Review Article

Aging, immune system, and physical activity: A review of recent studies

Abdolreza Kazemi[1*], Amir Hossein Ahmadi Hekmatikar[2]

Abstract

The immune system is one of the main defenders of human health. The immune system can fight off viruses in the body and kill them. Therefore, keeping the components of the immune system healthy is very important. With age, the immune system ages, and its function decreases. This decline in immune function can easily lead to viral infections in the elderly. Evidence is accumulated that the best solution to maintain and enhance the immune system in the elderly is physical activity. Regular physical activity can lead to healthy aging of the immune system. Therefore, in this review study, we have discussed the changes in the immune system during aging and physical activity suggestions for healthy aging of the immune system. Finally, future research needs are reported.

Key Words: **Aging, COVID-19, Immune system, Physical activity**

Introduction

The world is changing a lot, and the rate of aging in the general population has increased. It has recently been estimated that by 2050, nearly 2 billion people will age (Anastasilakis et al., 2014). An increase in longevity and a slowdown in human aging can be due to various factors, such as a healthy living environment, the development of public health, and social status (Li et al., 2021). With age, people's functional capacity decreases. This reduction in function can include muscle atrophy and inactivity as well as the reduction in the function of the immune system, which carry many risks. However, it is possible to keep the immune system healthy. With the sudden outbreak of COVID-19 in the world (Velavan & Meyer, 2020), older people were more likely to get the disease, and the disease was more severe in the elderly (Perrotta et al., 2020). Several clinical studies in the field of COVID-19 have reported older adults as their subjects in their research and the people available for clinical trials were initially all elderly (Abodonya et al., 2021; Betschart et al., 2021; Piquet et al., 2021a). Therefore, as there is a possibility of the recurrence of COVID-19 or similar diseases, effective strategies for healthy aging of the immune system must be adopted.

This view emphasizes the idea that the physiological foundations of sport are the main foundation for improving the physical condition and function of the immune system. Exercise is a natural medicine in humans and it is prescribed as a medicine every year (Pedersen & Saltin, 2015). It was Hippocrates who wrote two books on diet stating that eating alone could not be effective for human health. According to Hippocrates' theory, exercise must exist (Allbutt, 1924). The history of the past medical literature shows that exercise is very important for health (Méndez, 1960). Physicians reported that if exercise is done regularly, it deserves lofty praise as a blessed medicine that must be kept in high esteem (Méndez, 1960). Moreover, a lack of exercise is a major contributing factor to accelerated aging and age-associated chronic conditions, including cancer, obesity, and cardiovascular diseases (Booth et al, 2012). So, instead of spending and using expensive drugs

1. Associate Prof, Department of Physical Education, Faculty of Letters and Humanities, Vali-e-Asr University, Rafsanjan, Iran. 2. PhD Student in Exercise Physiology, Faculty of Humanities, Tarbiat Modares University, Tehran, Iran.

*Author for correspondence: a.kazemi@vru.ac.ir

A K: 0000-0003-1082-6335; AH AH: 0000-0003-1082-6335

Received 3 January 2023; Accepted 22 February 2023

for health, it is better to use this low-cost medicine, i.e., exercise. Throughout different decades of life, researchers have reported the importance of the immune system in the body health of people around the world. In this regard, training was able to establish a very good relationship with the immune system as a friend. Thus, the significant breakthroughs in this field were properly compiled in the so-called Exercise Immunology. However, the main point is to see if strenuous exercise can be effective for the immune system.

Moderate-intensity training (40%-69% VO2max, 30 to 60 minutes, 3-5 days/wk) to relatively intense volumes (70 to 85% VO2max, 30 to 45 minutes, 2-3 days/wk) are directly associated with a lower upper respiratory tract infection (URTI) incidence (Nieman & Wentz, 2019; Sellami et al., 2018). Thus, high-intensity training cannot be our goal right now. One of the effects of exercise on the immune system is cytokines (K Suzuki, 2019). Cytokines are divided into two categories (inflammatory and anti-inflammatory components). Cytokines have a long history in the body (Nathan & Sporn, 1991). Of the anti-inflammatory cytokines, interleukin 10 has the most powerful effect on the immune system during exercise (Helmark et al., 2010). Among the pro-inflammatory cytokines are prominent IL-1, IL-2, IL-12, IL-18, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) (Cannon, 2000). Moderate-intensity exercise can increase the number of neutrophils and natural killer (NK) cells, and increase salivary IgA concentrations (Miles, 2009). In addition, it increases hormones of stress-reducing excessive inflammation and leads to increased immunity against viral infections by altering the responses of Th1/Th2 cells influencing the immune response. Thus, the benefits of 'regular' physical activity include the improvement of immune function and reduction of the risk, duration, or severity of viral infections (Hall et al., 2021). Here, the word "regular" should be highlighted referring to exercising regularly. This is exactly what medical legends have mentioned in the past. Moderate-intensity regular exercise in the human lifestyle can improve the condition of the immune system. Improving the immune system can help people during illness. Therefore, the term healthy aging of the immune system with age can be new and very important. In this review article, we will try to examine and report the effects of exercise on healthy aging.

Aging of the immune system

As you grow older, your immune system will move in the aging direction. This can be due to one of the main physiological causes, namely physical inactivity (Sadighi Akha, 2018). The human body is closely related to the body's immune system to stay alive. History has shown that humans are constantly exposed to a variety of viruses but the consequences of infection are different in different individuals (Rouse & Sehrawat, 2010).

The immune system protects body against diseases, and thus, it plays a very important role in maintaining human health. The white blood cells have the key role in the immune system travelling throughout the body via the blood and lymph vessels. The immune system is divided into two categories (the innate immune system and the adaptive immune system). The innate immune system triggers fast and effective immune responses for the body while the adaptive immune system functions by precise recognition of antigen, memory formation, and adaptive proliferation of those cells that provide antigen-specific immunity. It has been shown that due to aging, the innate immune system also ages and will experience irregular inflammatory reactions (Shaw et al., 2013). Also, it is reported that neutrophils have a reduced function in the elderly (Shaw et al., 2013). With age, the function of TLR receptors in monocytes, macrophages, and dendritic cell (DC) populations decrease. Thus, decreased innate immune function leads to chronic inflammatory reactions that can lead to atherosclerosis and metabolic syndrome (Shaw et al., 2013). On the other hand, the ability of the adaptive immune system decreases with age which can be accompanied by a decrease in the number of lymphocytes and antibodies. It has also been observed that the number of T cells decrease significantly (Weng, 2006). Therefore, these changes in the immune system with age are called Immunosenescence. Immunosenescence describes the state of profound age-related changes in the immune system which are characterized by a general decrease in antigen immunity. A closer look revealed that at the cellular level one of the main features of immunosenescence is a dramatic decrease in lymphocytes and a decrease in T cell activation (Linton & Dorshkind, 2004). Therefore, it is easier to understand why older people get infectious diseases faster. Immunosenescence can be associated with decreased CD4+ T cell function which can reduce T cell receptor stimulation (Akha & Miller, 2005). NK cell depletion is also a cause of immunosenescence (See Figure1A) (Tarazona et al., 2001).

Recently, it has been discovered that the aging immune system and COVID-19 are closely related. In most clinical trials, patients with COVID-19 were middle-aged. With age and decreased immune system function, chronic inflammation increases in the body (Katsuhiko Suzuki, 2019). Therefore, it seems that chronic inflammation in the body can reduce the body's ability to fight new diseases (Ferrucci & Fabbri, 2018), one of which is COVID-19. SARS-CoV-2 is the causative agent of COVID-19, declared a global pandemic by the World Health Organization on March 11, 2020 (Zhou et al., 2020). COVID-19 can enter the body through the inhalation of fine particles in the air or in infected hands (See Figure1B) (Wang et al., 2020). When COVID-19 enters the body, it can cause a cytokine storm. Moreover, due to chronic inflammation in the body and a decline in the function of the immune system, the virus can easily multiply.

In aging, the primary goals of the innate immune system, i.e., to initiate a local inflammatory response to activate and recruit immune cells, to directly eliminate virally infected cells, and to prime the adaptive immune response, will not be effective (Bartleson et al., 2021). These goals are possible by activating T, B, NK cells from lymphocytes (See Figure1B, C). It has been shown that after 1 week of COVID-19 symptoms in the body, adaptive responses begin. This adaptive response increases CD4+ and CD8+ T cells after 4 days of COVID-19 symptoms in the body (Moderbacher et al., 2020). However, as the adaptive immune system ages, the function of T cells decreases, and this response can be very weak. Evidence suggests that newly generated naive T cells that do manage to enter the aged T cell repertoire display reduced T effector cell qualities upon activation and generate less effective memory cells (Agha-Alinejad et al., 2022; Gruver et al., 2007). Also, clinical studies have shown that, like T cells, B cells increase after one week of COVID-19 symptoms. An increase in B cells can increase the level of antibodies against the virus in the body (Moderbacher et al., 2020). However, with immunosenescence, the function of cells significantly reduce (Table 1). ‘

Physical activity and the immune system

By looking at history, we can see that physical activity is one of the main effective strategies to improve the immune system. Therefore, having a healthy lifestyle can be effective in the old age. Exercise immunology as a new science over the past 30 years has examined the responses or adaptations created to different types of exercise activities. More specifically, exercise immunology studies the acute and chronic effects of exercise on the immune system and its monitoring of pathogens (Eichner, 2020; Nieman & Pence, 2020).

Obesity is introduced as an important factor in the development of chronic diseases such as cardiovascular disease, hypertension, type 2 diabetes, stroke, osteoarthritis, and certain cancers (Pi-Sunyer, 2009; Rezaei et al., 2017). Inflammatory responses and immune system dysfunctions were observed in obese people (Bulló et al., 2007; Mahdieh et al., 2021).

It is approved that people with underlying diseases and obesity are more prone to infectious diseases, especially COVID-19 (Caussy et al., 2020; Dobner & Kaser, 2018). Moreover, lifelong physical activity can reduce the risk of non-communicable diseases such as cancer, cardiovascular disease, and inflammatory disorders by affecting immune system parameters (Sheikholeslami et al., 2018; Uddin et al., 2020). It has also been shown that a healthy lifestyle, regular and frequent physical activity can limit the suppression of the immune system and modulate inflammatory responses (Neil P Walsh et al., 2011). Regarding the intensity of exercise, most studies have shown that regular moderate-intensity exercise can prevent a weakened immune system (See Table 2 for more information) (Katsuhiko Suzuki, 2019). Therefore, lifelong moderate-intensity physical exercise can be a good strategy for strengthening the immune responses and controlling body composition that can be effective in preventing severe cases of COVID-19. People who are able to do moderate-intensity exercise in middle age can have a healthy immune system as they age.

Although physical exercise can have positive effects throughout life there are conflicting studies on physical exercise during treatment periods of infectious diseases. It seems that high-intensity and long-term physical activities can be effective in stimulating destructive effects on the immune system during infection. Depending on the pathogen, animal studies generally support the findings that one or two periods of exhaustive exercise following vaccination of the animal lead to a more frequent appearance of infection and a higher fatality rate (Nieman, 1998). It seems that exercise-induced changes in stress hormone and cytokines, body temperature, blood flow, and dehydration, etc., should be considered during infectious diseases. Therefore, physical exercises with inappropriate volume and intensity that induce immunological and physiological responses and can probably activate viral responses should not be considered (Table 3). In the elderly, regular exercise has been shown to increase the proliferation capacity of T cells and

Table 1. Immunosenescence and COVID-19.

Cell name	Function	Immunosenescence	Communication with COVID-19
T cell	T lymphocytes proliferate after binding to the antigen. Maintain T-cell receptor (TCR)	Decrease and T cell exhaustion	Increase CD4+ and CD8+ T cells and fight COVID-19 and decrease proinflammatory cytokines
B cell	Lymphocytes are from the immune system that produce antibodies against pathogens such as viruses.	Decrease	At the time of illness, the body produces a detectable level of immunoglobulin (Ig) M, IgG and IgA antibodies in the body.
NK cell	Lymphocytes are from the immune system that are involved in cellular and innate immunity. These cells are part of the body's innate immune system.	Decrease	(NK) cells are the first line of defense against the destruction of virus-infected cells.

Table 2. Recommended physical activity for the middle-aged adults and elderly

Exercise*	Intensity	volume	Age
Run	45-55 VO_2max Or Borg scale 2-6 (scale 1 to 10)	3 sessions per week	40-59 (middle-aged adults)
Walking	35-45 VO_2max Or Borg scale 2-6 (scale 1 to 10)	3 sessions per week	40-59 (middle-aged adults) And More than 60
Cycling	45-55 VO_2max Or Borg scale 2-6 (scale 1 to 10)	2 sessions per week	40-59 (middle-aged adults)
Resistance training	40-60 1RM	3 sessions per week	40-59 (middle-aged adults) People who do not have heart disease
Elastic bands	Borg scale 2-5 (scale 1 to 10)	2 sessions per week	More 60
Yoga	N/A	3 sessions per week	40-59 (middle-aged adults) And More than 60

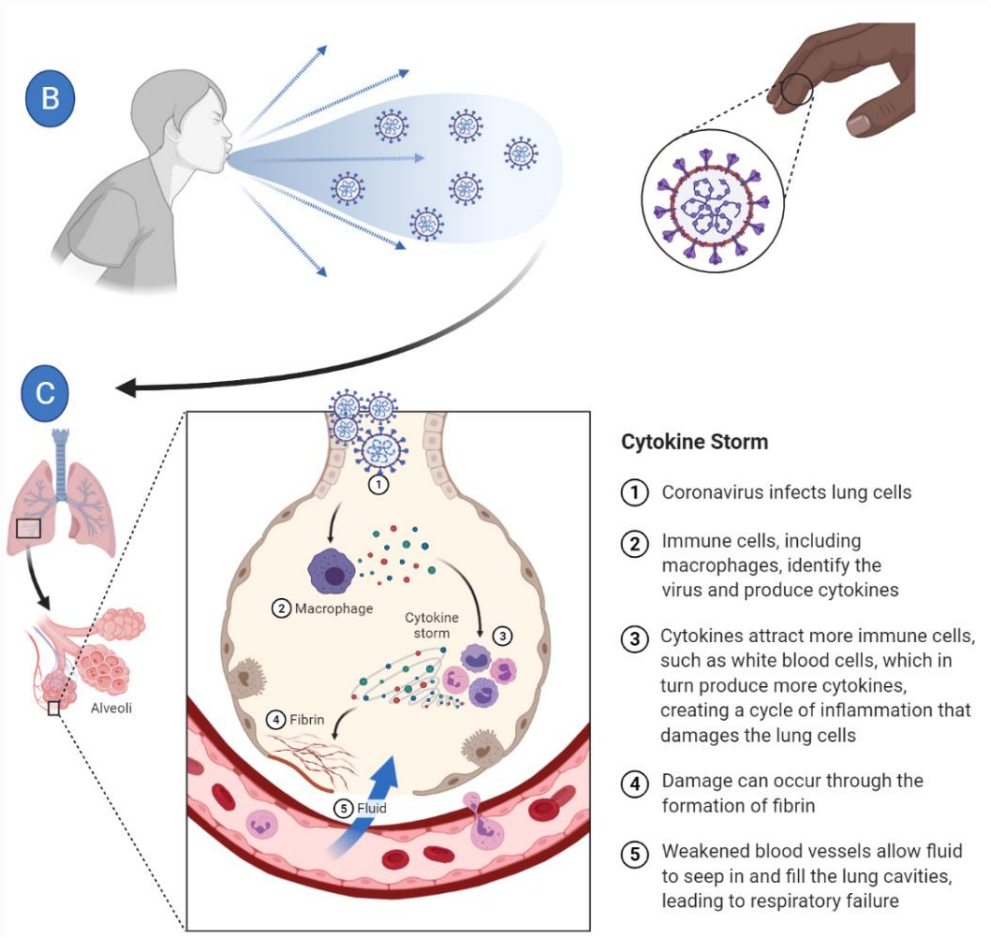

Figure 1. Changes in the immune system due to aging and COVID-19 pathology

decrease the level of inflammatory cytokines. It has also been shown that increased phagocytic activity of neutrophils is seen regularly after exercise (Simpson et al., 2012). However, volume and intensity of the physical activity are very important for the elderly (See Table 2).

Coronavirus is an RNA virus, a round molecule with a crown around it (Shang et al., 2020). The coronavirus with its effects on the immune system (decreased immune system) can cause death in acute conditions in patients with COVID-19. It has been shown that the corona virus can enter the lungs and begin to multiply in the body once it enters the body, with the main receptor for the virus in the lungs being angiotensin-converting enzyme 2 (ACE2) (Wan et al., 2020). Given that there was no vaccine associated with COVID-19 in the world, the immune sys-

-tem is the best factor in preventing diseases and viral infections such as COVID-19 (Chowdhury et al., 2020). In this regard, we can say that there are three types of immune system conditions in the body. The first type of immune system is the innate immune system, which is activated to a limited extent in COVID-19 proliferation. The innate immune system is also known as the rapid response (Ahmadi Hekmatikar et al., 2019; Quick et al., 2014; Suzuki et al., 2022; Tayebi et al., 2020). The second immune system that exists is the adaptive immune system, which has slow responses in the body. Finally, the third immune system is called the passive immune system (Chaussabel et al., 2010). When the immune system cells are strengthened, it is activated quickly when the infection spreads and multiplies in the body, and start re-circulating between the central and peripheral lymphatic organs through the bloodstream. Thus, blood flow can carry immune cells in the body to the affected areas (Krishnamurty & Turley, 2020). Therefore, when the body is exposed to viral infections, components of the immune system (T and B cells) multiply in the body to produce antibodies (Antibodies can prevent the virus from entering the cells) and promote cell differentiation and effector functioning (Kumar et al., 2020). Also, when a cell becomes infected with a virus and infection, T lymphocytes can activate an intracellular immune response, which in turn, play an important role in clearing the cell by cytotoxic T cells (Kumar et al., 2020).

One of the most effective ways to strengthen the immune system is to do exercise. It is generally believed that moderate-intensity exercise can enhance immune function and reduce the risk of upper respiratory tract infection. Conversely, prolonged bouts of strenuous exercise can result in a transient depression of immune function (Walsh et al., 2011). However, there is ample evidence that long-term exercise can trigger a strong anti-inflammatory response (Katsuhiko Suzuki, 2019). Therefore, it can be stated that professional athletes who have a history of strenuous exercise have better metabolic health in general and this factor can be one of the effective factors against viral infections (Laine et al., 2016). However, performing intense and long-term sports activities without proper recovery for too long periods of time will have chronic effects on the immune system. A gradual decrease in leukocyte count was observed following a short period of 4 weeks of extravagance accompanied by a sudden increase in exercise volume (Lehmann et al., 1996). It has also been reported that CD3+ CD4+ lymphocytes decrease due to strenuous exercise (Mackinnon et al., 1997). Decreased regulation of neutrophil function is mainly seen in prolonged and intense exercise and has been mainly associated with chronic inflammation (Smith, 1994). Also, a decrease in the number of NK cells during short periods (1 to 4 weeks) and long periods (7 months) of intense exercise has been observed (Gleeson et al., 1995). Therefore, it seems that it isn't possible to provide a single mechanism for changes in the cells of the immune system following intense and prolonged exercise.

Increased stress hormones such as cortisol and catecholamine's can also gradually alter the number and sensitivity of adrenergic receptors. Also, changes in other hormones such as insulin, growth hormone, prolactin, etc., can be part of these mechanisms. Another hypothesis that has been considered in recent years is the increase in inflammatory cytokines released by monocytes and macrophages as a result of persistent injury during strenuous exercise (Aguiar et al., 2020). This factor can lead to increased chronic inflammation and impaired immune function. Chronic increase in inflammatory markers, especially IL-6, is considered as a measure of overactivity and weakened immune system (Elevated interleukin 6 is very dangerous in COVID-19 patients) (Aguiar et al., 2020). The second hypothesis is to see whether moderate-intensity exercise can be effective in preventing viral infections such as COVID-19 during the treatment process.

On the other hand, researchers have reported moderate-intensity exercise as a golden way to improve the immune system (Khoramipour et al., 2021). Maintaining regular physical activity and daily exercise in a safe home environment is an important strategy for living a healthy life during a coronavirus crisis. Research has shown that moderate-intensity exercise can directly boost the immune system, antioxidant defenses, and anti-inflammatory responses (Ahmadi Hekmatikar, 2019). In this regard, regular exercise can have an anti-inflammatory effect on the body, as exercise has been shown to improve the immune response to the flu vaccine in the elderly (Zhu, 2020). Regular periods of short training (i.e., up to 45 minutes) with moderate intensity boost the immune system (Walsh et al., 2011). Aerobic exercise is an activity that is moderate in intensity and does not put much stress and pressure on the body. Regular exercise has been shown to improve infection, antibacterial and antiviral immunity, reduce inflammation, and delay immune aging (Campbell & Turner, 2018). Following moderate-intensity physical activity, an increase in the number of neutrophils and (NK) cells is detected and salivary IgA concentrations increase (Brolinson & Elliott, 2007). During exercise, rapid and general mobilization of NK cells is induced into the bloodstream by catecholamine's. Mobilized NK cells are affected by muscle-derived myokines, exercise-related hyperthermia, and coronary arteries circulation, which are affected by regulation, redistribution, and activation of mobilized NK cells (Brolinson & Elliott, 2007; Farhani et al., 2022). The results show a 20 to 30 percent reduction in upper respiratory tract infections in people

Table 3. Investigating the importance of research on the effect of exercise as a lifestyle to prevent suppression of the immune system during the coronavirus pandemic.

Author	Year	Title	Description	Suggested exercises	Reference
Jesus et al	2021	Promising effects of exercise on the cardiovascular, metabolic and immune system during COVID-19 period	Chronic moderate and adapted exercise may be doubly beneficial in T2DM and cardiovascular diseases for preventing inflammation and viral respiratory infections, including coronavirus infection. If the exercise is moderate intensity, there will be an improvement in the function of the immune system (increase in T cells) and if the exercise is more than long and heavy, there will be a decrease in the function of the immune system.	Exercise model: regular type of exercise: Moderate intensity	(Jesus et al., 2021)
Scudiero et al	2021	Exercise, immune system, nutrition, respiratory and cardiovascular diseases during COVID-19: A complex combination	At the same time, in order to prevent contagion, it is very important to adopt social distancing, the disinfection of common places, a suitable lifestyle that supports the immune system, personal hygiene. The knowledge acquired to date through sports medicine and laboratory diagnostics suggests that moderate exercise can help the human body live better; on the other hand, intense exercise, if done inadequately, can cause numerous pathologies leading to a malfunction of the immune system.	Exercise model: regular type of exercise: Moderate intensity	(Scudiero et al., 2021)
Saçma and Geiger	2021	Exercise generates immune cells in bone	Due to the fact that in the absence of exercise can reduce the function of the immune system, it has been shown that regular exercise can increase the function of the immune system by producing immune cells from the bone marrow.	Exercise model: regular type of exercise: Moderate intensity	(Saçma & Geiger, 2021)
Suzuki and Hayashida	2021	Effect of exercise intensity on cell-mediated immunity	Moderate-intensity exercise is considered to enhance immune function and to be useful for preventing acute upper respiratory infections and similar conditions, whereas high-intensity exercise induces systemic inflammation. Low-intensity exercises such as walking and yoga, which are helpful to relieve stress, cannot be considered as harmful to the immune system.	Exercise model: regular type of exercise: Moderate intensity	(Suzuki & Hayashida, 2021)
Yoon et al	2021	Exercise reduces metabolic burden while altering the immune system in aged mice	Exercising regularly can make a positive difference in your immune system. These changes can include a decrease in inflammatory cytokines and an increase in anti-inflammatory cytokines. Exercise can also prevent cytokine storms. However, exercise can increase T cells, B cells, NK cells and decrease TNF. These changes can reduce the metabolic load.	Exercise model: regular type of exercise: Moderate intensity	(Yoon et al., 2021)
Simpson and Pawelec	2021	Is mechanical loading essential for exercise to preserve the aging immune system?	Maintaining the function of immune cells, especially T cells, can cause a decline in the function of the immune system in the elderly. However, the mechanical load must be such that the suppression of the immune system does not occur.	Exercise model: regular type of exercise: Moderate intensity	(Simpson & Pawelec, 2021)
Moghadam et al	2021	Ramadanh fasting during the COVID-19 pandemic; observance of health, nutrition and exercise criteria for improving the immune system	Exercising regularly and with the right intensity can improve the functioning of the immune system. On the other hand, dieting can be one of the most important and effective strategies in improving the function of the immune system.	Exercise model: regular type of exercise: Moderate intensity	(Moghadam et al., 2021)
Do et al	2021	Regular physical exercise mediates the immune response in atherosclerosis.	Regular exercise can Lower systemic inflammation directly via modulation of the immune system or indirectly via altered myokine concentrations and metabolites. However, exercise can increase T cells, B cells, NK cells and decrease TNF.	Exercise model: regular type of exercise: Moderate intensity	(Do Brito Valente et al., 2021)

Table 3. (continue).

Papp et al	2021	Regular exercise may restore certain age-related alterations of adaptive immunity and rebalance immune regulation	It has been shown that changes that occur in the body as a result of moderate-intensity exercise on a regular basis can prevent viral infections in the long run. It has been shown that with regular exercise (NK), NKT cells, T and B lymphocytes increased. This increase can be a strong support to prevent infection. Thereby, regular exercise, besides improving physical condition and age-related sarcopenia, may also delay or even reverse immunosenescence therefore can be particularly beneficial in maintaining appropriate immune functions in older ages.	Exercise model: regular type of exercise: Moderate intensity	(Papp et al., 2021)
Suzuki	2019	Chronic inflammation as an immunological abnormality and effectiveness of exercise	Exercise is a medicine. Moderate-intensity exercise can boost your immune system. Intense exercise can increase inflammation and decrease the function of the immune system. The anti-inflammatory effects of exercise are becoming better understood at being effective for preventing chronic inflammation.	Exercise model: regular type of exercise: Moderate intensity	(Katsuhiko Suzuki, 2019)
Baker and Simpson	2021	Exercise to support optimal immune function	Exercise immunology as a new science in its movement over the past 30 years has examined the responses or adaptations created to different types of sports activities as part of it. More specifically, sports immunology studies the acute and chronic effects of exercise on the immune system and its monitoring of pathogens. Moderate-intensity exercise can cause physiological changes, including improved immune function, increased T-cells and anti-inflammatory cytokines, and prevent the spread of viral infections.	Exercise model: regular type of exercise: Moderate intensity	(Baker & Simpson, 2021)
Khoramipour et al	2021	Physical activity and nutrition guidelines to help with the fight against COVID-19	Given that no specific treatments have yet been identified, proper nutrition along with balanced diet and exercise are important factors to help us all to be safe in the pandemic. Unusual conditions in this pandemic situation may make it difficult to obtain and prepare nutritious food. Therefore, nutritional supplements might also be taken into consideration.	Exercise model: regular type of exercise: Moderate intensity	(Khoramipour et al., 2021)
Hekmatikar et al	2021	Exercise in an Overweight Patient with COVID-19: A Case Study	According to contradictory data, Low-intensity training such as resistance training with hand-trainer resistance and breathing exercises can improve strength performance in patients with COVID-19. These exercises can also restore normal blood oxygen levels. However, it has been suggested that researchers also look at changes in the immune system in the future.	Exercise model: regular type of exercise: Low intensity	(Hekmatikar et al., 2021)
Jee et al	2021	Acquired immunity and moderate physical exercise: 5th series of scientific evidence	Exercising with an intensity that is too Low does not significantly improve immune function, whereas excessively high exercise intensity causes a suppression of the body's immune function. Ultimately, it can be said that moderate exercise intensity creates an intramuscular environment that can activate immune function in a beneficial way.	Exercise model: regular type of exercise: Moderate intensity	(Jee, 2021)
Valizadeh et al	2021	The effect of one bout submaximal endurance exercise on the innate and adaptive immune responses of hypertensive patients.	Submaximal endurance exercise has been shown to improve immune system function and Lower blood pressure in hypertensive patients.	Exercise model: regular type of exercise: Moderate intensity	(Valizadeh et al., 2021)

Table 3. (continue).

Oh, et al	2021	Vitamin D and exercise are major determinants of (NK) cell activity, which is age- and gender-specific	Regular, moderate-intensity exercise can improve the functioning of the immune system by increasing NK cells. On the other hand, taking vitamin D can also help. However, researchers report that impaired immune function and NK cells are associated with age and gender, which decrease with age.	Exercise model: regular type of exercise: Moderate intensity	(Oh et al., 2021)
Córdova et al	2021	Effect of exercise in the recovery process after the inflammation process caused by coronavirus	In this context, we suggest that appropriate exercise programs could improve recovery of people who have suffered from COVID-19 disease, improving the quality of life and reinforcing the protection against future infections. The immunomodulatory properties of exercise and physical activity could act as prevention tools for different chronic diseases in healthy individuals and complementary therapeutic tools in sick patients.	Exercise model: regular type of exercise: Moderate intensity	(Córdova Martínez et al., 2021)
Rahayu et al	2021	Exercise and physical health in survivors of COVID-19: a scoping review	Exercising regularly can be effective. Moderate-intensity exercise was proven to have positive and safe effects that are recommended for COVID-19 survivors. It is recommended to increase the frequency of exercise from 150-300 to 200-400 minutes per week, including strengthening exercises.	Exercise model: regular type of exercise: Moderate intensity	(Rahayu et al., 2021)
Domin et al	2021	Effect of various exercise regimens on selected exercise-induced cytokines in healthy people	The amount and duration of exercise impact the release of the cytokines as well. Short-lasting or a single bout of an acute exercise has a different effect on cytokines than prolonged activity or repeated regular training. The baseline fitness level may modify the type, and extent of cytokine response to physical activity as some of these proteins are secreted or not, depending on whether someone is a worse or better fit.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Domin et al., 2021)
Fonseca et al	2021	Aerobic training modulates the increase in plasma concentrations of cytokines in response to a session of exercise	Moderate chronic aerobic exercise causes significant "training" for certain cytokine responses, including IL-6, sTNFR1, BDNF, and leptin. Trained immunity is known to be relevant in the context of infection but may contribute to the pathogenesis of certain conditions, such as sepsis.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Fonseca et al., 2021)
Scheffer and Latini	2020	Exercise-induced immune system response: anti-inflammatory status on peripheral and central organs	Regular practice of moderate-intensity physical exercise directs the immune response to an anti-inflammatory status. The beneficial consequences of physical exercise on the health outcomes involve the modulation of the immune system. This can include increasing the level of T and B cells and decreasing the level of TNF.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Scheffer & Latini, 2020)
Scartoni et al	2020	Physical exercise and immune system in the elderly: implications and importance in COVID-19 pandemic period	All physical activity is beneficial, and any practice is better than doing nothing. It is also essential to reduce the sedentary lifestyle and accumulate at least 150 min of moderate-intensity physical activity or 75 min of vigorous-intensity physical activity per week is mandatory.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Scartoni et al., 2020)
Simpson et al	2020	Can exercise affect immune function to increase susceptibility to infection?	Exercising regularly can be effective, but people who are recovering from COVID-19 have been suggested that moderate-intensity exercise can be considered safe. Moderate-intensity exercise was proven to have positive and safe effects that are recommended for COVID-19 survivors.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Simpson et al., 2020)
Silveira et al	2020	Physical exercise as a tool to help the immune system against COVID-19: an	During regular physical exercise practices, inflammatory responses and stress hormones are decreased; in contrast, lymphocytes, NK cells, immature B cells and monocytes are at	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(da Silveira et al., 2021)

Table 3. (continue).

		integrative review of the current literature	high levels. Thus, there is an improvement in immunovigilance, as well as a reduction in the systemic inflammatory process, factors that corroborate that regular physical activity helps to improve the immune system, while helping to prevent respiratory diseases and thus protect against infections such as COVID-19.		
Aktuğ et al	2020	COVID-19, immune system and exercise	Chronic moderate and adapted exercise may be doubly beneficial in T2DM and cardiovascular diseases for preventing inflammation and viral respiratory infections, including coronavirus infection. If the exercise is moderate intensity, there will be an improvement in the function of the immune system (increase in T cells) and if the exercise is more than long and heavy, there will be a decrease in the function of the immune system.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Aktuğ et al., 2020)
Wang et al	2020	Immune system and exercise	Regular exercise can Lower systemic inflammation directly via modulation of the immune system or indirectly via altered myokine concentrations and metabolites. However, exercise can increase T cells, B cells, NK cells and decrease TNF.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(J. Wang et al., 2020)
Abd and Osama	2020	Aerobic exercise affects sleep, psychological wellbeing and immune system parameters among subjects with chronic primary insomnia	It has been shown that aerobic exercise can improve immune function. This improvement in immune function can prevent insomnia. On the other hand, it can also prevent infection.	Exercise model: regular type of exercise: Moderate intensity	(Abd El-Kader & Al-Jiffri, 2020)
Yıldızgören	2020	How exercise may affect the immune system against COVID-19?	Home exercise program can be designed to include a combination of walking, strengthening, stretching and balance exercises. When possible, moderate intensity aerobic exercise, such as brisk walking outdoors is a good alternative if safe distancing can be maintained. As high intensity exercise in sports hall and crowded places has more risks than benefits, it should be avoided. It is important that a balanced diet is maintained with the intake of vitamin rich nutrients and fluid prior to exercise.	Exercise model: regular type of exercise: Moderate intensity and Low intensity	(Yıldızgören, 2020)

who do moderate levels of physical activity in their daily lives (Brolinson & Elliott, 2007). Therefore, it can be assumed that moderate-intensity training can be an effective way to strengthen the immune system.

Discussion

The main hypothesis of the study is to see what the beneficial effects of exercise are on the immune system during treatment. Due to the fact that patients with COVID-19 suffer from shortness of breath and fatigue during treatment, it is not possible to do moderate-intensity exercise. In a study of patients with COVID-19, it was reported that due to respiratory problems and fatigue in patients with COVID-19, training time should be less than 20 minutes and exercise intensity should be low (Piquet et al., 2021b). Therefore, it can be stated that low-intensity rehabilitation exercise can be effective. Research has shown that long-term low-intensity exercise can improve some components of the immune system (Rykova et al., 2008). The duration of hospitalization of COVID-19 patients is between 6 to 10 days. These patients also take medication during treatment that can help with the healing process. Short-term low-intensity exercise can speed up the healing process; however, choosing a training protocol for 6 to 10 days can be very important. In this regard, given that patients with COVID-19 lose their muscle strength, resistance training can be a good solution (Campos & Miguel, 2020). The point is that resistance training should be low-intensity in patients with COVID-19. In conclusion, low-intensity exercise does not play an effective role in improving the immune system, and during the treatment process in patients with COVID-19, it can only prevent some kind of decline in the physical function.

Physical activity as healthy lifestyle can be effective in improving

the function of the immune system (Khoramipour et al., 2021). Older people will suffer from a weakened immune system due to lack of physical activity. Given that the world is facing the COVID-19 virus, this decline in immune function can be very dangerous. Therefore, by exercising regularly and for a long time, the immune system can experience a healthy aging (Ahmadi Hekmatikar & Molanouri Shamsi, 2020). Also, a healthy lifestyle in the long run and moderate-intensity exercise can improve the immune system which protects a person from diseases such as COVID-19 (adaptive immune system). This healthy aging of the immune system can include increasing the function of T and B cells and reducing chronic inflammation in the body.

Considering the prevalence of COVID-19 in the world and many reports of hospitalization of the elderly due to viral infections, it is suggested that in the future, researchers study the impact of physical activity at the time of illness. Although Hekmatikar et al. (2021) examined the effect of exercise on the COVID-19 patients in a case study, there are some limitations in this study (Hekmatikar et al., 2021), and given that older people are more susceptible to infectious diseases, in future research, the effect of physical activity at the time of illness on the elderly needs to be done with strict protocols.

Conclusion

The present study showed that with increasing age, the function of the body's immune system will decline. This can be due to reduced physical activity, changes in eating habits and other factors. This study showed that regular physical activity 3 days a week with low to moderate intensity (aerobic and resistance exercises) can be a suitable strategy to improve the immune system. Increasing the function of the body's immune system can lead to a reduction in the severity of the COVID-19 disease in the elderly.

What is already known on this subject?

With age, the function of the immune system decreases, and this can increase the severity of the disease in the elderly and lead to death in most cases.

What this study adds?

Moderate intensity training (aerobic and resistance training) under the supervision of an expert can lead to the improvement of the body's immune system and reduce the severity of the disease in the elderly.

Acknowledgements

None.

Funding

None.

Compliance with ethical standards

Conflict of interest The author declare that she has no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

Author contributions

Conceptualization: A.K.; Methodology: Ah.Ah.; Software: None.; Validation: A.K.; Formal analysis: None.; Investigation: Ah.Ah.; Resources: Ah.Ah.; Data curation: A.K.; Writing - original draft: Ah.Ah.; Writing - review & editing: A.K.; Visualization: Ah.Ah.; Supervision: Ah.Ah.; Project administration: A.K.; Funding acquisition: Ah.Ah.

References

Abd El-Kader, S. M., & Al-Jiffri, O. H. (2020). Aerobic exercise affects sleep, psychological wellbeing and immune system parameters among subjects with chronic primary insomnia. African health sciences, 20(4), 1761-1769. doi: https://doi.org/10.4314/ahs.v20i4.29

Abodonya, A. M., Abdelbasset, W. K., Awad, E. A., Elalfy, I. E., Salem, H. A., & Elsayed, S. H. (2021). Inspiratory muscle training for recovered COVID-19 patients after weaning from mechanical ventilation: A pilot control clinical study. Medicine, 100(13). doi: https://doi.org/10.1097/MD.0000000000025339

Agha-Alinejad, H., Ahmadi Hekmatikar, A. H., Ruhee, R. T., Shamsi, M. M., Rahmati, M., Khoramipour, K., & Suzuki, K. (2022). A Guide to Different Intensities of Exercise, Vaccination, and Sports Nutrition in the Course of Preparing Elite Athletes for the Management of Upper Respiratory Infections during the COVID-19 Pandemic: A Narrative Review. International Journal of Environmental Research and Public Health, 19(3), 1888. doi: https://doi.org/10.3390/ijerph19031888

Aguiar, S. S., Sousa, C. V., Deus, L. A., Rosa, T. S., Sales, M. M., Neves, R. V. P., . . . Simões, H. G. (2020). Oxidative stress, inflammatory cytokines and body composition of master athletes: the interplay. Experimental gerontology, 130, 110806. doi: https://doi.org/10.1016/j.exger.2019.110806

Ahmadi Hekmatikar, A., Haghshenas, R., & Mohammad Sadeghipor, A. (2019). The effect of carbohydrate supplementation and pure water on interleukin 10, glucose and hematological indexes in male football players. Sport Physiology & Management Investigations, 11(4), 135-145.

Ahmadi Hekmatikar, A. H., R.; Mohammad Sadeghipor, A. . (2019). The effect of carbohydrate supplementation and pure

water on interleukin 10, glucose and hematologicalindexes in male football players. Sport Physiol. Manag. Investig. 2019, 11, 135–145.

Akha, A. A. S., & Miller, R. A. (2005). Signal transduction in the aging immune system. Current opinion in immunology, 17(5), 486-491. doi: https://doi.org/10.1016/j.coi.2005.07.004

Aktuğ, Z. B., İri, R., & Demir, N. A. (2020). COVID-19 immune system and exercise: COVID-19 immün system ve egzersiz. Journal of Human Sciences, 17(2), 513-520. doi: https://doi.org/10.1016/j.coi.2005.07.004

Allbutt, C. (1924). Hippocrates-Hippocrates. With English Translation by WHS Jones, St. Catherine's College, Cambridge (Loeb Classical Library.) Vol. II. Pp. Ivi+ 336: London: Heinemann; New York: GP Putnam's Sons, 1923.-Hippocrates and his Successors in Relation to the Philosophy of their Time. By RO Moon, MD, FRCP The Fitzpatrick Lectures, RCP, 1921–22. London: Longmans, 1923. 6s. The Classical Review, 38(7-8), 175-177.

Anastasilakis, A. D., Polyzos, S. A., Saridakis, Z. G., Kynigopoulos, G., Skouvaklidou, E. C., Molyvas, D., . . . Siopi, A. (2014). Circulating irisin in healthy, young individuals: day-night rhythm, effects of food intake and exercise, and associations with gender, physical activity, diet, and body composition. The Journal of Clinical Endocrinology & Metabolism, 99(9), 3247-3255. doi: https://doi.org/10.1210/jc.2014-1367

Baker, F. L., & Simpson, R. J. (2021). Exercise to Support Optimal Immune Function. ACSM's Health & Fitness Journal, 25(1), 5-8. doi: https://doi.org/10.1097/FTD.0000000000000640

Bartleson, J. M., Radenkovic, D., Covarrubias, A. J., Furman, D., Winer, D. A., & Verdin, E. (2021). SARS-CoV-2, COVID-19 and the aging immune system. Nature Aging, 1(9), 769-782. https://doi.org/10.1038/s43587-021-00114-7 doi: https://doi.org/10.1038/s43587-021-00114-7

Betschart, M., Rezek, S., Unger, I., Beyer, S., Gisi, D., Shannon, H., & Sieber, C. (2021). Feasibility of an Outpatient Training Program after COVID-19. International Journal of Environmental Research and Public Health, 18(8), 3978. doi: https://doi.org/10.3390/ijerph18083978

Booth, F. W., Roberts, C. K., & Laye, M. J. (2012). Lack of exercise is a major cause of chronic diseases. Comprehensive physiology, 2(2), 1143. doi: https://doi.org/10.1002/cphy.c110025

Brolinson, P. G., & Elliott, D. (2007). Exercise and the immune system. Clinics in sports medicine, 26(3), 311-319. doi: https://doi.org/10.1007/978-981-15-1792-1_27

Bulló, M., Casas-Agustench, P., Amigó-Correig, P., Aranceta, J., & Salas-Salvadó, J. (2007). Inflammation, obesity and comorbidities: the role of diet. Public health nutrition, 10(10A), 1164-1172. doi: https://doi.org/10.23736/S2724-6507.20.03361-1

Campbell, J. P., & Turner, J. E. (2018). Debunking the Myth of Exercise-Induced Immune Suppression: Redefining the Impact of Exercise on Immunological Health Across the Lifespan. Frontiers in immunology, 9, 648. doi: https://doi.org/10.3389/fimmu.2018.00648

Campos, M. V. A., & Miguel, H. (2020). Elastic resistance training: resistance exercise alternative in the home environment during Covid-19 pandemic. InterAmerican Journal of Medicine and Health, 3.

Cannon, J. G. (2000). Inflammatory Cytokines in Nonpathological States. News Physiol Sci, 15, 298-303. doi: https://doi.org/10.1152/physiologyonline.2000.15.6.298

Caussy, C., Wallet, F., Laville, M., & Disse, E. (2020). Obesity is associated with severe forms of COVID‐19. Obesity, 28(7), 1175-1175. PMID: 32959515; PMCID: PMC7536951.

Chaussabel, D., Pascual, V., & Banchereau, J. (2010). Assessing the human immune system through blood transcriptomics. BMC biology, 8(1), 1-14. doi: https://doi.org/10.1161/CIRCRESAHA.120.316770

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. doi: https://doi.org/https://doi.org/10.1016/j.jiph.2020.07.001

Córdova Martínez, A., Pérez-Valdecantos, D., Caballero-García, A., Sarabia, J. M., & Roche, E. (2021). Effect of exercise in the recovery process after the inflammation process caused by coronavirus. 6;127(11):1437-1455. doi: https://doi.org/10.1161/CIRCRESAHA.120.316770

da Silveira, M. P., da Silva Fagundes, K. K., Bizuti, M. R., Starck, É., Rossi, R. C., & de Resende e Silva, D. T. (2021). 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. doi: https://doi.org/10.1007/s10238-020-00650-3

do Brito Valente, A. F., Jaspers, R. T., & Wüst, R. C. (2021). Regular physical exercise mediates the immune response in atherosclerosis. Exercise immunology review, 27, 42-53. doi: http://europepmc.org/abstract/MED/33965897

Dobner, J., & Kaser, S. (2018). Body mass index and the risk of infection - from underweight to obesity. Clinical Microbiology and Infection, 24(1), 24-28. https://doi.org/https://doi.org/10.1016/j.cmi.2017.02.013

Domin, R., Dadej, D., Pytka, M., Zybek-Kocik, A., Ruchała, M., & Guzik, P. (2021). Effect of Various Exercise Regimens on Selected Exercise-Induced Cytokines in Healthy People. International Journal of Environmental Research and Public Health, 18(3), 1261. doi: https://www.mdpi.com/1660-4601/18/3/1261

Eichner, E. R. (2020). Exercise Immunology Reconsidered. Current sports medicine reports, 19(9), 341-342. doi: https://doi.org/10.1249/JSR.0000000000000743

Farhani, F., Shahrbanian, S., Auais, M., Hekmatikar, A. H. A., & Suzuki, K. (2022). Effects of aerobic training on brain plasticity in patients with mild cognitive impairment: a systematic review of randomized controlled trials. Brain Sciences, 12(6), 732. doi: https://doi.org/10.3390/brainsci12060732

Ferrucci, L., & Fabbri, E. (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nature Reviews Cardiology, 15(9), 505-522. doi: https://doi.org/10.1038/s41569-018-0064-2

Fonseca, T. R., Mendes, T. T., Ramos, G. P., Cabido, C. E. T., Morandi, R. F., Ferraz, F. O., . . . Teixeira, M. M. (2021). Aerobic Training Modulates the Increase in Plasma Concentrations of Cytokines in response to a Session of Exercise. Journal of Environmental and Public Health, 2021, 1304139. doi: https://doi.org/10.1155/2021/1304139

Gleeson, M., McDonald, W., Cripps, A., Pyne, D., Clancy, R., & Fricker, P. (1995). The effect on immunity of long‐term intensive training in elite swimmers. Clinical & Experimental Immunology, 102(1), 210-216. doi: https://doi.org/10.1111/j.1365-2249.1995.tb06658.x

Gruver, A., Hudson, L., & Sempowski, G. (2007). Immunosenescence of ageing. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 211(2), 144-156. doi: https://doi.org/10.1038/s41586-021-03547-7

Hall, G., Laddu, D. R., Phillips, S. A., Lavie, C. J., & Arena, R. (2021). A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? Progress in cardiovascular diseases, 64, 108. doi: https://doi.org/10.1016/j.pcad.2020.04.005

Hekmatikar, A. H. A., Shamsi, M. M., Ashkazari, Z. S. Z., & Suzuki, K. (2021). Exercise in an overweight patient with COVID-19: a case study. International Journal of Environmental Research and Public Health, 18(11), 5882. doi: https://doi.org/10.3390/ijerph18115882

Helmark, I. C., Mikkelsen, U. R., Børglum, J., Rothe, A., Petersen, M. C., Andersen, O., . . . Kjaer, M. (2010). Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: a randomized controlled trial. Arthritis research & therapy, 12(4), 1-11. doi: https://doi.org/10.1186/ar3064

Jee, Y.-S. (2021). Acquired immunity and moderate physical exercise: 5th series of scientific evidence. Journal of exercise rehabilitation, 17(1), 2.

Jesus, I., Vanhee, V., Deramaudt, T. B., & Bonay, M. (2021). Promising effects of exercise on the cardiovascular, metabolic and immune system during COVID-19 period. Journal of Human Hypertension, 35(1), 1-3. doi: https://doi.org/10.1038/s41371-020-00416-0

Khoramipour, K., Basereh, A., Hekmatikar, A. A., Castell, L., Ruhee, R. T., & Suzuki, K. (2021). Physical activity and nutrition guidelines to help with the fight against COVID-19. Journal of Sports Sciences, 39(1), 101-107. doi: https://doi.org/10.1080/02640414.2020.1807089

Krishnamurty, A. T., & Turley, S. J. (2020). Lymph node stromal cells: cartographers of the immune system. Nat Immunol, 21(4), 369-380. doi: https://doi.org/10.1038/s41590-020-0635-3

Kumar, S., Nyodu, R., Maurya, V. K., & Saxena, S. K. (2020). Host immune response and immunobiology of human SARS-CoV-2 infection. In Coronavirus Disease 2019 (COVID-19) (pp. 43-53). Springer. doi: https://doi.org/10.1016/j.pulmoe.2021.03.008

Laine, M., Eriksson, J., Kujala, U., Kaprio, J., Loo, B. M., Sundvall, J., . . . Sarna, S. (2016). Former male elite athletes have better metabolic health in late life than their controls. Scandinavian Journal of Medicine & Science in Sports, 26(3), 284-290. doi: https://doi.org/10.1111/sms.12442

Lehmann, M., Mann, H., Gastmann, U., Keul, J., Vetter, D., Steinacker, J. M., & Häussinger, D. (1996). Unaccustomed high-mileage vs intensity training-related changes in performance and serum amino acid levels. International journal of sports medicine, 17(03), 187-192. doi: https://doi.org/10.1055/s-2007-972830

Li, X., Ploner, A., Wang, Y., Zhan, Y., Pedersen, N. L., Magnusson, P. K., . . . Hägg, S. (2021). Clinical biomarkers and associations with healthspan and lifespan: evidence from observational and genetic data. EBioMedicine, 66, 103318. doi: https://doi.org/10.1016/j.ebiom.2021.103318

Linton, P. J., & Dorshkind, K. (2004). Age-related changes in lymphocyte development and function. Nature immunology, 5(2), 133-139. doi: https://doi.org/10.1038/ni1033

Mackinnon, L. T., Hooper, S. L., Jones, S., Gordon, R. D., & Bachmann, A. W. (1997). Hormonal, immunological, and hematological responses to intensified training in elite swimmers. Med Sci Sports Exerc, 29(12), 1637-1645. doi: https://doi.org/10.1097/00005768-199712000-00014

Mahdieh, M. S., Maryam, J., Bita, B., Neda, F., Motahare, M., Mahboobeh, B., . . . Kalani Behrooz, S. (2021). A pilot study on the relationship between Lactobacillus, Bifidibactrium counts and inflammatory factors following exercise training. Archives of Physiology and Biochemistry, 1-10. doi: https://doi.org/10.1080/13813455.2021.1871763

Méndez, C. (1960). Book of bodily exercise. Licht.

Miles, M. P. (2009). Moving Toward Solid Ground on Exercise and Immune Defense Against Viral Infection. Exercise and sport sciences reviews, 37(4), 155. doi: https://doi.org/10.1097/JES.0b013e3181b7ba03

Moderbacher, C. R., Ramirez, S. I., Dan, J. M., Grifoni, A., Hastie, K. M., Weiskopf, D., . . . Choi, J. (2020). Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell, 183(4), 996-1012. e1019. doi: https://doi.org/10.1016/j.cell.2020.09.038

Moghadam, M. T., Taati, B., Paydar Ardakani, S. M., & Suzuki, K. (2021). Ramadan Fasting During the COVID-19 Pandemic; Observance of Health, Nutrition and Exercise Criteria for Improving the Immune System [Review]. Frontiers in nutrition, 7(349). doi: https://doi.org/10.3389/fnut.2020.570235

Nathan, C., & Sporn, M. (1991). Cytokines in context. Journal of Cell Biology, 113(5), 981-986.

Nieman, D. C. (1998). Exercise and resistance to infection. Canadian journal of physiology and pharmacology, 76(5), 573-580. doi: https://doi.org/10.1016/j.immuni.2019.03.012

Nieman, D. C., & Pence, B. D. (2020). Exercise immunology: future directions. Journal of Sport and Health Science, 9(5), 432-445. doi: https://doi.org/10.1016/j.jshs.2019.12.003

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. doi: https://doi.org/10.1016/j.jshs.2018.09.009

Oh, S., Chun, S., Hwang, S., Kim, J., Cho, Y., Lee, J., . . . Choi, S.-W. (2021). Vitamin D and Exercise Are Major Determinants of Natural Killer Cell Activity, Which Is Age- and Gender-Specific [Original Research]. Frontiers in Immunology, 12(2488). doi: https://doi.org/10.3389/fimmu.2021.594356

Papp, G., Szabó, K., Jámbor, I., Mile, M., Berki, A. R., Arany, A. C., . . . Balogh, L. (2021). Regular Exercise May Restore Certain Age-Related Alterations of Adaptive Immunity and Rebalance Immune Regulation [Original Research]. Frontiers in Immunology, 12(1279). doi: https://doi.org/10.3389/fimmu.2021.639308

Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports, 25, 1-72. doi: https://doi.org/10.1111/sms.12581

Perrotta, F., Corbi, G., Mazzeo, G., Boccia, M., Aronne, L., D'Agnano, V., . . . Bianco, A. (2020). COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging clinical and experimental research, 1-10. doi: https://doi.org/10.1007/s40520-020-01631-y

Pi-Sunyer, X. (2009). The medical risks of obesity. Postgraduate medicine, 121(6), 21-33.

Piquet, V., Luczak, C., Seiler, F., Monaury, J., Martini, A., Ward, A. B., . . . Chambard, L. (2021a). Do patients with Covid-19 benefit from rehabilitation? Functional outcomes of the first 100 patients in a Covid-19 rehabilitation unit. Archives of Physical Medicine and Rehabilitation, 102(6), 1067-1074. doi: https://doi.org/10.1016/j.apmr.2021.01.069

Piquet, V., Luczak, C., Seiler, F., Monaury, J., Martini, A., Ward, A. B., . . . Chambard, L. (2021b). Do Patients with Covid-19 Benefit from Rehabilitation? Functional outcomes of the first 100 patients in a Covid-19 rehabilitation unit. Archives of physical medicine and rehabilitation. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Quick, E. D., Leser, J. S., Clarke, P., & Tyler, K. L. (2014). Activation of intrinsic immune responses and microglial phagocytosis in an ex vivo spinal cord slice culture model of West Nile virus infection. Journal of virology, 88(22), 13005-13014. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Rahayu, U. B., Rahman, F., Alis Setiyadi, N., & Azizan, A. (2021). Exercise and Physical Health in Survivors of COVID-19: A scoping review. Journal of Medicinal and Chemical Sciences, 4(2), 154-162. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Rezaei, S., Shamsi, M. M., Mahdavi, M., Jamali, A., Prestes, J., Tibana, R. A., . . . Voltarelli, F. A. (2017). Endurance exercise training decreased serum levels of surfactant protein D and improved aerobic fitness of obese women with type-2 diabetes. Diabetology & metabolic syndrome, 9(1), 1-8.

Rouse, B. T., & Sehrawat, S. (2010). Immunity and immunopathology to viruses: what decides the outcome? Nature Reviews Immunology, 10(7), 514-526. doi: https://doi.org/10.1038/nri2802

Rykova, M. P., Antropova, E. N., Popov, D. V., Vinogradova, O. L., & Larina, I. M. (2008). [The activation processes of the immune system during low intensity exercise without relaxation]. Ross Fiziol Zh Im I M Sechenova, 94(2), 212-219.

Saçma, M., & Geiger, H. (2021). Exercise generates immune cells in bone. In: Nature Publishing Group.

Sadighi Akha, A. A. (2018). Aging and the immune system: An overview. Journal of Immunological Methods, 463, 21-26. doi: https://doi.org/https://doi.org/10.1016/j.jim.2018.08.005

Scartoni, F. R., Sant'Ana, L. d. O., Murillo-Rodriguez, E., Yamamoto, T., Imperatori, C., Budde, H., . . . Machado, S. (2020). Physical Exercise and Immune System in the Elderly: Implications and Importance in COVID-19 Pandemic Period [Mini Review]. Frontiers in Psychology, 11(3215). doi: https://doi.org/10.3389/fpsyg.2020.593903

Scheffer, D. d. L., & Latini, A. (2020). Exercise-induced immune system response: Anti-inflammatory status on peripheral and central organs. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1866(10), 165823. doi: https://doi.org/https://doi.org/10.1016/j.bbadis.2020.165823

Scudiero, O., Lombardo, B., Brancaccio, M., Mennitti, C., Cesaro, A., Fimiani, F., . . . Frisso, G. (2021). Exercise, Immune System, Nutrition, Respiratory and Cardiovascular Diseases during COVID-19: A Complex Combination. International Journal of Environmental Research and Public Health, 18(3), 904. doi: https://www.mdpi.com/1660-4601/18/3/904

Sellami, M., Gasmi, M., Denham, J., Hayes, L. D., Stratton, D., Padulo, J., & Bragazzi, N. (2018). Effects of acute and chronic exercise on immunological parameters in the elderly aged: can physical activity counteract the effects of aging? Frontiers in Immunology, 9, 2187. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., . . . Li, F. (2020). Structural basis of receptor recognition by SARS-CoV-2. Nature, 581(7807), 221-224. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Shaw, A. C., Goldstein, D. R., & Montgomery, R. R. (2013). Age-dependent dysregulation of innate immunity. Nature Reviews Immunology, 13(12), 875-887. doi: https://doi.org/10.1038/nri3547

Sheikholeslami, S., Ghanbarian, A., & Azizi, F. (2018). The impact of physical activity on non-communicable diseases: Findings from 20 years of the Tehran Lipid and Glucose Study. International journal of endocrinology and metabolism, 16(4 Suppl).

Simpson, R. J., Campbell, J. P., Gleeson, M., Krüger, K., Nieman, D. C., Pyne, D. B., . . . Walsh, N. P. (2020). Can exercise affect immune function to increase susceptibility to infection? Exercise immunology review, 26, 8-22.

Simpson, R. J., Lowder, T. W., Spielmann, G., Bigley, A. B., LaVoy, E. C., & Kunz, H. (2012). Exercise and the aging immune system. Ageing Res Rev, 11(3), 404-420. doi: https://doi.org/10.1016/j.arr.2012.03.003

Simpson, R. J., & Pawelec, G. (2021). Is mechanical loading essential for exercise to preserve the aging immune system? Immunity & Ageing, 18(1), 26. doi: https://doi.org/10.1186/s12979-021-00238-9

Smith, J. A. (1994). Neutrophils, host defense, and inflammation: a double‐edged sword. Journal of leukocyte biology, 56(6), 672-686.

Suzuki, K. (2019). Characterization of exercise-induced cytokine release, the impacts on the body, the mechanisms and modulations. Int. J. Sports Exerc. Med, 5, 1-13.

Suzuki, K. (2019). Chronic inflammation as an immunological abnormality and effectiveness of exercise. Biomolecules, 9(6), 223.

Suzuki, K., & Hayashida, H. (2021). Effect of exercise intensity on cell-mediated immunity. Sports, 9(1), 8.

Suzuki, K., Hekmatikar, A. H. A., Jalalian, S., Abbasi, S., Ahmadi, E., Kazemi, A., . . . Khoramipour, K. (2022). The Potential of Exerkines in Women's COVID-19: A New Idea for a Better and More Accurate Understanding of the Mechanisms behind Physical Exercise. International Journal of Environmental Research and Public Health, 19(23), 15645.

Tarazona, R., DelaRosa, O., Alonso, C., Ostos, B., Espejo, J. n., Peña, J., & Solana, R. (2001). Increased expression of NK cell markers on T lymphocytes in aging and chronic activation of the immune system reflects the accumulation of effector/senescent T cells. Mechanisms of ageing and development, 121(1-3), 77-88.

Tayebi, S. M., Hekmatikar, A. A., Ghanbari-Niaki, A., & Fathi, R. (2020). Ghrelin behavior in exercise and training. J Med. Sci, 27, 85-111.

Uddin, R., Lee, E.-Y., Khan, S. R., Tremblay, M. S., & Khan, A. (2020). Clustering of lifestyle risk factors for non-communicable diseases in 304,779 adolescents from 89 countries: A global perspective. Preventive medicine, 131, 105955.

Valizadeh, R., Karampour, S., Saiiari, A., & Sadeghi, S. (2021). The effect of one bout submaximal endurance exercise on the innate and adaptive immune responses of hypertensive patients. The Journal of sports medicine and physical fitness. doi: https://doi.org/10.23736/s0022-4707.21.11941-3

Velavan, T. P., & Meyer, C. G. (2020). The COVID‐19 epidemic. Tropical medicine & international health, 25(3), 278.

Walsh, N. P., Gleeson, M., Shephard, R. J., Gleeson, M., Woods, J. A., Bishop, N., . . . Hoffman-Goete, L. (2011). Position statement part one: immune function and exercise.

Walsh, N. P., Gleeson, M., Shephard, R. J., Gleeson, M., Woods, J. A., Bishop, N. C., . . . Simon, P. (2011). Position statement. Part one: Immune function and exercise. Exerc Immunol Rev, 17, 6-63.

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. Journal of virology, 94(7).

Wang, J., Liu, S., Li, G., & Xiao, J. (2020). Exercise Regulates the Immune. Physical Exercise for Human Health, 1228, 395.

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., . . . Yuen, K.-Y. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell, 181(4), 894-904. e899.

Weng, N.-p. (2006). Aging of the Immune System: How Much Can the Adaptive Immune System Adapt? Immunity, 24(5), 495-499. doi: https://doi.org/https://doi.org/10.1016/j.immuni.2006.05.001

Yıldızgören, M. T. (2020). How Exercise May Affect The Immune System Against COVID-19? Spor Hekimliğ i Dergisi, 55(2), 186-187. doi: https://doi.org/10.26655/jmchemsci.2021.2.62s5

Yoon, K. J., Ahn, A., Park, S. H., Kwak, S. H., Kwak, S. E., Lee, W., . . . Kim, H.-R. (2021). Exercise reduces metabolic burden while altering the immune system in aged mice. Aging (Albany NY), 13(1), 1294. doi: https://doi.org/10.26655/jmchemsci.2021.2.6

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., . . . Huang, C.-L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579(7798), 270-273. doi: https://doi.org/10.26655/jmchemsci.2021.2.6 695

Zhu, W. (2020). Should, and how can, exercise be done during a coronavirus outbreak? An interview with Dr. Jeffrey A. Woods. Journal of sport and health science, 9(2), 105. doi: https://doi.org/10.26655/jmchemsci.2021.2.6