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The relationship of COVID-19 and Physical Exercise: Are sports THE solution?

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Abstract

COVID-19, is the disease caused by infection of the Severe Acute Respiratory Syndrome Corona Virus 2, that currently has pandemic influence on daily life, economics and lifestyle. Corona viruses are common knowledge, however COVID-19 pathology, physiology and long term consequences still are not completely known and of interest in current research. This review is meant to provide overview of research done on COVID-19 related to immune responses and physical exercise. Specifically the influence of physical exercise have been evaluated in COVID-19 immune response and long term sequelae progression and prevention. Physical exercise have been reported beneficial in prevention of non-communicable diseases and supportive in immune responses.

The first section of the review focuses on the general influence of physical exercise on immune responses. It is shown that exercise intensity and workload are able to modulate immune responses regarding neutrophil count increasement, immunoglobulin level modulation, interleukin-6 modulation and the Renin-Angiotensin-Aldosteron-System (RAAS) modulation. Acute and intense exercise negatively influences immune response whereas moderate exercise shows beneficial effects.

The second part focuses specifically on physical exercise response on immune regulation in COVID-19. Immune effects related to physical exercise also are shown in COVID-19 cases. Interesting are the lifestyle and mental effects. Social confinement due to COVID-19 restrictions influence physical activity and therefore the immune regulation.

The last part focuses on the long term effects of COVID-19 and the role of physical exercise in this process. Currently there is little information known on mechanisms involved in long term sequelae. Frequent symptoms of long-covid are fatigue, dyspnea, palpitations, hair loss, anxiety/depression and cognitive disturbance. It is unknown whether the immune response modulation due to physical exercise also influences initiation and progression of long term sequelae. One current hypothesis is the involvement of latent immune memory because of sensitizing the immune system to viral particles even though they are eliminated from the organism.

This review suggests a potential significant role for physical exercise in COVID-19 disease onset, progression and prevention, but certain mechanisms need to be clarified to be able to conclude. Longitudinal cohort studies can contribute in clarification of the Covid 19 pathophysiology and treatment possibilities.

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1. Introduction

Since 2019, a worldwide pandemic outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been seen. SARS-CoV-2 is an enveloped RNA virus closely related to other coronaviruses, such as SARS-CoV and MERS-CoV (1). Coronaviruses mainly cause 'cold-like' symptoms except for SARS-CoV and MERS-CoV, that can cause fatal respiratory disease. SARS-CoV-2 possesses symptom-similarities with SARS-CoV.
The main target of the virus are the respiratory organs but research also showed organ damage in the circulatory system, urogenital system, gastrointestinal system and nervous system (2). Some of the infection related consequences are symptoms of a sore throat, fever, cough, shortness of breath and loss of taste and smell (3). Loss of taste or smell is a hallmark symptom of infection of SARS-CoV-2 infection. WHO also uses this as a definition for a probable case of COVID-19 disease (4).
SARS-CoV-2 can infect the human cell by binding to the angiotensin-conversing enzyme 2 (ACE2) via the spike protein binding (2, 5, 6). ACE2 is a component of the Renin-Angiotensin-aldosterone system (RAAS). This system functions as an arterial blood pressure regulator and extracellular volume regulation (7). ACE2 receptor is highly abundant in tissues throughout the body which possibly explains the broad range of damage caused by the covid-19 virus. Interesting is the interaction with the immune system of ACE2. Several studies including Crowley et al. showed decreased macrophage expression as well as pro-inflammatory cytokines expression by inactivation of angiotensin type II (ATII) by ACE2 (8).
Early studies show increased levels of pro-inflammatory cytokines in serum. The level of cytokines can be associated with disease severity (9). The cytokine storm is indicated by increase of interleukin-1/2/6/7, interferon-γ inducible protein 10 and TNF-α (10, 11).

Several studies showed association between physical activity and better health. A systematic review of longitudinal studies on long-term health benefits of physical activity from Reiner et al. showed positive long-term influence on physical activity and the incidence of noncommunicable diseases (12). Mechanisms attributed to improvement of human health by physical activity are reduced adiposity, maintenance of muscle mass, improvement of cardiorespiratory functioning and circulating lipid reduction (13).
The World Health Organisation (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure (14). About 80% of the world's adolescent population is insufficiently physical active and therefore 20-30% more susceptible for increased risk of death compared to sufficiently physically active people (14). Physical inactivity is known to be a major risk to develop noncommunicable diseases, e.g. cardiovascular diseases (15), type II Diabetes (16), respiratory diseases (17) and cancers (18). Guidelines, according the WHO, for the amount of physical exercise for adolescents (18-64 years) should be at least 150-300 minutes moderate-intensity aerobic exercise per week (14).
'Physical activity' and 'exercise' are terms that can be interpreted differently among the readers and even the community. As described previously, the WHO defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure.

Exercise on the other hand was defined by Caspersen et al. (1985) as a subcategory of physical activity defined as planned, structured movement undertaken to improve or maintain one or more aspects of physical fitness (19). These two terms are often interchangeable and during this review this will be the case.

The goal of this review is to emphasis the importance of physical activity on human health especially in COVID-19 prevention, disease severity and recovery after infection. By addressing the literature on COVID-19 pathophysiology and relating this to physical exercise the importance of being physically active will be discussed. Specifically, three sub questions are tackled: the relation of physical exercise on the human immune system, the relation of physical exercise on COVID-19 and the relation of physical exercise on long-covid. Also the intensity level at which the exercise should be performed to benefit health is widely researched. A case study was included to connect literature to practise. It is hypothesized that regular and moderate exercise benefits human health by modulation of the immune response and influences antiviral activity to function as a possible lifestyle factor in susceptibility to reduce disease severity and long-lasting sequelae. In this review this hypothesis will be tested using literature.

2. Physical exercise involvement in immune response

Exercise can modulate the immune system in various ways. Several studies have shown the differences between moderate exercise and acute/intense exercise. It is believed that acute/intense exercise may lead to suppressing of the immune response, however moderate exercise may enhance the immune response (20). There are a few cellular mechanisms known underlying the modulation of the immune response caused by different forms of exercise. Moderate activity led to an increase of neutrophil counts and a decrease of eosinophil counts (20). Neutrophils play an important role in innate and adaptive immune responses including involvement in immunomodulatory cytokine synthesis and release, clearance of extracellular pathogens and contribute to activation and expression of the adaptive immune response (21). Eosinophils play an important role in allergic responses, under influence of Interleukin-5, and stimulates B-cell growth and immunoglobulin secretion (22).

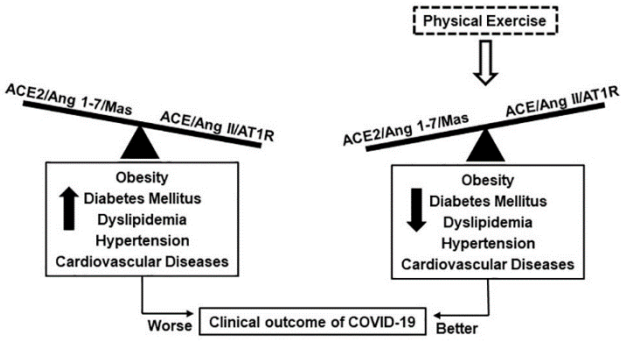
Immunoglobulin-A is a secretory immunoglobin which prevents colonization of mucosal surfaces and developmental local growth of pathogens. Exercise can affect levels of this immunoglobulin, therefore modulating the first line of defence. A longitudinal study of Fahlman and Engels (2005) showed an inverse reaction on IgA levels and acute/intense exercise (23). One year of American Football significantly decreased secretory IgA levels and respectively an increased risk for developing upper respiratory tract infections (23). The decrease of salivary IgA was also observed in the study of S.J. Laing et al (2005) (24). This study determined the effects of prolonged exercise in hot conditions on salivary IgA levels in trained cyclists. There was no significant influence observed on salivary IgA levels during prolonged exercise under hot conditions. Thus, the role of exercise on secretory IgA levels has been determined in several studies with conclusive evidence for beneficial immunomodulatory influence of moderate exercise on salivatory IgA levels. This is

confirmed by a study of Mohammad Ghaderi et al. 2011 in which they showed the effect of maximal progressive exercise on serum cortisol levels and immunoglobulin levels in young elite athletes (65). The study showed no significant change in immunoglobulin-A excretion in maximal progressive exercise but a significant increase in cortisol levels. The study showed no significant change in immunoglobulin-A excretion in maximal progressive exercise but a significant increase in cortisol levels. This indicates the importance of exercise intensity and workload. Klentrou et al. (25) investigated the role of moderate exercise on salivatory IgA levels and infection risk in humans. By using an aerobic exercise programme, the hypothesis of his study was tested. The study showed significantly increased IgA levels and significantly reduced number of upper respiratory tract infections in the moderate exercise group. This study indicates a possible enhancement of the immune response as a result of the increased IgA levels because of moderate exercise whereas intense/acute exercise is possibly able to induce an immunosuppressive response.

Another molecular response of exercise on immune health is the modulation of interleukin 6. Interleukin-6 is a pro-inflammatory cytokine produced in an acute phase response to infections and tissue damage (26). Interleukin-6 stimulates specific differentiation of naïve $CD4^+$ T cells and therefore it functions as an important link between innate and adaptive immune responses. Although Interleukin-6 functions as a pro-inflammatory factor in immune response, it is also known that the acute phase proteins induced by Interleukin-6 have anti-inflammatory and immunosuppressive effect when derived from skeletal muscles (myokine function) (27). Exercise primarily causes an upregulation (up to 100-fold) of Interleukin-6 in the circulation, followed by an increase in interleukin-1 receptor antagonist and interleukin-10 which are respectively a cytokine inhibitor and anti-inflammatory cytokine. Relating the excretion rate to physical exercise, researched showed limited response on short bouts of exercise at low intensity. Prolonged moderate exercise will systemically induce interleukin-6 response resulting in an enhancement of anti-inflammatory responses(28).

Different studies have showed the effect of physical activity on RAAS system (29, 30). Physical exercise can induce systemic and tissue-specific ACE/ANGII/AT1R axis downregulation (31). This axis has effects on vasoconstriction, cell proliferation and sodium retention (32). Hyperactivation of the axis is associated with noncommunicable diseases such as Diabetes Mellitus, obesity and inflammation (33). The opposite axis of the ACE/ANGII/AT1R axis is the ACE2/ANG 1-7/MAS axis. Stimulation of this axis promotes anti-inflammatory, cardioprotective and vasodilative responses (34). Physical exercise is able to stimulate this axis and shift the balance toward the ACE2/ANG 1-7/MAS axis (29, 30). This modulation toward the

Figure 1: RAAS axis modulation



protective arm by physical exercise indicates a protective role in immune response.
In addition, Magalhães et al. (2020) showed that moderate physical exercise causes an acute increase in activity of the ACE2/ANG 1-7/MAS axis, leading to increased plasma and urinary levels of ACE2 (35). During this study two protocols were included, tested on physically active men, a High-Intensity Interval Exercise (HIIE) and a Moderate-intensity Continuous Exercise (MICE). Increased activity of the ACE2/ANG 1-7/MAS axis, determined by a greater increased urinary concentrations of ANG1-7, is caused by aerobic physical exercise, mostly in the MICE protocol compared to HIIE protocol. The results of this (and other) studies indicate the importance of the type and duration of physical exercise.

3. Physical exercise related to COVID-19

At the time of writing this thesis, there is no cure for COVID-19 severe implications. The beneficial role of physical activity on the immune response has been described widely, so in this review the effect of physical activity on COVID-19 and vice versa will be discussed. It is alarming that during COVID-19 physical activity decreased because of the confinement. Castañeda-Babarro et al. (2020) showed this alarming observation among 3800 healthy adults (18-64 years) from Spain (36). There was a significant decrease noted in self-reported physical activity in vigorous activity (16.8%) and walking time (58.2%) alongside an increased sedentary time (23.8%). However, on a slightly positive note, there was no significant decrease noticed in the people who reached the recommended 150 min/week of moderate exercise (1.4%). The longitudinal study of Feifei Bu et al. (2021) showed similar patterns in the physical inactivity because of the social confinement during Covid-19 (37). To conclude, (Social) confinement because of COVID-19 is therefore likely to cause a decrease of physical activity. As discussed in the previous paragraph, one of the results of physical inactivity is modulation of the immune system. Over the time, increased systemic inflammation and reduced T-cell proliferation and cytokine production is also noticed (38). Also, lower Natural Killer cell activity in physical inactive people is shown (39).

A Longitudinal study of Jing Liu (2020) showed significant and sustained decrease in lymphocyte counts and increase in neutrophil counts and cytokine release (Interleukin-6, IFN-γ and Interleukin-10) in patients suffering COVID-19, and basically severe disease (40). Relating this longitudinal study to be more susceptible for physical inactivity during COVID-19 confinement, which can cause immune modulation and increased systemic inflammation, the role of physical activity can be of a great interest, e.g. possible prevention of severe disease and accelerate recovery of disease.
Interferon modulation by physical exercise is one of the mechanisms of the immune system to induce a more adequate immune response. Moderate exercise is associated with a rise in Interferon-2 (41). Interferons possess antiviral actions via RNA-dependent Protein Kinase (PKR), induction of inducible nitric oxide synthase (iNOS2) and histocompatibility complex I and II proteins (42). Physical exercise might be able via interferon modulation to stimulate the immune system for antiviral activity and control of viral replication.
Another mechanism is to modulate the response of a viral infection by innate immune cells through physical exercise. Viruses are detected by pattern-recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) which can lead to activation of

downstream signalling pathways and type-I or type-III interferon production (43). An immune response against SARS-CoV-2 is initiated after activation of PRR by the recognition of binding to viral PAMPs such as Toll-like receptors, single- and double-stranded DNA or Interferon-regulatory factors (44). Several PAMPs are involved in SARS-CoV-2. PAMP1 is initiated in the recognition of viral lipopolysaccharide (LPS) followed by excretion of different cytokines (interleukin-1β/6/8/12) and interferons (44). Interferons are capable of activation of Natural Killer cells (45). As described earlier in this chapter, physical inactivity causes a decrease of natural killer cell activity. Nieman et al. (1993), some time ago, already showed the beneficial effects of moderate exercise on Natural Killer cell activity (46). A protocol of treadmill exercise was initiated with high intensity (80% VO_2Max) and moderate intensity (50% VO_2Max). The study showed significant shifts in circulating NK cells during and 2 hours after the exercise. This indicates the possible important role for exercise in COVID-19 pathophysiology.

Besides the physiological benefits of physical activity there is also evidence for the importance of physical exercise on mental health and well-being of the people during COVID-19 pandemic. A study of Grazia Maugeri et al. (2020) showed in an online survey of 2524 Italian subjects a significant decrease of physical activity between before and during COVID-19 pandemic (47). Especially men showed a significant decrease in physical activity. Also, a significant correlation was determined in physical activity variation and mental well-being. Reduction of the physical activity had a profoundly negative effect on the psychological well-being of the population.

4. Long-COVID and Physical Exercise

Long-Covid or Post-acute COVID-19 syndrome is the non-resolving result of a SARS-CoV-2 infection. After recovery of the acute infection, patients retain prolonged and persistent symptoms. Usually the acute effects of SARS-CoV-2 infection lasts up to 4 weeks after onset of symptoms. Therefore, any sequelae of COVID-19 that remain after 4 weeks from the first symptoms is called long-covid or post-acute COVID-19 syndrome. From this point on, the term long-covid will be used. Frequent symptoms of long-covid are fatigue, dyspnea, palpitations, hair loss, anxiety/depression and cognitive disturbance (48). Long-Covid, because of the recent onset of the COVID-19 pandemic, there is not much information on long-term sequelae, which is currently of major interest in longitudinal cohort studies. The incidence of long-covid shows a lot of fluctuations in studies, ranging from 30-90% (49, 50), with most patients experiencing fatigue, dyspnea and chest pain. The design of the studies is often heterogenous regarding epidemiological criteria since the variation in local prevalence of COVID-19 (51).
The university of Washington performed a longitudinal prospective cohort study of adults with confirmed SARS-CoV-2 infection to conduct follow-up in the nine months after illness (52). The results showed approximately 30% of persistent sequelae. The most common sequelae experienced were fatigue and loss of smell and taste.

Although the high number of studies conducting research on symptoms and incidence, treatment opportunities are less known. There is limited information on treatment specific

for long-covid. General treatment advice for COVID-19 is currently use of IL-6 receptor inhibitors, antisense RNA, monoclonal antibodies and systemic corticosteroids, but none of them function as a dealbreaker (53). The role of vitamins as a preventive therapy for development of COVID-19 or even as a treatment is researched by Dehghani-Samani A et al. (2020) (54). Vitamins function as important micronutrients on the immune system and have been repeatedly reported as essentials in cellular immunity, intestinal immune defence and tolerance and anti-inflammatory effects. (55, 56). The study of Dehghani-Samani A et al. showed, among all vitamins, roles of vitamin A, C, D and E to be more effective on the immune system and possibly of interest for research to prevent viral infections like SARS-CoV-2. However vitamin metabolism is a precise process and possible toxicity should be considered. At least the beneficial effects of vitamins on human health status can affect COVID-19 pathophysiology and recovery. Relating this to a retrospective multinomial logistic regression study by Alipio et al. (2020), statistical analysis showed correlation between disease severity and vitamin D level deficiency (57) indicating an increase in serum vitamin D could possibly improve clinical outcome.

Physical exercise is a lifestyle factor previously described to benefit immune response and human health. There is sufficient evidence suggesting the contributing role of physical exercise for long-covid therapy, despite the need of further evidence for the type and workload management of the exercise. Physical exercise prevents both the onset and development of cardiovascular disease (58), improves neurocognitive abilities such as brain plasticity and psychological well-being through contraction-induced myokines release and brain-derived neurotrophic factor (59) and functions as an effective treatment in pulmonary disease through concurrent training to improve oxygen uptake, muscle strength, oxidative stress, muscle size and quality of life (60). The multiorgan nature of long covid sequelae invites people to improve physical health generally by tailored exercise to boost the immune system and decrease disease severity of SARS-CoV-2 infection.

Molecular mechanisms responsible for SARS-CoV-2 related symptoms and organ modulation are widely describe in the literature. However, whether these mechanisms are also responsible for persistent sequelae after months of onset of the infection is currently unknown. One current hypothesis is the involvement of latent immune memory because of sensitizing the immune system to viral particles even though they are eliminated from the organism (61).

The following case study is described to indicate the broad and extensive sequelae six months after onset of the laboratory confirmed SARS-CoV-2 infection.

‘A female (25 years) elite athlete was infected with the SARS-CoV-2 virus six months prior to this writing. Daily routine prior to the infection existed of tailored and reviewed moderate and intense exercise, consisting of cycling, speedskating and muscle strength trainings. Patient is known to have exercise-induced asthma. Immediately after onset of symptoms related to Covid 19, infection was confirmed by laboratory PCR test followed by self-quarantine. She experienced symptoms like fever, dry cough, chest pain, muscle strain, headaches and fatigue. Symptoms can be described as moderate severity, but medical

intervention was never in need. Symptoms lasted for 10 days after which self-quarantine was cancelled. Two weeks after onset of the symptoms, exercise schedule was resumed in a reduced way. Training intensity never reached the same level prior to the infection of SARS-CoV-2, expressed by up and downs during regular daily life and exercise experience and never fully relieved of the symptoms. After five months medical examination was done by the sports doctor using a cycle exercise test to indicate the maximum aerobic and anaerobic power (Watts/kg body weight) during exercise. Also, an ElectroCardioGram (ECG) was performed to test cardiac function, and a long function test to indicate the long function. The main result indicated an increase of respiratory rate of 1.5 times during rest with a normal lung function (FEV1/FVC). This phenomenon showed proportionate results during exercise. This can indicate autonomous dysfunction of the respiratory rate caused by the SARS-CoV-2 infection. The autonomous dysfunction can explain the daily fatigue and reduced exercise capacity. Treatment advice is a reset of the autonomous respiratory rate signal using speech therapy.'

NB. Prior to the infection, the patient had antibiotic administration for three months, probably influencing the immune response and therefore correlating with disease severity and the long-term sequelae.

Interesting is the 'hyperventilation-like' response of the autonomous respiratory system. Mechanism underlying this was described by Motiejunaite et al. (2021) (62). A case series of eight patients with exertional dyspnea at three months after onset was reported. All patients had no previous cardiovascular or pulmonary medical history. All patients showed normal lung function tests and significant impaired exercise tolerance. Five out of eight patients showed elevated VE/VCO_2 ratios suggesting exercise hyperventilation. The study hypothesized hyperventilation-induced hypocapnia might be responsible for symptoms like dyspnea, fatigue and chest pain.
Relating this to the case study, there is suggesting evidence for autonomous respiratory dysfunction because of SARS-CoV-2 infection and possible target for research.

5. Conclusion/Discussion

The goal of this review study was to relate physical activity to immune response and the immune response in covid 19 infection to describe variable outcomes of physical activity. The study was divided into three sub parts to describe the role of physical exercise to immune system, covid 19 and long covid.

Relation physical exercise to immune system

The intensity of the exercise in relation to beneficial effects on the immune response has been widely researched. Compelling evidence has been provided that moderate exercise enhances immune response whereas acute/intense exercise may lead to suppression of the immune response. Enhancement of the immune response was characterized by induced neutrophil counts and decreased eosinophil counts. The study of Romeo J et al. discussed has some limitations. Study design didn't control for sex differences, only adult men were

included. Other studies showed limited neutrophil infiltration as a response on tissue repair caused by acute exercise in women. It is thought this response is modulated by estrogenic levels and includes changes in cytokine production and cell proliferation and -activation (63). The differences in immune response between the sexes could potentially be mediated by adiposity (64). Also study design didn't include cytokine level counts which might provide different interpretation of the results.
Physical exercise also influences immunoglobulin excretion, particularly immunoglobulin-A. Intense/acute exercise showed an inverse excretion rate and moderate exercise showed increased excretion rate.
The effects of physical exercise on interleukin responses have been described to respond on tissue damage and infections. Especially interleukin 6. Interleukin-6 primarily is a pro-inflammatory cytokine in the immune response. However, the acute phase protein of interleukin-6 has anti-inflammatory and immunosuppressive effect when derived from skeletal muscles (myokine function). Exercise primarily causes an upregulation (up to 100-fold) of Interleukin-6 in the circulation, followed by an increase in interleukin-1 receptor antagonist and interleukin-10.
Physical exercise plays in important role in RAAS modulation. Figure 1 shows overview on two axes involved in immune response of the RAAS system. Increased activation of the ACE2/ANG 1-7/MAS axis by moderate exercise provides anti-inflammatory responses. Magalhães et al. (2020) showed this principle. Limitations in this study include again low and inclusive number of participants. Also, the major involvement in other physiological processes like blood pressure and extracellular fluid regulation can possibly influence the role of physical activity on RAAS modulation. Extra inclusion criteria should be added to limit this.

Relation physical activity on Covid 19

During Covid 19 confinement significant decreases in physical activity were noticed because of social isolation and quarantine. Result of physical inactivity is modulation of the immune response by systemic inflammation, reduced T-cell proliferation and cytokine production. Governmental restrictions have been implied in the Netherlands during high infection rate of Covid 19. One of the restrictions included limitations on group exercises and amateur sports because of the outdoor transmission concern. A review study of Mike Weed et al. (2020) consisting of 14 sources investigated the outdoor transmission of Covid 19 (66). Among 25.000 cases, a very few cases showed outdoor transmission indicating the very little incidence of transmission in outdoor places. Relating this to the physical inactivity because of social isolation and quarantine, this evidence is considerably important to stimulate physical activity during quarantine to influence the beneficial effects on the immune response.

A few mechanisms are responsible for the immune system to induce a more adequate immune response, also in Covid 19. Interferon modulation and modulation the response of a viral infection by innate immune cells, both under influence of physical activity. A cross-sectional study of Schmidt F. et al (2016) to characterize a profile of pro- and anti-inflammatory cytokines and the impact of physical activity in patients with obesity (67).

Results showed significant up-regulation of pro-inflammatory cytokines in obesity. The role of physical activity has been described in the reduction of incidence of noncommunicable diseases, like obesity. This study again indicates the important need for a physical active lifestyle to encounter immune related diseases.

Since the short onset of the Covid 19 pandemic, relatively little longitudinal data is available, simply due the limited timeframe. Analysis performed are likely to indicate responses on short-term notice but are unknown on the long-term. Therefore future research should focus on longitudinal cohort research to indicate long-term consequences of Covid 19 infections and the role of physical activity.

Relation physical activity and Long Covid

The term Long Covid is a collective name for the persistent sequelae of SARS-CoV-2 infection after acute infection. Sequelae often consist of fatigue, dyspnea, palpitations, hair loss, anxiety/depression and cognitive disturbance. Since the sequelae are multifactorial, underlying mechanism are currently not completely understood. Heterogeneous study designs, because of the variation in local prevalence, are providing data possible inconsistent which makes it difficult to interpretate. Currently latent immune memory is hypothesized to cause persistent sequelae. Longitudinal cohort studies with consistent criteria can help in the understanding of underlying mechanisms responsible for persistent sequelae and whether disease severity plays a role in the development of these sequelae.
The case study provided a possible role for SARS-CoV-2 in autonomous organ dysfunction, in this case respiratory dysfunction. The study of Motiejunaite et al. (2021) showed a case series of eight patients with exertional dyspnea at three months after onset. Normal lung function was determined. Specifically the autonomous respiratory response was targeted by the virus. Studies also reported loss of taste and smell function after SARS-CoV-2 infection which indicates modulation of the Central Nervous System by the virus. José Vergara et al. (2021) studied the potential influence of Olfactory, Gustatory, and Pharyngolaryngeal Sensory dysfunction on swallowing physiology in Covid 19 (68). Taste, smell and pharyngolaryngeal sensory function are important for normal swallowing function (69). Swallowing is an autonomous process. The study of José Vergara showed considerable evidence for Covid 19 as a potential neurologic invader, able to affect certain brain regions, in this case regions for smell, taste and perhaps swallowing. Covid 19 possibly act resemblant in autonomous respiratory dysfunction. Further research needs to be done.

To conclude, physical activity is proved to play an role in innate and adaptive immune responses and therefore of interest in Covid 19 research. Due to the short onset of the pandemic, long-term consequences of Covid 19 are largely unknown and currently researched. Longitudinal cohort studies can contribute in clarification of the Covid 19 pathophysiology and treatment possibilities.

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