pelliccia, A., Solberg, E. E., Papadakis, M., Adami, P. E., Biffi, A., Caselli, S., La Gerche, A., Niebauer, J., Pressler, A., Schmied, C. M., Serratosa, L., Halle, M., Van Buuren, F., Borjesson, M., Carrè, F., Panhuyzen-Goedkoop, N. M., Heidbuchel, H., Olivetto, I., Corrado, D., . . . Sharma, S. (2018). Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *European Heart Journal*, 40(1), 19-33. <https://doi.org/10.1093/eurheartj/ehy730>
- Peters, H. P., De Vries, W. R., Vanberge-Henegouwen, G. P., & Akkermans, L. M. (2001). Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut*, 48(3), 435-439. <https://doi.org/10.1136/gut.48.3.435>



- Peters, H. P. F. (2001). Potential benefits and hazards of physical activity and exercise on the gastrointestinal tract. *Gut*, 48(3), 435-439. <https://doi.org/10.1136/gut.48.3.435>
- Prompetchara, E., Ketloy, C., & Palaga, T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pacific journal of allergy and immunology*, 38(1), 1-9. <https://doi.org/10.12932/AP-200220-0772>
- Puetz, T. W. (2006). Physical Activity and Feelings of Energy and Fatigue. *Sports Medicine*, 36(9), 767-780. <https://doi.org/10.2165/00007256-200636090-00004>
- Raiol, R. A. (2020). Praticar exercícios físicos é fundamental para a saúde física e mental durante a Pandemia da COVID-19. *Brazilian Journal of Health Review*, 3(2), 2804-2813. <https://doi.org/10.34119/bjhrv3n2-124>
- Sanchis-Gomar, F., Lavie, C. J., Mehra, M. R., Henry, B. M., & Lippi, G. (2020). Obesity and Outcomes in COVID-19: When an Epidemic and Pandemic Collide. *Mayo Clinic Proceedings*, 95(7), 1445-1453. <https://doi.org/10.1016/j.mayocp.2020.05.006>
- Shin, K. C. (2018). Physical activity in chronic obstructive pulmonary disease: clinical impact and risk factors. *The Korean Journal of Internal Medicine*, 33(1), 75-77. <https://doi.org/10.3904/kjim.2017.387>
- Simpson, R. J., Campbell, J. P., Gleeson, M., Krüger, K., Nieman, D. C., Pyne, D. B., Turner, J. E., & Walsh, N. P. (2020). Can exercise affect immune function to increase susceptibility to infection?. *Exercise immunology review*, 26, 8-22.
- Søgaard, K., & Sjøgaard, G. (2017). Physical Activity as Cause and Cure of Muscular Pain: Evidence of Underlying Mechanisms. *Exercise and Sport Sciences Reviews*, 45(3), 136-145. <https://doi.org/10.1249/jes.0000000000000112>
- Steinacker, J., Bloch, W., Halle, H., Mayer, F., Meyer, T., Hirschmüller, A., Röcker, K., Nieß, A., Scharhag, J., Reinsberger, C., Scherr, J., Niebauer, J., Wolfarth, B., Hannafin, J., Hiura, M., Wilkinson, M., Koubaa, D., Poli, P., Smoljanovic, T., . . . Wilson, F. (2020). Fact Sheet: Health Situation for Athletes in the Current Coronavirus Pandemic (SARS-CoV-2 / COVID-19). *Deutsche Zeitschrift für Sportmedizin*, 71(4), 85-86. <https://doi.org/10.5960/dzsm.2020.431>
- Svendsen, I. S., Hem, E., & Gleeson, M. (2016). Effect of acute exercise and hypoxia on markers of systemic and mucosal immunity. *European Journal of Applied Physiology*, 116(6), 1219-1229. <https://doi.org/10.1007/s00421-016-3380-4>
- Ter Steege, R. W. F., Van Der Palen, J., & Kolkman, J. J. (2008). Prevalence of gastrointestinal complaints in runners competing in a long-distance run: An internet-based observational study in 1281 subjects. *Scandinavian Journal of Gastroenterology*, 43(12), 1477-1482. <https://doi.org/10.1080/00365520802321170>
- Timpka, T. (2020). Sports Health During the SARS-Cov-2 Pandemic. *Sports Medicine*, 50(8), 1413-1416. <https://doi.org/10.1007/s40279-020-01288-7>
- Troosters, T., Scirba, F., Battaglia, S., Langer, D., Valluri, S. R., Martino, L., Benzo, R., Andre, D., Weisman, I., & Decramer, M. (2010). Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respiratory Medicine*, 104(7), 1005-1011. <https://doi.org/10.1016/j.rmed.2010.01.012>
- Wang, X., Liu, W., Zhao, J., Lu, Y., Wang, X., Yu, C., Hu, S., Shen, N., Liu, W., Sun, Z., & Li, W. (2020). Clinical characteristics of 80 hospitalized frontline medical workers infected with COVID-19 in Wuhan, China. *Journal of Hospital Infection*, 105(3), 399-403. <https://doi.org/10.1016/j.jhin.2020.04.019>
- Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new coronavirus associated with human respiratory disease in China. *Nature*, 579(7798), 265-269. <https://doi.org/10.1038/s41586-020-2008-3>

WHO. World Health Organization. Coronavirus disease (COVID- 19) Pandemic [Internet]. 2020. Retrieved from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> Access 1 august 2020.



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