Sports Medicine and Health Science xxx (xxxx) xxx

Contents lists available at ScienceDirect

Sports Medicine and Health Science

journal homepage: www.keaipublishing.com/smhs

Review

Physical activity during COVID-19 pandemic: A 5-year retrospect

Jeffrey A. Woods [a,b], Noah T. Hutchinson [a,b], Scott K. Powers [c], Mari Carmen Gomez-Cabrera [d], Zsolt Radak [e,f], Christiaan Leeuwenburgh [g], Stefano Cacciatore [h], Emanuele Marzetti [h,i], Tianou Zhang [j], Ronaldo Garza [k], Corby Sidebottom [k], Elizabeth Anderson [l], J. Larry Durstine [l], Junzhi Sun [m], Li Li Ji [n,*]

[a] Department of Health and Kinesiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[b] Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[c] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA
[d] Freshage Research Group, Department of Physiology, Faculty of Medicine, University of Valencia and CIBERFES, Fundación Investigación Hospital Clínico Universitario/INCLIVA, Valencia, Spain
[e] Hungarian University of Sport Science, Budapest, Hungary
[f] Waseda University, Tokyo, Japan
[g] College of Medicine, University of Florida, Gainesville, FL, USA
[h] Department of Geriatrics, Orthopedics and Rheumatology, Università Cattolica del Sacro Cuore, Rome, Italy
[i] Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[j] Department of Health and Exercise Sciences, University of the Pacific, Stockton, CA, USA
[k] Department of Kinesiology, The University of Texas at San Antonio, San Antonio, TX, USA
[l] Department of Exercise Science, University of South Carolina, Columbia, SC, USA
[m] Institute of Sports Medicine and Health, Chengdu Sport University, Chengdu, China
[n] School of Kinesiology, University of Minnesota Twin Cities, Minneapolis, MN, USA

ARTICLE INFO

Keywords:
Aging
Brain
Cardiac intolerance
Covid-19
Immune system
Long-COVID
Musculoskeletal
Physical activity

ABSTRACT

The purpose of this article is to provide a follow-up review of the impact of the SARS-CoV-2 Disease or Coronavirus Disease 2019 (COVID-19) pandemic on human health and the role of physical activity (PA) during the 5-year pandemic. We aim to cover the immune system, the cardiopulmonary system, the musculoskeletal system, and the central nervous system (brain function), particularly among older adults, college students, and individuals with post-acute sequelae of COVID-19 (Long-COVID). The COVID-19 pandemic has given us many lessons, learned from the death of six million lives and tremendous disturbance to human life. First, we need to continue to investigate cellular and molecular mechanisms that mediate various organistic failures resulting from the viral infection. Such investigations are the only way to completely understand the etiology of the diseases and to develop new drugs and vaccines. The molecular pathways that transmit the signals of viral infection to each organ system are different requiring both basic and clinical research. Available evidence suggests that mitochondrial dysfunction, reduced microcirculation and latent immune activation play a major role, eventually impairing cardiovascular tolerance and peripheral bioenergetics. Second, the COVID-19 pandemic has manifested major disturbances to human lifestyles with reduced PA and exercise standing out as a major factor. Conversely, physical inactivity due to social confinement and mental/psychological stresses has been clearly linked to intensified pathogenic symptoms and amplification of adverse effects on multiple physiological systems. If not intervened, this interaction can lead to Long-COVID, a dangerous futile circle to cause systemic failure. Finally, the COVID-19 pandemic has exerted differential impacts on different populations. Thus, the strategy to develop and conduct to cope with the negativity of pandemic needs to be specific, flexible and tailored to fit different patient populations.

* Corresponding author. School of Kinesiology, University of Minnesota Twin Cities, Minneapolis, MN, 55455, USA.
E-mail address: llji@umn.edu (L.L. Ji).

Peer review under the responsibility of Editorial Board of Sports Medicine and Health Science

https://doi.org/10.1016/j.smhs.2025.11.001

Available online xxxx

2666-3376/© 2025 Chengdu Sport University. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Please cite this article as: Woods JA et al., Physical activity during COVID-19 pandemic: A 5-year retrospect, Sports Medicine and Health Science, https://doi.org/10.1016/j.smhs.2025.11.001

List of abbreviations

ACE2	Angiotensin-converting enzyme 2
APCs	Antigen presenting cells
BDNF	Brain-derived neurotrophic factors
PA	Physical activity
EVS	Exercise vital sign
HIIT	High-intensity interval training
IFN	Interferon
IL-1	Interleukin-1
IL-6, IL-1β, IL-8	Interleukins
MHC	Major histocompatibility complex
$\dot{V}O_2$max	Maximal oxygen consumption
MACs	Membrane attack complexes
NK	Natural killer
Long-COVID	Post-acute sequelae of COVID-19
POTS	Postural orthostatic tachycardia syndrome
RIG-1	Retinoic acid-inducible gene-I-like receptors
COVID-19	SARS-CoV-2 Disease or Coronavirus Disease 2019
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor-alpha

1. Introduction

Since the publication of our first paper *on Sport Medicine and Health Science* in 2020,[1] which cautioned against a potential second-waive health hazard due to physical inactivity resulting from quarantine during SARS-CoV-2 Disease or Coronavirus Disease 2019 (COVID-19) development, great attention has been paid to the role and benefit of exercise in dealing with the pandemic. A total of 10 000 articles has been published on this subject since 2000 based on PubMed database alone. Despite intense research, vaccine development and clinical practices in its prevention and treatment, COVID-19 virus remains a major threat to human health and wellbeing worldwide. Over the past five years, it has become increasingly clear that COVID-19 not only can cause major adverse effects on organs and tissues, leading to several well-defined acute and chronic diseases, but can also negatively influence people's motor behavior, levels of habitual physical activity (PA), susceptibility to viral infection, eating and nutritional patterns, and psychological status. For example, it is reported that 35% of patients have not returned to pre-COVID-19 PA levels one year after infection.[2] The percentage reduction in total daily PA among children and adolescents from before to during COVID-19 was −20%.[3] The changes were larger for higher-intensity activities (−32%; range −44% to −16%), corresponding to a 17-minute (min) reduction in children's daily moderate-to-vigorous PA. Furthermore, the pandemic caused a negative impact on special populations such as black individuals, cigarette smokers, the obese, and low-income people in the United States.[4] No evidence exists that moderate to vigorous PA may reduce the odds of contracting SARS-CoV-2 infection, hospitalization, and mortality due to COVID-19 compared to no PA. Especially, when METs $\geq$ 500 min/week expenditures were linked to decreased morbidity and mortality of COVID-19[5] Being physically active before and immediately after a severe infection episode substantially lowers the risk of developing post-acute sequelae of COVID-19 (Long-COVID).[6]

While most research on the relationship of PA and COVID-19 caused health issues has been focused on behavior changes, a significant portion of studies have addressed specific physiological consequences due to reduced PA, such as the immune system,[7] cardiac complications,[8] neurological disorders,[9] diabetes,[10] and mental health.[11] The aged population is particularly vulnerable to viral infection and systemic damage. Organs and cells harboring angiotensin-converting enzyme 2 (ACE2) surface receptors are the primary targets of the SARS-Cov-2 virus; however, once entering the body through the respiratory system, the virus spreads hematogenously to infect other body organs.[12] In addition, the emergence of individual studies revealing molecular mechanisms underlying Covid virus-induced cellular changes such as endocrine-inflammatory responses,[13] mitochondrial dysfunction.[14,15] Overall, a paucity of data exists investigating cellular mechanisms underlying adverse effects caused by sedentary behavior due to COVID-19 pandemic.

The goal of this review is to provide a 5-year retrospect on various physiological fields potentially affected by insufficient PA and exercise. Original authors were called upon to update his/her points of view since the last review. Invariably, they provided new perspectives on our understanding of the viral impact on the systems and areas of effort in which we need to defeat the pandemic.

2. Role of the immune system

Since the outset of the pandemic, numerous studies have been published analyzing the association between PA and exercise and outcomes related to COVID-19 infection. Perhaps the most significant of these outcomes are work performed by Sallis and colleagues who leveraged Kaiser Permanente electronic health records and their Exercise Vital Sign (EVS) self-report data on PA levels.[16] EVS was shown to have good validity with accelerometry data,[17] and minutes per week of moderate-vigorous PA is used to calculate PA categories.

Using a retrospective cohort study with 48 440 adults, Sallis et al. found that patients with COVID-19 who were physically inactive had a higher risk for hospitalization (odds ratio 2.3x), admission to the ICU (odds ratio 1.7x), and death (odds ratio 2.5x) when compared to those meeting recommended PA guidelines $\geq$ 150 min per week.[18] Benefits, even for those individuals engaging in some PA (11–149 min per week) compared to those individuals that did not. In a longer (17 vs 10 mos) and larger (194 191 patients) follow-up study from this same group. Young et al. found that PA-COVID-19 outcome associations were consistent across demographic (race/ethnicity, age, BMI, smoking) and chronic disease subgroups (diabetes, cardiovascular, renal, cancer, hypertension).[16] COVID-19 vaccinations were just becoming available during the latter part of this study, so differences as to whether PA improved outcomes among vaccinated individuals were made. These findings were corroborated by Munoz-Vergara et al. who found that among 61 557 patients, those individuals that adhered to PA guidelines pre-pandemic had lower odds of developing or being hospitalized for COVID-19.[19] Important to note is that a smaller (n = 209) cohort study in Brazil found that PA was not associated with hospital length of stay or other clinically relevant outcomes.[20]

These largely intriguing findings raise the question '*What is it about physical activity that promotes better COVID-19 infection outcomes?*' The question is difficult to address but is likely either a *direct* effect of PA on the immune system or an *indirect* effect of PA in preventing and treating chronic conditions like diabetes, obesity, hypertension, and cardiovascular disease that seem to put people at risk for poorer COVID-19 outcomes, or both. This section will explore the former, whether PA affects immune functioning.

To better understand whether PA provides a protective effect through improving immune function, an understanding of the immune response to COVID-19 infection is needed. The COVID-19 spike protein interacts with the host ACE-2 receptor and transmembrane serine protease 2 for the entry of SARS-CoV-2 into the cell cytosol. Initial COVID-19 infection and tropism largely occur in nasal epithelial cells and lung tissue where both proteins are heavily co-expressed.[21,22] Upon infection, various Toll-like receptors (TLRs), Retinoic acid-inducible gene-I-like receptors (RIG-1)-like receptors, or complement proteins recognize the SARS-CoV-2 envelope protein, RNA, or spike protein and initiate the innate immune response.[23] In ideal conditions, this recognition quickly initiates proinflammatory cytokine (tumor necrosis factor-alpha [TNF-α] and interleukin-1 [IL-1]) and interferon [IFN] release by infected cells and immune cells such as macrophages, dendritic cells,

and natural killer (NK) cells and implements various antiviral defenses such as granulocyte recruitment, killing/death of infected cells, and the formation of various antiviral factors such as membrane attack complexes (MACs) to lyse viral particles and limit viral replication. Concurrently, this signaling cascade recruits antigen presenting cells (APCs) such as dendritic cells, macrophages, and B cells to initiate the adaptive immune response consisting of cytolytic T $CD8^+$ cells and antibody-producing B cells. To initiate the adaptive response, recruited APCs endocytose viral antigen for proteolytic processing and formation of a major histocompatibility complex (MHC) class I and II.[24] MHC I is presented along with other APC intrinsic co-stimulators to $CD8^+$ T cells, promoting their activation and virus specific cytotoxicity.[25] MHC II is introduced to $CD4^+$ or helper T cells, which traffic to lymph tissue to promote B cell maturation and ultimately the production of virus specific antibodies which efficiently neutralize and promote opsonization of the target pathogen.[26] This process usually takes 4–7 days to complete and as a result, the body is ultimately equipped with highly effective, specific, and prolonged immune defenses against SARS-CoV-2. Most individuals who have previously been infected with COVID-19 produce high levels of IgM, IgG, and IgA antibodies specific to the SARS-CoV-2 spike protein, a characteristic which is predictive of protection from severe infection.[27] Given the prevalence of COVID-19, many individuals have already mounted adaptive immune responses and began producing COVID-19 antibodies either through prior infection, vaccination, or both. Vaccinations have been widely available in several different forms that demonstrated effectiveness to protect against COVID-19.

Several possibilities are presented as to how PA might affect the virus-specific defenses outlined above. One could argue that exercise might increase the risk for COVID-19 due to increased movement of air across respiratory epithelial surfaces, however that would not explain the improvements in COVID-19 outcomes seen to date. In humans, aerobic exercise induces an increase in plasma ACE2 in some individuals,[28] however, to our knowledge, protein expression in the upper respiratory tract has not been examined. One suggested hypothesis is exercise-induced activation of ACE-2 pathways in humans leads to anti-inflammation which could benefit COVID-19 infection.[29] Animal studies have found either an exercise-induced increase[30] or a decrease[31] in ACE-2 mRNA lung gene expression. Tamura et al.[32] demonstrated an exercise-training induced increase in ACE-2 receptor protein expression in mice in tissues susceptible to COVID-19 infection, including lung tissue which also is not consistent with a potential for improvements in COVID-19 outcomes in physically active subjects. To our knowledge, no studies exist examining the influence of PA on IFN levels in humans. This finding is important because COVID-19 reduces IFN production as part of IFN's immune evasion tactics.[33] In the few animal studies performed using various models to stimulate IFN, acute strenuous exercise appears either has no impact[34] or inhibits[35,36] IFN. Kohut et al. found that exhaustive exercise increased alveolar macrophage IFN, but the authors hypothesized that increased viral infectivity of macrophages from exercised animals was responsible.[37] A limitation of these studies is that a) no work has been done on moderate levels of exercise, and b) the animal models of exercise used were forced (treadmill) not volitional (running wheel).

More general explanations exist as to how PA and exercise might impact viral infection and the immune response in general. Exercise is known to increase the circulation of immune cells, especially memory and effector cells that have higher functionality. Baker et al. recently reported that acute exercise was capable of mobilizing SARS-CoV-2 specific $CD8^+$ T cells in individuals with natural immunity, and transiently increased neutralizing antibodies.[38] A common observation among severe cases of COVID-19 is termed NK cell 'exhaustion', meaning impaired proliferative and cytotoxic function ex vivo, yet transcriptional profiles indicating high levels of activation.[39] As such, Bao et al. found that of all leukocyte counts in the serum, NK cell count was correlated the most with survival rate and least with severity of disease.[40] Also known is that exercise increases NK cell numbers and their function.[41] Llaver et al. recently found that 4 weeks of moderate-intensity continuous training followed by 4 weeks of high intensity interval training was capable of improving NK cell cytotoxicity and favorable regulation of proteomic pathways associated with various aspects of immune function such as transmembrane transport or oxidation reduction reactions.[42] This favorable regulation is thought to increase immunity by increasing the probability that immune-competent cells will encounter their respective antigens (an increase in immunosurveillance), thus reducing infection outcomes. While logical, this favorable regulation has not been proven experimentally.

PA has also been associated with anti-inflammation, especially chronic low-level inflammation.[43] While the mechanisms are unknown several factors may contribute to this anti-inflammatory effect including, exercise-induced reductions in TOLL-like receptor (TLR) expression, increases in interleukin-6, reductions in inflamed body fat, and activation of the hypothalamic-pituitary adrenal axis. While some level of inflammation is necessary to mount an effective immune response, a reduction in exaggerated inflammation, like which occurs during COVID-19, may improve symptoms and disease positive course change.

Immune responses to vaccination can inform about the generation of protective T cells and antibodies. Although not a typical route of entry for respiratory viral infections, evidence exists for the beneficial effects of exercise on immune responses to vaccination which are generally given intramuscularly. As examples, multiple studies have shown moderate exercise training to improve the serum antibody response to intramuscularly administered vaccinations (i.e., influenza), or a primary experimental protein antigen (i.e., keyhole limpet hemocyanin), especially in those with poorer vaccine responses.[44,45] With respect to COVID-19 vaccination, Hallam et al. recently reported that a single 90 min cardiovascular aerobic exercise session immediately after vaccination improved IgG responses to the Pfizer mRNA vaccine.[46] In an immunocompromised population, Gualano et al. found that physically active participants had better responses to COVID-19 vaccination when compared to relatively inactive participants.[47] These data support the contention that physically active people mount better immune responses than sedentary people.

In summary, PA is associated with better outcomes after COVID-19 infection and regular exercise plays a role in supporting immune function. Engaging in PA can help strengthen the immune system, making immunity more resilient to infections. Present studies show consistent exercise enhances the production of antibodies and mobilizes leukocytes, which are essential for fighting off viruses and bacteria. Additionally, exercise and PA promote better circulation, which allows immune cells to move more efficiently throughout the body. As the world continues to navigate the challenges of COVID-19, prioritizing PA and exercise as part of a healthy lifestyle contributes to overall well-being and improved immunity.

3. Mechanism(s) responsible for Long-COVID exercise intolerance

The COVID-19 pandemic resulted in high morbidity in patients with increased risk for severe COVID infections. Key risk factors for morbidity with COVID-19 infection include old age, male sex, obesity, pre-existing morbidities, and high levels of circulating pro-inflammatory cytokines.[48] Patients with risk factors for severe COVID-19 were often hospitalized and many received ventilator support due to the development of respiratory failure.[48] Moreover, the World Health Organization estimates that 10%–20% of COVID-19 survivors worldwide suffer from Long-COVID.[49] Long-COVID often involves multiple symptoms including exercise intolerance, fatigue, dyspnea, headache, change in taste or smell, and stomach pain.[50]

One of the most debilitating symptoms of Long-COVID is exercise intolerance. Long-COVID exercise intolerance is a complex clinical problem broadly defined as the inability to comfortably perform a session of muscular exercise due to exacerbation of symptoms. Hallmarks of

exercise intolerance are dyspnea and fatigue upon exertion.[51]

Submaximal and maximal oxygen consumption ($\dot{V}O_2$max) during exercise is defined by the Fick equation as the product of cardiac output and the arteriovenous oxygen difference. Thus, cardiac output is heart rate times stroke volume, and the arteriovenous oxygen difference reflects the peripheral oxygen extraction and utilization in tissues.[48] Hence, exercise intolerance in patients is expected to involve limitations in ventilatory function, cardiovascular function, and/or peripheral delivery and utilization of oxygen. Therefore, the mechanisms responsible for Long-COVID exercise intolerance likely involve one or more physiological factors[51]: 1) impaired pulmonary gas exchange and/or dyspnea; 2) diminished submaximal and/or maximal cardiac output; and/or 3) decreased uptake and utilization of oxygen in the working muscles. A summary of our understanding of each of these factors follows.

3.1. Pulmonary dysfunction

Although mild cases of COVID-19 may not result in lung injury, moderate-to-severe COVID-19 infections can promote significant lung damage.[48] Moreover, COVID-19-related lung injury is often exacerbated when patients are exposed to prolonged mechanical ventilation.[52,53] Specifically, post-mortem examination of lungs from patients who died from COVID-19 infection reveals significant alveolar membrane damage, alveolar and interstitial edema, endothelial cell injury, and damage to capillaries surrounding the alveoli.[48] Collectively, these COVID-19-related changes in lung structure can negatively impact both respiratory mechanics and blood flow to the lung. Further, damage to alveoli results in a reduction of the alveolar surface area available for the diffusion of gases. Indeed, approximately 40% of survivors from severe COVID-19 suffer from impaired pulmonary diffusion capacity.[54] It follows that impaired pulmonary diffusion could result in exercise-induced hypoxemia, decreased oxyhemoglobin saturation, and therefore, a reduction in oxygen content of arterial blood. Moreover, studies reveal that > 50% of Long-COVID survivors complain of dyspnea upon exertion.[51] Hence, in theory, COVID-induced lung injury can contribute to the exercise intolerance associated with Long-COVID due to exercise-induced hypoxema and/or exertional dyspnea.

To date, limited evidence supports the concept that exercise-induced hypoxemia is a key contributor to Long-COVID exercise intolerance. In fact, even in Long-COVID patients with below normal pulmonary diffusion capacities, frank exercise-induced hypoxemia has not been reported in this population.[55–60]

Although exercise-induced hypoxemia may not contribute to exercise intolerance in Long-COVID patients, exertional dyspnea is predicted to promote exercise intolerance in many patients.[51,61] For example, dyspnea upon mild exertion exists in > 50% of Long-COVID patients.[51,61] Interestingly, many studies involving Long-COVID patients do not report a strong correlation between dyspnea and abnormal pulmonary function tests.[51] This lack of association is surprising given that the major receptors responsible for the sensation of dyspnea include chemoreceptors, mechanoreceptors, and lung receptors.[62,63] However, two recent studies report that dysfunctional breathing (i.e., excessive hyperventilation) occurs during exercise in > 88% of Long-COVID patients.[61,64] Both studies conclude that dyspnea was a major factor in limited exercise tolerance in these patients. Regardless of the cause of dyspnea in Long-COVID patients, exertional dyspnea is likely a key contributor to exercise intolerance in > 50% of Long-COVID patients.[51]

3.2. Impaired cardiac function

As introduced earlier, impairments in cardiac output during exercise are a potential contributor to exercise intolerance in Long-COVID patients. Cardiac injury has been reported in a small fraction of COVID patients but the mechanisms responsible for cardiac damage are not fully understood.[65] Regardless of the mechanism(s) responsible for COVID-induced cardiac injury, a decreased maximal cardiac output has been reported in Long-COVID patients who exhibit exercise intolerance (reviewed in Refs. [66,67]). Indeed, compared to healthy individuals, some Long-COVID patients exhibit lower stroke volumes during exercise at or near $\dot{V}O_2$max.[68,69] Nonetheless, not all reports agree that the Long-COVID decrease in $\dot{V}O_2$max is due to decreases in stroke volume.[70] The potential contribution of impaired peripheral oxygen consumption as a causative for exercise intolerance in Long-COVID patients is discussed in the next segment.

3.3. Impaired peripheral oxygen delivery/utilization

Finally, a peripheral limitation to oxygen delivery and utilization has also been postulated to contribute to exercise intolerance in Long-COVID patients.[51] Again, as defined by the Fick equation, $\dot{V}O_2$max is computed as cardiac output X arteriovenous oxygen difference. Therefore, limitations in the delivery of oxygen to working muscles and/or impaired mitochondrial respiration can result in decreases in both oxygen consumption and exercise intolerance. To date, only one study has directly measured cardiac output and the arteriovenous oxygen difference during exercise in Long-COVID patients. This study demonstrated that, compared to healthy controls, the reduction in peak $\dot{V}O_2$ in Long-COVID patients is due to peripheral limitations (i.e., decreased arteriovenous oxygen difference) rather than a decrease in cardiac output.[70] Two additional studies reported that in Long-COVID patients with normal cardiac output during exercise, the oxygen pulse (i.e., $\dot{V}O_2$/heart rate) was diminished, suggestive of impaired peripheral oxygen delivery and/or extraction.[57,71]

Although Long-COVID patients have been postulated to suffer peripheral limitation due to impaired diffusion of oxygen to muscle fibers,[70] direct experimental evidence to support this conclusion does not currently exist. Indeed, a decrease in the arteriovenous oxygen difference during exercise in Long-COVID patients could be due to either diffusion limitations or mitochondrial dysfunction. Although electron micrographs of skeletal muscle biopsies from Long-COVID patients show a disrupted mitochondrial network in muscle fibers,[72] direct measurements of mitochondrial oxidative phosphorylation in these mitochondria have not been performed; this area is important for future work.

Predictions of 10%–20% of COVID-19 survivors worldwide suffer from Long-COVID; Long-COVID is associated with multiple symptoms including exercise intolerance. Proposed mechanisms responsible for Long-COVID exercise intolerance include impaired pulmonary gas exchange and/or dyspnea, diminished cardiac output, and/or decreased uptake and utilization of oxygen in skeletal muscles. Evidence exists to support each of these proposed mechanisms for exercise intolerance. Specifically, although research does not support the idea that impaired pulmonary gas exchange limits exercise tolerance in Long-COVID patients, > 50% of Long-COVID patients suffer from exertional dyspnea and likely contributes to exercise tolerance. Evidence also indicates that in select Long-COVID patient populations, a decrease in maximal cardiac output (due to the inability to increase augment stroke volume) is another potential mechanism that promotes exercise intolerance. Finally, data exist that an impaired ability to deliver and/or use oxygen in the working muscles is present in some Long-COVID patients. Together, these findings indicate that dyspnea likely contributes to exercise intolerance in > 50% of Long-COVID patients. Nonetheless, other mechanisms (decreased cardiac output and peripheral limitations) may also contribute to exercise intolerance in some patients.

4. Impact of COVID-19 on musculoskeletal system

Our ability to move, maintain body posture, swallow, and breathe depends on our skeletal muscle, the largest organ in our body that makes up approximately 40% of our total body mass.[73] Movement is natural to

us, and our muscles are devised to mechanically comply with our daily command.[74,75] Muscles involved in locomotion are continuously exposed to stress and strain leading to functional impairment.[76]

COVID-19 is an infectious disease that can lead to Long-COVID. Skeletal muscle-related symptoms are common in both acute COVID-19 and Long-COVID patients. These symptoms include muscle pain and weakness (mild to severe), fatigue, and exercise intolerance.[77] Disability caused by remaining symptoms after the initial SARS-CoV-2 infection has also been reported.[78]

The recently published comprehensive study of global health (Global Burden of Disease 2021 Collaborators 1990–2021) loss clearly shows that disability has been growing in the last decades mainly due to an increase in non-communicable diseases.[79] The Global Burden of Disease 2021 Collaborators presents, for the first time, estimates of health loss due to the COVID-19 pandemic. The emergence of the COVID-19 pandemic has prompted a reevaluation of global health priorities, highlighting the importance of conducting a comprehensive assessment of disease impact.[79]

Most patients with COVID-19 recover relatively quickly, do not require hospitalization, only experience mild symptoms, or are asymptomatic. However, an important proportion of Long-COVID patients experience persistent symptoms such as fatigue and dyspnea.[72] The high prevalence of skeletal muscle-related symptoms suggests both functional and structural alterations in skeletal muscle in COVID-19 patients. Structurally speaking, the patients show a very significant reduction in skeletal muscle mass that is accompanied by muscle fiber necrosis, signs of regeneration, disruption in sarcomeric ultrastructure, myofibrillar disarray, and loss of myosin and Z disk organization[77] Functionally speaking, the specific muscular alterations found in patients with COVID-19 include significant reductions in power and strength related to the duration of the hospital stay.[77] Although viral particles have been found in skeletal muscle from COVID patients, the low virus levels prevent determining whether the SARS-CoV-2 virus directly causes muscle atrophy and weakness.[80] Skeletal muscle functional loss resides in the muscle itself, but also a significant portion seems accounted for by neural changes operating at the peripheral and central levels in Long-COVID patients.[81]

The molecular mechanism involved in the loss of muscle mass in COVID-19 patients includes the activation of calpains and the ubiquitin-proteasome pathway,[82] alterations in mitochondrial quality control (mitophagy) and dynamics (fusion and fission), and inflammation.[72] The cytokine storm of pro-inflammatory mediators plays an important role in developing skeletal muscle atrophy and altered metabolic function in acute patients with COVID-19. Plasma levels of C-reactive protein, interleukins (IL-6, IL-1β, IL-8), and TNF-α have been found elevated in COVID-19 patients.[77] Increased plasma levels of pro-inflammatory proteins are related to increased protein breakdown and inhibited muscle protein synthesis.[83] Moreover, skeletal muscle samples from people who died of severe COVID-19 show substantial infiltration of leukocytes, T-cells, and natural killer cells. This filtration is accompanied by an increase in circulating markers of skeletal muscle breakdown, such as creatine kinase.[72]

During hospitalization, patients with severe COVID-19 are susceptible to the development of an acute myopathy, known as critical illness myopathy.[84] Risk factors for developing this illness include sepsis, respiratory failure, the need for mechanical ventilation, and treatment with corticosteroids or neuromuscular junction-blocking agents. Neuromuscular junction-blocking agents can aid in promoting patient-ventilator synchrony and decreasing the driving pressure required during mechanical ventilation. These agents are also beneficial during endotracheal intubation to reduce the risk of patient coughing and potentially infecting healthcare personnel.[85]

Three main factors involved in the development of skeletal muscle-related symptoms found in Long-COVID patients include: 1) adverse effects of medications used in the management of patients (hydrocortisone and neuromuscular junction-blocking agents); 2) muscle disuse and mechanical unloading, and 3) malnutrition.[72] Physical inactivity impairs muscle function and metabolic health, leading to reductions in $\dot{V}O_2$max, increased fatigability, and exercise intolerance.[74] Skeletal muscle deconditioning does not require prolonged periods of bed rest. The greatest rate of muscle strength weakness and atrophy occurs in the earliest stages of bed rest (first five days), plateauing later.[81]

Malnutrition is very prevalent in COVID-19 patients.[86] The bioavailability of dietary amino acids, their splanchnic extraction, plasma transport, and absorption by the skeletal muscle for the subsequent activation of protein synthesis, determines the skeletal muscle anabolic response. No consensus exists regarding the most effective management strategies to improve exercise tolerance in acute COVID-19 and Long-COVID patients. Physical therapy has shown effectiveness in preventing and ameliorating illness myopathy.[86] Exercise is one of the most frequently prescribed therapies both in health and disease.[87] Exercise training is essential in preserving muscle mass and function through the activation of muscle protein synthesis.[88] On the contrary, the lack of muscle contractile activity during inactivity, especially in old individuals, is a leading cause of anabolic resistance and muscle atrophy.[74] Recent work has highlighted the potential effectiveness of neuromuscular electrical stimulation on the recovery of ICU-admitted patients with COVID-19.[89] Tailored interventions based on a deeper understanding of skeletal muscle changes and their root causes are necessary to mitigate clinical symptoms and enhance the quality of life for patients with acute COVID-19 and Long-COVID.

5. Exercise, COVID-19 and brain health

COVID-19 is a systemic disease, and as predicted, the brain is also targeted by this virus.[1] The susceptibility to infection-caused health problems is dependent upon genetic, health, environmental, and lifestyle factors. A higher level of physical fitness has powerful preventive effects in a wide range of diseases,[90] however, COVID-19 infection and co-infections with a wide range of health-damaging effects do not spare well-trained individuals. The COVID-19-associated inflammatory storm not only targets the cardio-pulmonary system but also causes serious cerebrovascular alterations, which have worse therapeutic outcomes.[91] Indeed, COVID-19 viruses can cause large-vessel ischemic stroke,[92] suggested as a result of inflammatory storm, subsequent hypercoagulability, and vasculitis.[93] COVID-19 increases blood clotting, via cascades that include angiotensin II, oxidative stress, and related endothelial dysfunction, platelet aggregation, and blood clots.[94] Among other organs, the brain and vessels express a high level of ACE2, which are the gates of the virus into cells. Because ACE2 receptors are on the surface of endothelial cells, COVID-19 can readily cause endothelial dysfunction and related hemorrhage which in the capillaries of the brain is especially dangerous. The damage to endothelial changes the permeability and exposes cells to inflammatory infiltration and related cell death. The consequences of cytokine storm-associated events in the nervous system are life-threatening. COVID-19 infections directly affect the health status of subjects and easily could cause hospitalization, and a cascade of lifestyle-changing events. Turns out that nutritional and exercise and PA habits, especially the level of cardiovascular fitness were influencing the severity of infections[95] and the efficiency of recovery, namely, more exercise was associated with faster recovery.[96]

The effects of the pandemic, especially the lockdown on the level of physical fitness, brain function, and mental health are well documented.[97] During the pandemic, Americans ate more fast food, smoked more, drank more alcohol, had increased screen time, and performed less PA than before the appearance of COVID-19.[98] The results of a Brazilian study suggest that physically active elderly subjects suffered less from COVID-19-related mood changes than physically inactive aged-matched sedentary.[99] Italy was severely hit by COVID-19, showing the highest case fatality rate, and was one of the first countries to introduce a lockdown, which caused drastic lifestyle changes and the

development of depressive symptoms. Ricci et al.[100] revealed that during lockdown periods both moderate and vigorous PA were important protective tools for preserving mental health, and these results further underscored the powerful effects of regular exercise on cognitive and mental well-being. Indeed, the pandemic-associated increase in physical inactivity and other adverse habits and unhealthy lifestyle changes was associated with increased mental problems.[98]

Exercise is known to have a powerful effect on brain health and is associated with exercise-induced beneficial regulation of molecular pathways, and the production of neurotrophins, neurotransmitters, hormones, and associated peptides like oxytocin, and serotonin. Moreover, exercise helps to maintain structural features of the brain.[101] This exercise benefit is partly the opposite of the causative factors of depression, which include decreased availability of monoamines (especially serotonin, noradrenaline, and dopamine) in the synaptic cleft.[102] Brain-derived neurotrophic factors (BDNF) are one of the most well-studied exercise-induced antidepressants.[103] The molecular mechanism by which BDNF exerts antidepressant effects is suggested to include neurogenesis, brain plasticity, and upregulation of serotonin, dopamine, and irisin. The exercise-induced upregulation of peroxisome proliferator-activated receptor-gamma coactivator-1alpha, which leads to the activation of irisin precursor Fibronectin type III Domain-Containing protein 5.[104] Circulating irisin is neuroprotective and activates BDNF, and higher levels of irisin are associated with increased memory in healthy subjects.[105] In an animal model, supplementation of irisin decreased depression and increased mobility.[106]

In addition, the gut-brain axis is implicated in the regulation of certain cognitive and behavioral functions, and exercise has been proposed in the exercise-mediated antidepressant role, and at least a part is due to attenuated serotonin uptake into the gut microbiome.[107] Overall, exercise is one of the most powerful tools to cope with neurodegenerative diseases[108] and improve mental health.[109]

Vaccination provides significant protection against the very serious effects of the COVID-19 virus, but as with all of the vaccinations, COVID-19 vaccinations also could have side effects. The adenovirus-vectored vaccines are very safe and after many millions of shots, very few studies have found a causative relationship between COVID-19 vaccination and neurodegenerative disorders. One possible, but not well-proven relationship to COVID-19 vaccination is to Guillain-Barré syndrome,[110] an autoimmune disorder with symptoms that include muscle weakness.

The COVID-19 pandemic and lockdowns negatively changed the lifestyle of billions of people, partly because we were unprepared. On the other hand, this experience could be very useful to cope with the next epidemics with greater success. Although a high level of physical fitness does not appear to prevent infections, an elevated level of the immune system, which is a result of regular exercise provides greater protection against the severity of infections. Regular exercise and PA are extremely important to mental and cognitive health and are a natural means to stay healthy even in stressful periods, like a pandemic. Important to note, due to the super complexity of exercise-induced adaptation no alternative to substitute for exercise exists by any mimetics.

6. The consequences of COVID-19 in older adults

Since the onset of the SARS-CoV-2 pandemic, older adults clearly face the most severe consequences of COVID-19. Between 2020 and 2021, more than 80% of COVID-19-related deaths worldwide occurred in individuals 60 years or older,[111] with advancing age being one of the most prominent risk factors for severe and critical disease.[112] The development of safe and effective SARS-CoV-2 vaccines contributed to reducing the contagion in the latest years.[113] However, a concern remains that older adults might experience a reduced response to vaccination.[114,115] highlighting the need for ongoing vigilance and tailored strategies to protect this vulnerable population.

6.1. Acute SARS-CoV-2 infection in older adults

Immunosenescence, non-communicable diseases, sarcopenia, multimorbidity, and frailty increase both the incidence of COVID-19 infections and severity.[116–118] Besides biological factors, a significant share of the COVID-19 impact in older adults is attributed to social vulnerability, including social isolation, living in long-term care facilities, limited access to technology, low income, and poor education.[119,120] Atypical presentation of COVID-19 has frequently led to delayed recognition and intervention.[121,122] When severe cases were identified, access to noninvasive ventilation and intensive care unit (ICU) were often restricted during peak periods of the pandemic, with chronological age used as the sole factor for determining eligibility for intensive care, overlooking frailty, and other health considerations.[123] COVID-19 hospital and ICU admissions have been associated with incident sarcopenia,[86] malnutrition,[124,125] and progression of frailty,[126,127] which increases complications,[126,128] prolonged length of stay,[129–131] readmissions,[132] disability,[133] and mortality.[125,126,134–138] To reduce the impact of SARS-CoV-2 infection among older adults, the recommendation is for comprehensive geriatric assessments to be prioritized, moving beyond mere age considerations. These assessments should involve complete evaluations of frailty, nutritional status, and physical function, tracing personalized care strategies to meet individual needs. Moreover, tailored programs aimed at reducing immobility, deconditioning, functional impairment, and disability following hospitalization for COVID-19 should be implemented.[139–141]

6.2. Impact of Long-COVID on older adults

Both mild and severe COVID-19 may be followed by signs and symptoms persisting weeks to months after resolution of the acute infection phase. Long-COVID[142,143] pathogenesis is not fully understood and is likely multifactorial, involving persistent viral reservoirs, immune system dysregulation, organ damage, and psychosocial factors.[142,143] In older adults, the effects of Long-COVID can be particularly pronounced due to pre-existing physiological vulnerabilities and the higher prevalence of chronic conditions.[144–146] Prolonged inflammatory response and immune dysregulation leave older individuals more prone to chronic inflammation, which manifests as fatigue, muscle weakness, and cognitive disturbances[147–151] Direct damage inflicted by SARS-CoV-2 to lungs, heart, and kidney exacerbates existing conditions, resulting in breathlessness, palpitations, and renal dysfunction.[12,152] Endothelial dysfunction can hesitate into vascular inflammation and thrombosis, impairing blood flow and oxygenation, thereby contributing to fatigue and exercise intolerance.[153,154]

Available evidence supports tailored interventions aimed at facilitating recovery and rehabilitation after acute COVID-19.[155] Comprehensive nutritional assessment and therapy should be implemented to tackle malnutrition, treat sarcopenia, and prevent functional decline. Some bioactive foods and supplements may help mitigate post-acute symptoms.[156–158]

6.3. The indirect effects of SARS-CoV-2 pandemic in older adults

Even in older adults who never contracted COVID-19 infection, the measures implemented to prevent the spread of the virus such as social distancing, lockdowns, and isolation, as well as the fear of the contagion, heavily impacted physical and psychological health.[156,159]

Reduced mobility, unhealthy behaviors, and decreased access to regular healthcare services and planned surgery have led to a deterioration in physical health for many, exacerbating chronic conditions and hindering routine medical management.[160–163] The isolation from family, friends, and community networks took a significant toll, contributing to the increase in the incidence of sleep disturbances, feelings of loneliness, anxiety, and depression among older

adults.[164–166] These contributing factors led to increased frailty, deterioration of physical function, and disability, and overall worsening of quality of life.[167–169] Moreover, reduced activity levels and decreased physical performance have a negative impact on the immune system, thereby reducing the response to COVID-19 vaccines.[170]

Lifestyle changes and impact on quality of life are highly dependent on both personal and environmental factors. Among possible coping mechanisms, COVID-19 pandemic contributed to raise awareness on the importance of PA and exercise, and, to some extent, increased positive behaviors.[171] However, reduced social support and isolation, frailty, living in disadvantaged areas without facilities, and home confinement were particularly relevant in determining decreased PA levels.[172,173] Moreover, COVID-19 restrictions had a considerable impact on exercise detraining both in patients undergoing specific rehabilitation and in those practicing PA.[174,175]

To prevent social isolation among older adults in the post-pandemic world, fostering community engagement is essential through safe and organized social activities that encourage interaction and rebuilding social networks. Addressing mobility decline requires accessible, tailored physical therapy and exercise and PA programs catering to varying levels of ability and mobility, ensuring older adults can safely improve their physical health.

6.4. Exercise programs for older adults in the post-pandemic era: one size does not fit all

The development of exercise programs for older adults in the post-pandemic era should consider not only the diverse health needs, but also economic disparities and social vulnerabilities, as well as the residential context. Studies highlighted the protective role of PA for overcoming the physical and mental consequences of isolation during COVID-19 pandemic[176,177] and post-acute sequelae of the infection.[155,178]

Community-based interventions have emerged as a crucial strategy to enhance the health and well-being of older adults.[179] These programs aim to foster social connections while promoting physical health, thereby addressing the isolation and sedentary lifestyles that were exacerbated during the pandemic. By providing accessible, tailored physical activities, these interventions play a pivotal role in encouraging older adults to remain active and engaged in their communities, contributing to improved physical resilience and mental health outcomes.

Home-based exercises offer a safe and accessible option ensuring continuity in PA and exercise[180,181] Supervised exercises, conducted by healthcare professionals, provide tailored support and adjustments crucial for managing complex health conditions, whereas unsupervised exercises encourage independence and self-management, and are suitable for those with mild limitations.[182] Group exercise offers a dynamic and supportive environment, motivating individuals to achieve their fitness goals while fostering a sense of community and accountability.

COVID-19 revealed that higher familiarity with technology was associated with greater resilience during the pandemic. Technology-based methods, including mobile apps and tele-exercise programs, have emerged as important tools, offering guided workouts that older adults can follow from anywhere and bridging the gap between traditional in-person sessions and the need for remote options.[183–186]

The availability and nature of PA and exercise programs vary significantly across the world due to differences in healthcare systems, economic resources, and public health strategies. Within individual countries, living in rural areas may be a barrier to the implementation of effective and continuous PA programs in older adults.[187] During the latest years, COVID-19 has been a major factor in exacerbating inequality, especially in the most vulnerable social groups.[188] Current evidence highlights that PA is associated with lower odds of SARS-CoV-2 infection, lower chances of developing severe COVID-19, enhanced efficacy of vaccines, and benefits in recovering from the infection.[189] However, not only did restrictions and lockdowns decrease opportunities to engage in PA, but also PA and exercise are overlooked by public health research and policies and poorly implemented in primary care settings, despite guidelines issued by scientific societies.[190] In Italy, PA was included in the National Prevention Plan 2020–2025. However, Italian older adults are significantly less active than their European peers, and national data highlight significant disparities between northern, central, and southern regions, and inequalities according to the level of education (https://www.istat.it/it/files/2022/12/Sport-attività-fisica-sedentarietà-2021.pdf). In the United States, a mix of healthcare interventions, community-based programs, and technology-driven solutions to support older adults during and after the pandemic has been proposed. However, access to PA and exercise programs varies significantly by State, location, income, internet access, as well as social and environmental conditions (e.g., limited space at home).[189]

Although physical literacy is increasing globally, structured programs currently fail to be included in public health policies, especially for older adults. The design of specific measures must consider not only the health and personal needs of individuals, but also potential economic, geographical, and social limitations, in order to overcome inequalities and make PA and exercise programs available for all in the post-pandemic future. Hybrid models combining in-person and virtual components offer a flexible and comprehensive approach, accommodating personal preferences and public health guidelines. Multicomponent interventions, which integrate PA and exercise with cognitive and social activities, enhance physical function and improve quality of life, highlighting the importance of personalized, adaptable exercise regimens in the post-pandemic era.[191]

7. PA among college students during/long-COVID-19 pandemic

7.1. PA and healthy diet: two pillars of wellness

The U.S. Department of Health and Human Services PA guidelines recommend individuals engage in at least 150-min/week of moderate-intensity, or 75-min/week of vigorous-intensity PA, or a combination of the two, to achieve health benefits.[192] Most universities and colleges announced campus closure in March 2020, and this restrained students' physical activities.[193] In addition, students spent less time on transportation-related physical activities (e.g., walking, biking, etc.) and sports-related exercises. During home confinement, significant decreases in the frequency (−35%), duration (−34%), and intensity (−42.7%) of PA worldwide were reported.[193] For example, only 10% and 30% of Canadian university students met the guidelines of 150-min of moderate-vigorous PA and 8-h or less of sedentary activity,[194] and university students reduced moderate (−29.5%) and vigorous (−18.3%) PA during the confinement and increased sedentary time (+52.7%) in Spain.[195] PA frequency decreased at vigorous, moderate, and light intensity levels, while sedentary behavior increased by 2.66-h per day in southern Texas.[196]

Decreased PA and increased sedentary behavior are linked to multiple adverse health outcomes, including poor dietary behaviors, metabolic disorders, overweight and obesity, as well as mental health issues.[1] A high prevalence of depression, anxiety, and stress was observed among university students due to a reduction in social interactions and the transition to online learning, particularly among female and graduate students.[197] These behaviors, in turn, lead to emotional and binge eating disorders,[198] which can result in increased energy intake and the development of higher fat mass and lower muscle mass, overweight and obesity.[199] A notable increase in meals cooked at home, alcohol consumption, and food insecurity (e.g., unable to afford healthy food and daily meals)[196] was also reported. Poor sleep, snacking after dinner, lack of dietary restraint, pre-existing overweight status, emotional eating due to stress and decreased PA and exercise are risk factors for weight gain during the pandemic.[200]

7.2. Post-pandemic era: A delayed recovery for PA

Most higher education institutions started to lift the restrictions resuming in-person classes and campus activities from Fall 2021 to Spring 2022 depending on institutional and regional guidelines; however, PA and exercise levels have not returned to pre-pandemic levels in early 2022.[201] Although the campus recreation center and gym were back in operation, both male and female students continued to experience reduced PA levels during a phase of gradually easing national restrictions.[202] This delayed recovery has led to decreased PA and exercise and increased unhealthy eating habits (e.g., binge eating), and these changes have had lasting detrimental effects on their overall health and wellness.[203] Long-term negative impacts on physical fitness were observed in young adults, by reducing their anaerobic and aerobic capacities, explosive powers, and upper-body strength, and these effects persisted even a year after the lockdowns.[204] In addition, weight gain persisted in almost half of the students who continued to follow unhealthy dietary behaviors and inadequate PA, and the increased post-pandemic body mass index was shown to be linked with this excessive weight gain.[205]

7.3. A new trend of PA among college students

Outdoor activities such as running, cycling, and yoga became popular alternatives for maintaining physical fitness while adhering to safety protocols.[206] College students prefer engaging more in outdoor activities such as hiking, biking, jogging, and walking, which allow for social distancing while still being physically active. As a transition to counteract the pandemic lockdown, most universities offered recreational or fitness services and outdoor activities that help students to enhance their overall wellness and fitness through more engaged physical activities.[207]

High-intensity interval training (HIIT) offers numerous physiological benefits, enhancing aerobic and anaerobic capacities, improving cardiovascular and mitochondrial functions, and aiding in weight management while preserving muscle mass.[208] HIIT and mind-body activities (e.g., yoga) were increased by 18.2% and 80.0%, respectively, among Spanish university students during the pandemic.[195] HIIT has gained popularity among students due to its flexibility, minimal need for expensive gym equipment, and the increased demand for home workouts and technology integration. The combination of aerobic and resistance exercise training (e.g., HIIT) also showed improvements in physical fitness and mental health in college students after the lockdown.[209]

In fact, college students reported having more flexibility and positive exercise mindsets during COVID-19 to explore various exercises they enjoy for their workout routines.[210] Many students reported engaging more in walking, muscle-strengthening exercises, and yoga/Pilates/-stretching at home, while a few participated in informal sports practice, play, and recreational activities.[206] While virtual PA and exercise training classes offered students convenience and flexibility, as well as improvements in physical fitness and performance for both male and female students, a study on web-based physical education courses during the lockdown, Xia et al. reported an increase in overweight and obesity rates among male students.[211] The use of wearable technology in fitness, such as fitness trackers, smartwatches, and virtual reality fitness programs grew rapidly during and post-pandemic,[212] and these tools can provide motivation, track progress, and offer interactive workout experiences.

8. Exercise and PA with Long-COVID

Many individuals recovering from COVID-19 disease have symptom persistence for long periods or are referred to as Long-COVID. Reported Long-COVID symptoms include cough, fatigue, chest tightness and palpitations, breathlessness, myalgia, metabolic disorders, dyspnea, arthralgia, and cognitive impairment.[213–215] Risk factors for COVID-19 infection, severity, and disease-related death include sex, age, ethnicity, disability status, and pre-existing comorbidities, including cardiovascular disease, respiratory disease, hypertension, and obesity. These risk factors also apply to the risk of acquiring Long-COVID.[213,215] Severe health conditions present in Long-COVID patients include cardiac injury and sustained cardiovascular abnormalities,[227] reduced functional reserve, compromised respiratory function,[216,217] and encephalopathy or encephalitis.[224] Treatment and management of Long-COVID requires a multi-disciplinary approach and is individualized based on the types and severity of the symptoms.[213,218–222]

8.1. Exercise and PA health benefits

Countless scientific investigations have established acute and chronic health benefits from PA and exercise.[223] However, physical inactivity is associated with a higher risk of severe COVID-19 outcomes while high fitness levels are shown to reduce hospitalization due to COVID-19,[18,224] In healthy populations, exercise and PA are known to improve and enhance the same physiological systems that demonstrate dysfunction in patients with Long-COVID.[224,225] For example, PA and exercise are known to enhance the immune health, musculoskeletal health, pulmonary function, cardiovascular health, nervous system, cognitive function, and psychological well-being.[224,225]

As viral infections recruit and activate inflammatory cells associated with tissue damage or dysfunction, exercise and PA act as modulators in the immune system reducing the risk of systemic inflammatory processes. Other PA and exercise health benefits include reduced respiratory infections and recovery rates following infection.[219] Exercise rehabilitation has shown health benefits in Long-COVID symptoms including positive changes in dyspnea, fatigue, depression, aerobic fitness, vital capacity, and quality of life.[225,226]

8.2. Special considerations

The use and safety of PA and exercise during COVID rehabilitation and/or as treatment for Long-COVID have been extensively studied. Because of the pathophysiology and symptoms of Long COVID, exercise intolerance is likely present. Aerobic capacity, muscle strength, and orthostatic tachycardia are reported among non-hospitalized patients with Long-COVID.[227,228] Individuals have reduced functional capacity, oxygen consumption efficiency, anaerobic threshold, oxidative capacity, and also experience below normal limits in autonomic nervous system measures and function.[228,229] These findings suggest mitochondrial pathology, ultimately reducing exercise performance.[229]

When using PA and exercise as a rehabilitation strategy for Long-COVID, one must consider the patient's physical and mental function, social status, and available individual resources. For instance, one must consider[222]: heart health, including myocarditis, risk for cardiovascular disease, and postural orthostatic tachycardia syndrome (POTS); environmental attributes, including venue, infection protection initiatives, and available equipment; skeletal muscle health, including myopathy, deconditioning, and functional impairment; mental health, including post-traumatic stress disorder, brain fog, and timing; comorbidities, including respiratory conditions, cardiovascular disease, and type 2 diabetes; functional status, including pre-COVID-19 health status, previous experience with exercise; lung health, including presence of fibrosis, bronchopulmonary dysplasia, pulmonary embolism; and social factors, such as social distancing, lockdowns and isolation, and the fear of contagion.

Return to sport, exercise, or PA and exercise programming is individually based on the persistence and intensity of symptoms during COVID or Long-COVID. Physician clearance must be considered if cardiac arrhythmia is present. Respiratory symptoms are carefully monitored, especially in patients who have underlying pulmonary diseases. An increased risk for venous thromboembolism is a concern during

COVID-19 and Long-COVID, and prolonged sitting is minimized while avoiding high-intensity exercise without proper progression programs.[220]

Athletes of all levels must consider the type of PA or exercise training when returning from a COVID-19 infection, and decisions are guided by clinical symptoms. In addition, injury risk is likely elevated due to exercise or physical inactivity and deconditioning that took place during the presence of COVID-19 and Long-COVID symptoms.[219,228] Symptomatic athletes should only perform low-intensity PA or exercise. A gradual return to PA and exercise is emphasized and pre-COVID-19 PA and exercise patterns may take months to attain. High-intensity exercise should be avoided because of increased injury risk, respiratory infection, and potential cardiac complications.[219]

PA should be discontinued if fluctuation in internal temperature (> 37.2 °C) is experienced, exacerbation of respiratory symptoms, fatigue is persistent after rest, the presence of chest tightness, pain, cough, dizziness, headache, heart palpitations, gait instabilities, or profuse sweating.[230]

8.3. Exercise and PA recommendations

Scientists and clinicians have developed recommendations regarding the use of PA and exercise as part of rehabilitation for COVID-19 and Long-COVID. The use of respiratory rehabilitation prior to starting PA or exercise is a consideration and should be completed just above low intensity levels.[219,230] The benefits of PA and exercise with and without respiratory therapies have been investigated[228–232]

Once physician clearance has been obtained, the basic frequency, intensity, time, type principles (FITT) to transition into an active lifestyle should be followed.[225,233,234]

1) Frequency: Start 2 sessions per week, build to 3–5 sessions per week.
2) Intensity: Start low intensity, build to moderate intensity.
3) Time: Start 15–30 min/session, build to 20–60 min/session.
4) Type: Aerobic, resistance, respiratory, flexibility, and balance exercises.
5) Recumbent or semi-recumbent exercise is recommended in patients unable to tolerate upright exercise.

Recent data suggests recommendations for the different types of exercises or PA, including exercises to strengthen respiratory muscles as follows.[218]

1) Aerobic training: 40%–60% maximum heart rate or 4–6 RPE Borg Scale
2) Resistance training: Upper and lower body exercises, 30%–80% of 1 RM, 8–12 reps
3) Respiratory training: Commercial handheld resistance, 3 sets of 10 breaths, 60% maximal expiratory mouth pressure, 1 min rest between sets, 2 times/day
4) Cough exercise: 3 sets of 10 active coughs
5) Diaphragmatic muscle training: 30 maximum voluntary diaphragmatic contractions in the supine position with medium weight on anterior abdomen
6) Stretching exercise: Supine or lateral decubitus position with knees bent, shoulder flexion, horizontal extension, abduction, and external rotation.

One should always keep in mind that PA and the type of exercise programming prescribed does depend on the amount of post-exertional malaise commonly seen in Long-COVID.[228,235]

9. Conclusions

Debate still exists as to whether the COVID-19 pandemic that has killed six million people and infected many more has officially ended. A considerable number of patients who contracted SARS-CoV-2 virus are affected by persistent multi-systemic symptoms, referred to as Long-COVID. How to deal with this multifaceted health threat becomes a major challenge to doctors, researchers and health practicians. This 5-year pandemic has given us many lessons, which may be summarized in part from the current retrospective review. First, we need to continue to investigate cellular and molecular mechanisms that mediate various organistic failures resulting from the viral infection and the only way to completely understand the etiology of the diseases and to develop new drugs and vaccines. Available evidence suggests that mitochondrial dysfunction, reduced microcirculation and latent immune activation play a major role, eventually impairing cardiovascular tolerance and peripheral bioenergetics. Second, the COVID-19 pandemic has manifested major disturbances to human lifestyles with reduced PA and exercise standing out as a major factor. If not intervened in, this interaction can lead to Long-COVID, a dangerous, futile circle that can cause systemic failure. Finally, the COVID-19 pandemic has exerted differential impacts on different populations Thus, the strategy to develop and conduct to cope with the negativity of pandemic needs to be specific, flexible and tailored to fit different patient populations.

CRediT authorship contribution statement

All coauthors contributed to the writing of the manuscript.

Declaration of competing interest

Jeffrey A. Woods, Scott K. Powers, Mari Carmen Gomez-Cabrera, Zsolt Radak, Christiaan Leeuwenburgh, J. Larry Durstine, and Li Li Ji are Editorial Board Members for *Sports Medicine and Health Science* and were not involved in the editorial review or the decision to publish this article. Otherwise, the authors have no conflicts of interest to declare.

References

1. Woods JA, Hutchinson NT, Powers SK, et al. The COVID-19 pandemic and physical activity. *Sports Med Health Sci*. 2020;2(2):55–64. https://doi.org/10.1016/j.smhs.2020.05.006.
2. Glace BW, Kremenic IJ, Hogan DE, et al. Habitual physical activity and COVID-19. *J Sports Med Phys Fit*. 2024;64(7):685–693. https://doi.org/10.23736/s0022-4707.24.15516-8.
3. Neville RD, Lakes KD, Hopkins WG, et al. Global changes in child and adolescent physical activity during the COVID-19 pandemic: a systematic review and meta-analysis. *JAMA Pediatr*. 2022;176(9):886–894. https://doi.org/10.1001/jamapediatrics.2022.2313.
4. AlDukhail S, Bahdila D. Self-perception of health and physical activity among adults before and amidst the COVID-19 pandemic: united States, 2019-2020. *Prev Med*. 2022;158:107037. https://doi.org/10.1016/j.ypmed.2022.107037.
5. Rejeki PS, Witarto BS, Witarto AP, et al. Importance of moderate-to-vigorous physical activity during the COVID-19 pandemic: a systematic review and meta-analysis. *J Basic Clin Physiol Pharmacol*. 2023;34(3):311–320. https://doi.org/10.1515/jbcpp-2023-0040.
6. Lai CC, Hsu CK, Yen MY, et al. Long COVID: an inevitable sequela of SARS-CoV-2 infection. *J Microbiol Immunol Infect*. 2023;56(1):1–9. https://doi.org/10.1016/j.jmii.2022.10.003.
7. Chastin SFM, Abaraogu U, Bourgois JG, et al. Effects of regular physical activity on the immune system, vaccination and risk of community-acquired infectious disease in the general population: systematic review and meta-analysis. *Sports Med*. 2021;51(8):1673–1686. https://doi.org/10.1007/s40279-021-01466-1.
8. Smer A, Squires RW, Bonikowske AR, et al. Cardiac complications of COVID-19 infection and the role of physical activity. *J Cardpulm Rehabil Prev*. 2023;43(1):8–14. https://doi.org/10.1097/hcr.0000000000000701.
9. Singh S, Ahirwar AK, Asia P, et al. COVID-19 and neurology perspective. *Horm Mol Biol Clin Invest*. 2021;42(1):69–75. https://doi.org/10.1515/hmbci-2020-0069.
10. Heshmati HM. Interactions between COVID-19 infection and diabetes. *Front Endocrinol*. 2023;14:1306290. https://doi.org/10.3389/fendo.2023.1306290.
11. Wolf S, Seiffer B, Zeibig JM, et al. Is physical activity associated with less depression and anxiety during the COVID-19 pandemic? A rapid systematic review. *Sports Med*. 2021;51(8):1771–1783. https://doi.org/10.1007/s40279-021-01468-z.
12. Rabaan AA, Smajlović S, Tombuloglu H, et al. SARS-CoV-2 infection and multi-organ system damage: a review. *Biomol Biomed*. 2023;23(1):37–52. https://doi.org/10.17305/bjbms.2022.7762.

13. Alves HR, Lomba GSB, Gonçalves-de-Albuquerque CF, Burth P. Irisin, exercise, and COVID-19. *Front Endocrinol*. 2022;13:879066. https://doi.org/10.3389/fendo.2022.879066.
14. Castro-Sepulveda M, Tapia G, Tuñón-Suárez M, et al. Severe COVID-19 correlates with lower mitochondrial cristae density in PBMCs and greater sitting time in humans. *Physiol Rep*. 2022;10(14):e15369. https://doi.org/10.14814/phy2.15369.
15. Molnar T, Lehoczki A, Fekete M, et al. Mitochondrial dysfunction in long COVID: mechanisms, consequences, and potential therapeutic approaches. *GeroScience*. 2024;46(5):5267–5286. https://doi.org/10.1007/s11357-024-01165-5.
16. Young DR, Sallis JF, Baecker A, et al. Associations of physical inactivity and COVID-19 outcomes among subgroups. *Am J Prev Med*. 2023;64(4):492–502. https://doi.org/10.1016/j.amepre.2022.10.007.
17. Kuntz JL, Young DR, Saelens BE, et al. Validity of the exercise vital sign tool to assess physical activity. *Am J Prev Med*. 2021;60(6):866–872. https://doi.org/10.1016/j.amepre.2021.01.012.
18. Sallis R, Young DR, Tartof SY, et al. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. *Br J Sports Med*. 2021;55(19):1099–1105. https://doi.org/10.1136/bjsports-2021-104080.
19. Muñoz-Vergara D, Wayne PM, Kim E, et al. Prepandemic physical activity and risk of COVID-19 diagnosis and hospitalization in older adults. *JAMA Netw Open*. 2024;7(2):e2355808. https://doi.org/10.1001/jamanetworkopen.2023.55808.
20. Pinto AJ, Goessler KF, Fernandes AL, et al. No independent associations between physical activity and clinical outcomes among hospitalized patients with moderate to severe COVID-19. *J Sport Health Sci*. 2021;10(6):690–696. https://doi.org/10.1016/j.jshs.2021.08.001.
21. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26(5):681–687. https://doi.org/10.1038/s41591-020-0868-6.
22. Lukassen S, Chua RL, Trefzer T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. *EMBO J*. 2020;39(10):e105114. https://doi.org/10.15252/embj.20105114.
23. Sapir T, Averch Z, Lerman B, et al. COVID-19 and the immune response: a multiphasic approach to the treatment of COVID-19. *Int J Mol Sci*. 2022;(15):23. https://doi.org/10.3390/ijms23158606.
24. Roche PA, Furuta K. The ins and outs of MHC class II-mediated antigen processing and presentation. *Nat Rev Immunol*. 2015;15(4):203–216. https://doi.org/10.1038/nri3818.
25. Sigal LJ. Activation of CD8 T lymphocytes during viral infections. *Encycloped Immunobiol*. 2016:286–290. https://doi.org/10.1016/B978-0-12-374279-7.14009-3. Epub 2016.
26. Chattopadhyay P, Khare K, Kumar M, et al. Single-cell multiomics revealed the dynamics of antigen presentation, immune response and T cell activation in the COVID-19 positive and recovered individuals. *Front Immunol*. 2022;13:1034159. https://doi.org/10.3389/fimmu.2022.1034159.
27. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205–1211. https://doi.org/10.1038/s41591-021-01377-8.
28. Magalhães FC, Fernandes T, Bassaneze V, et al. High-volume endurance exercise training stimulates hematopoiesis by increasing ACE NH2-terminal activity. *Clin Sci (London, England : 1979)*. 2021;135(20):2377–2391. https://doi.org/10.1042/cs20210739.
29. Arazi H, Falahati A, Suzuki K. Moderate intensity aerobic exercise potential favorable effect against COVID-19: the role of renin-angiotensin system and immunomodulatory effects. *Front Physiol*. 2021;12:747200. https://doi.org/10.3389/fphys.2021.747200.
30. Lestari YM, Tarawan VM, Achadiyani A, et al. Exercise intensities modulate ACE2/MasR/eNOS pathway in Male Wistar rat's lung. *Physiol Rep*. 2023;11(17):e15803. https://doi.org/10.14814/phy2.15803.
31. Klöting N, Schwarzer M, Heyne E, et al. Intrinsic exercise capacity affects glycine and angiotensin-converting enzyme 2 (ACE2) levels in sedentary and exercise trained rats. *Metabolites*. 2022;12(6). https://doi.org/10.3390/metabo12060548.
32. Tamura Y, Jee E, Kouzaki K, et al. Effects of endurance training on the expression of host proteins involved in SARS-CoV-2 cell entry in C57BL/6J mouse. *Physiol Rep*. 2021;9(17):e15014. https://doi.org/10.14814/phy2.15014.
33. Xia H, Cao Z, Xie X, et al. Evasion of type I interferon by SARS-CoV-2. *Cell Rep*. 2020;33(1):108234. https://doi.org/10.1016/j.celrep.2020.108234.
34. Uchida M, Oyanagi E, Kremenik MJ, et al. Interferon-beta, but not tumor necrosis factor-alpha, production in response to poly I:C is maintained despite exhaustive exercise in mice. *J Physiol Sci : JPS*. 2012;62(1):59–62. https://doi.org/10.1007/s12576-011-0177-4.
35. Mignot CC, Pirottin D, Farnir F, et al. Effect of strenuous exercise and ex vivo TLR3 and TLR4 stimulation on inflammatory gene expression in equine pulmonary leukocytes. *Vet Immunol Immunopathol*. 2012;147(3–4):127–135. https://doi.org/10.1016/j.vetimm.2012.04.004.
36. Yano H, Uchida M, Nakai R, et al. Exhaustive exercise reduces TNF-α and IFN-α production in response to R-848 via toll-like receptor 7 in mice. *Eur J Appl Physiol*. 2010;110(4):797–803. https://doi.org/10.1007/s00421-010-1560-1.
37. Kohut ML, Davis JM, Jackson DA, et al. Exercise effects on IFN-beta expression and viral replication in lung macrophages after HSV-1 infection. *Am J Physiol*. 1998;275(6):L1089–L1094. https://doi.org/10.1152/ajplung.1998.275.6.L1089.
38. Baker FL, Zúñiga TM, Smith KA, et al. Exercise mobilizes diverse antigen specific T-cells and elevates neutralizing antibodies in humans with natural immunity to SARS CoV-2. *Brain Behav Immun Health*. 2023;28:100600. https://doi.org/10.1016/j.bbih.2023.100600.
39. Lee MJ, Blish CA. Defining the role of natural killer cells in COVID-19. *Nat Immunol*. 2023;24(10):1628–1638. https://doi.org/10.1038/s41590-023-01560-8.
40. Bao C, Tao X, Cui W, et al. Natural killer cells associated with SARS-CoV-2 viral RNA shedding, antibody response and mortality in COVID-19 patients. *Exp Hematol Oncol*. 2021;10(1):5. https://doi.org/10.1186/s40164-021-00199-1.
41. Simpson RJ, Boßlau TK, Weyh C, et al. Exercise and adrenergic regulation of immunity. *Brain Behav Immun*. 2021;97:303–318. https://doi.org/10.1016/j.bbi.2021.07.010.
42. Llavero F, Alejo LB, Fiuza-Luces C, et al. Exercise training effects on natural killer cells: a preliminary proteomics and systems biology approach. *Exerc Immunol Rev*. 2021;27:125–141.
43. Gleeson M, Bishop NC, Stensel DJ, et al. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11(9):607–615. https://doi.org/10.1038/nri3041.
44. Woods JA, Keylock KT, Lowder T, et al. Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: the immune function intervention trial. *J Am Geriatr Soc*. 2009;57(12):2183–2191. https://doi.org/10.1111/j.1532-5415.2009.02563.x.
45. Grant RW, Mariani RA, Vieira VJ, et al. Cardiovascular exercise intervention improves the primary antibody response to keyhole limpet hemocyanin (KLH) in previously sedentary older adults. *Brain Behav Immun*. 2008;22(6):923–932. https://doi.org/10.1016/j.bbi.2008.01.006.
46. Hallam J, Jones T, Alley J, Kohut ML. Exercise after influenza or COVID-19 vaccination increases serum antibody without an increase in side effects. *Brain Behav Immun*. 2022;102:1–10. https://doi.org/10.1016/j.bbi.2022.02.005.
47. Gualano B, Sieczkowska SM, Lemes ÍR, et al. Physical activity: a strategy to improve antibody response to a SARS-CoV-2 vaccine booster dose in patients with autoimmune rheumatic diseases. *J Phys Activ Health*. 2023;20(4):311–316. https://doi.org/10.1123/jpah.2022-0332.
48. Swenson KE, Swenson ER. Pathophysiology of acute respiratory distress syndrome and COVID-19 lung injury. *Crit Care Clin*. 2021;37(4):749–776. https://doi.org/10.1016/j.ccc.2021.05.003.
49. World Health Organization. *Incidence of Long COVID*. World Health Organization; 2024 [Internet]. Available from: https://www.who.int/home/search-results?indexCatalogue=genericsearchindex1&searchQuery=long%20covid&wordsMode=AnyWord.
50. Motiejunaite J, Balagny P, Arnoult F, et al. Hyperventilation: a possible explanation for long-lasting exercise intolerance in mild COVID-19 survivors? *Front Physiol*. 2020;11:614590. https://doi.org/10.3389/fphys.2020.614590.
51. Aparisi Á, Ladrón R, Ybarra-Falcón C, et al. Exercise intolerance in post-acute sequelae of COVID-19 and the value of cardiopulmonary exercise Testing- a mini-review. *Front Med*. 2022;9:924819. https://doi.org/10.3389/fmed.2022.924819.
52. Cronin JN, Camporota L, Formenti F. Mechanical ventilation in COVID-19: a physiological perspective. *Exp Physiol*. 2022;107(7):683–693. https://doi.org/10.1113/ep089400.
53. Gosangi B, Rubinowitz AN, Irugu D, et al. COVID-19 ARDS: a review of imaging features and overview of mechanical ventilation and its complications. *Emerg Radiol*. 2022;29(1):23–34. https://doi.org/10.1007/s10140-021-01976-5.
54. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. *Pulmonology*. 2021;27(4):328–337. https://doi.org/10.1016/j.pulmoe.2020.10.013.
55. Clavario P, De Marzo V, Lotti R, et al. Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. *Int J Cardiol*. 2021;340:113–118. https://doi.org/10.1016/j.ijcard.2021.07.033.
56. Jahn K, Sava M, Sommer G, et al. Exercise capacity impairment after COVID-19 pneumonia is mainly caused by deconditioning. *Eur Respir J*. 2022;59(1). https://doi.org/10.1183/13993003.01136-2021.
57. Ribeiro Baptista B, d'Humières T, Schlemmer F, et al. Identification of factors impairing exercise capacity after severe COVID-19 pulmonary infection: a 3-month follow-up of prospective COVulnerability cohort. *Respir Res*. 2022;23(1):68. https://doi.org/10.1186/s12931-022-01977-z.
58. Rinaldo RF, Mondoni M, Parazzini EM, et al. Severity does not impact on exercise capacity in COVID-19 survivors. *Respir Med*. 2021;187:106577. https://doi.org/10.1016/j.rmed.2021.106577.
59. Rinaldo RF, Mondoni M, Parazzini EM, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur Respir J*. 2021;58(2). https://doi.org/10.1183/13993003.00870-2021.
60. Vonbank K, Lehmann A, Bernitzky D, et al. Predictors of prolonged cardiopulmonary exercise impairment after COVID-19 infection: a prospective observational study. *Front Med*. 2021;8:773788. https://doi.org/10.3389/fmed.2021.773788.
61. van Voorthuizen EL, van Helvoort HAC, Peters JB, et al. Persistent exertional dyspnea and perceived exercise intolerance after mild COVID-19: a critical role for breathing dysregulation? *Phys Ther*. 2022;(10):102. https://doi.org/10.1093/ptj/pzac105.
62. Swinburn CR, Mould H, Stone TN, et al. Symptomatic benefit of supplemental oxygen in hypoxemic patients with chronic lung disease. *Am Rev Respir Dis*. 1991;143(5 Pt 1):913–915. https://doi.org/10.1164/ajrccm/143.5_Pt_1.913.
63. Swinburn CR, Wakefield JM, Jones PW. Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia. *Clin Sci (London, England : 1979)*. 1984;67(5):515–519. https://doi.org/10.1042/cs0670515.
64. Mancini DM, Brunjes DL, Lala A, et al. Use of cardiopulmonary stress testing for patients with unexplained dyspnea post-coronavirus disease. *JACC Heart fail*. 2021;9(12):927–937. https://doi.org/10.1016/j.jchf.2021.10.002.
65. Serviente C, Decker ST, Layec G. From heart to muscle: pathophysiological mechanisms underlying long-term physical sequelae from SARS-CoV-2 infection.

Journal of applied physiology (Bethesda, Md : 1985). 2022;132(3):581–592. https://doi.org/10.1152/japplphysiol.00734.2021.
66. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur Heart J*. 2022;43(11):1157–1172. https://doi.org/10.1093/eurheartj/ehac031.
67. Ejt Weldon, Hong B, Hayashi J, et al. Mechanisms and severity of exercise intolerance following COVID-19 and similar viral infections: a comparative review. *Cureus*. 2023;15(5):e39722. https://doi.org/10.7759/cureus.39722.
68. Brown JT, Saigal A, Karia N, et al. Ongoing exercise intolerance following COVID-19: a magnetic resonance-augmented cardiopulmonary exercise test study. *J Am Heart Assoc*. 2022;11(9):e024207. https://doi.org/10.1161/jaha.121.024207.
69. Szekely Y, Lichter Y, Sadon S, et al. Cardiorespiratory abnormalities in patients recovering from coronavirus disease 2019. *J Am Soc Echocardiogr : Off Publ Am Soc Echocardiogr*. 2021;34(12):1273–1284.e9. https://doi.org/10.1016/j.echo.2021.08.022.
70. Singh I, Joseph P, Heerdt PM, et al. Persistent exertional intolerance after COVID-19: insights from invasive cardiopulmonary exercise testing. *Chest*. 2022;161(1):54–63. https://doi.org/10.1016/j.chest.2021.08.010.
71. Alba GA, Ziehr DR, Rouvina JN, et al. Exercise performance in patients with post-acute sequelae of SARS-CoV-2 infection compared to patients with unexplained dyspnea. *eClinicalMedicine*. 2021;39:101066. https://doi.org/10.1016/j.eclinm.2021.101066.
72. Soares MN, Eggelbusch M, Naddaf E, et al. Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachex Sarcop Muscle*. 2022;13(1):11–22. https://doi.org/10.1002/jcsm.12896.
73. Schiaffino S, Reggiani C. Fiber types in mammalian skeletal muscles. *Physiol Rev*. 2011;91(4):1447–1531. https://doi.org/10.1152/physrev.00031.2010.
74. Nascimento CM, Ingles M, Salvador-Pascual A, et al. Sarcopenia, frailty and their prevention by exercise. *Free Radic Biol Med*. 2019;132:42–49. https://doi.org/10.1016/j.freeradbiomed.2018.08.035.
75. Roman W, Muñoz-Cánoves P. Muscle is a stage, and cells and factors are merely players. *Trends Cell Biol*. 2022;32(10):835–840. https://doi.org/10.1016/j.tcb.2022.03.001.
76. Roman W, Pinheiro H, Pimentel MR, et al. Muscle repair after physiological damage relies on nuclear migration for cellular reconstruction. *Science (New York, NY)*. 2021;374(6565):355–359. https://doi.org/10.1126/science.abe5620.
77. Gautam N, Madathil S, Tahani N, et al. Medium-term outcomes in severely to critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2022;74(2):301–308. https://doi.org/10.1093/cid/ciab341.
78. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment 3 months after recovery from acute coronavirus disease 2019 (COVID-19). *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2021;73(5):e1089–e1098. https://doi.org/10.1093/cid/ciaa1750.
79. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Lancet (London, England)*. 2024;403(10440):2133–2161. https://doi.org/10.1016/s0140-6736(24)00757-8.
80. Aschman T, Schneider J, Greuel S, et al. Association between SARS-CoV-2 infection and immune-mediated myopathy in patients who have died. *JAMA Neurol*. 2021;78(8):948–960. https://doi.org/10.1001/jamaneurol.2021.2004.
81. Marusic U, Narici M, Simunic B, et al. Nonuniform loss of muscle strength and atrophy during bed rest: a systematic review. *J Appl Physiol*. 2021;131(1):194–206. https://doi.org/10.1152/japplphysiol.00363.2020.
82. Ferrando B, Gomez-Cabrera MC, Salvador-Pascual A, et al. Allopurinol partially prevents disuse muscle atrophy in mice and humans. *Sci Rep*. 2018;8(1):3549. https://doi.org/10.1038/s41598-018-21552-1.
83. Ji LL, Gomez-Cabrera MC, Vina J. Role of nuclear factor kappaB and mitogen-activated protein kinase signaling in exercise-induced antioxidant enzyme adaptation. *Appl Physiol Nutr Metabol = Physiol Appl Nutrit Metabol*. 2007;32(5):930–935. https://doi.org/10.1139/h07-098.
84. Frithiof R, Rostami E, Kumlien E, et al. Critical illness polyneuropathy, myopathy and neuronal biomarkers in COVID-19 patients: a prospective study. *Clin Neurophysiol : Off J Int Federat Clin Neurophysiol*. 2021;132(7):1733–1740. https://doi.org/10.1016/j.clinph.2021.03.016.
85. Chaves-Cardona H, Hernandez-Torres V, Kiley S, Renew J. Neuromuscular blockade management in patients with COVID-19. *Korean J Anesthesiol*. 2021;74(4):285–292. https://doi.org/10.4097/kja.21106.
86. Wierdsma NJ, Kruizenga HM, Konings LA, et al. Poor nutritional status, risk of sarcopenia and nutrition related complaints are prevalent in COVID-19 patients during and after hospital admission. *Clin Nutr ESPEN*. 2021;43:369–376. https://doi.org/10.1016/j.clnesp.2021.03.021.
87. Vina J, Sanchis-Gomar F, Martinez-Bello V, Gomez-Cabrera MC. Exercise acts as a drug; the pharmacological benefits of exercise. *Br J Pharmacol*. 2012;167(1):1–12. https://doi.org/10.1111/j.1476-5381.2012.01970.x.
88. Bowden Davies KA, Pickles S, Sprung VS, et al. Reduced physical activity in young and older adults: metabolic and musculoskeletal implications. *Therapeut Adv Endocrinol Metabol*. 2019;10:2042018819888824. https://doi.org/10.1177/2042018819888824.
89. Burgess LC, Venugopalan L, Badger J, et al. Effect of neuromuscular electrical stimulation on the recovery of people with COVID-19 admitted to the intensive care unit: a narrative review. *J Rehabil Med*. 2021;53(3). https://doi.org/10.2340/16501977-2805. jrm00164.
90. Radak Z, Torma F, Berkes I, et al. Exercise effects on physiological function during aging. *Free Radic Biol Med*. 2019;132:33–41. https://doi.org/10.1016/j.freeradbiomed.2018.10.444.
91. Lou M, Yuan D, Liao S, et al. Potential mechanisms of cerebrovascular diseases in COVID-19 patients. *J Neurovirol*. 2021;27(1):35–51. https://doi.org/10.1007/s13365-021-00948-2.
92. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. 2020;382(20):e60. https://doi.org/10.1056/NEJMc2009787.
93. Rhodes RH, Love GL, Da Silva Lameira F, et al. Acute neutrophilic vasculitis (Leukocytoclasia) in 36 COVID-19 autopsy brains. *Diagn Pathol*. 2024;19(1):33. https://doi.org/10.1186/s13000-024-01445-w.
94. Janardhan V, Janardhan V, Kalousek V. COVID-19 as a blood clotting disorder masquerading as a respiratory illness: a cerebrovascular perspective and therapeutic implications for stroke thrombectomy. *J Neuroimaging : Off J Am Soc Neuroimag*. 2020;30(5):555–561. https://doi.org/10.1111/jon.12770.
95. Harber MP, Peterman JE, Imboden M, et al. Cardiorespiratory fitness as a vital sign of CVD risk in the COVID-19 era. *Prog Cardiovasc Dis*. 2023;76:44–48. https://doi.org/10.1016/j.pcad.2022.12.001.
96. Peterson BM, Unger I, Sun S, et al. The vital role of exercise and nutrition in COVID-19 rehabilitation: synergizing strength. *Front Sports Act Liv*. 2023;5:1305175. https://doi.org/10.3389/fspor.2023.1305175.
97. Zhao Z, Li L, Sang Y. The COVID-19 pandemic increased poor lifestyles and worsen mental health: a systematic review. *Am J Tourism Res*. 2023;15(5):3060–3066.
98. Chen L, Li J, Xia T, et al. Changes of exercise, screen time, fast food consumption, alcohol, and cigarette smoking during the COVID-19 pandemic among adults in the United States. *Nutrients*. 2021;(10):13. https://doi.org/10.3390/nu13103359.
99. Andrade A, D'Oliveira A, Dos Santos KM, et al. Impact of social isolation caused by the COVID-19 pandemic on the mood profile of active and sedentary older adults: physical activity as a protective factor. *Front Public Health*. 2023;11:1221142. https://doi.org/10.3389/fpubh.2023.1221142.
100. Ricci P, Pallocci M, Treglia M, et al. The effect of physical exercise during COVID-19 lockdown. *Healthcare (Basel, Switzerland)*. 2023;11(11). https://doi.org/10.3390/healthcare11111618.
101. Colcombe SJ, Kramer AF, McAuley E, et al. Neurocognitive aging and cardiovascular fitness: recent findings and future directions. *J Mol Neurosci: MN*. 2004;24(1):9–14. https://doi.org/10.1385/jmn:24:1:009.
102. Carrera-González MDP, Cantón-Habas V, Rich-Ruiz M. Aging, depression and dementia: the inflammatory process. *Adv Clin Exp Med : Off Organ Wroclaw Med Univer*. 2022;31(5):469–473. https://doi.org/10.17219/acem/149897.
103. Kramer BA, Jaehn A, Grützner TM, et al. Exercise elevates serum brain-derived neurotrophic factor in partially remitted depression. *Psychiatry Res*. 2023;326:115283. https://doi.org/10.1016/j.psychres.2023.115283.
104. Boström P, Wu J, Jedrychowski MP, et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*. 2012;481(7382):463–468. https://doi.org/10.1038/nature10777.
105. Jokai M, Torma F, McGreevy KM, et al. DNA methylation clock DNAmFitAge shows regular exercise is associated with slower aging and systemic adaptation. *GeroScience*. 2023;45(5):2805–2817. https://doi.org/10.1007/s11357-023-00826-1.
106. Pignataro P, Dicarlo M, Zerlotin R, et al. Antidepressant effect of intermittent long-term systemic administration of irisin in mice. *Int J Mol Sci*. 2022;23(14). https://doi.org/10.3390/ijms23147596.
107. Watanabe C, Oyanagi E, Aoki T, et al. Antidepressant properties of voluntary exercise mediated by gut microbiota. *Biosci Biotechnol Biochem*. 2023;87(11):1407–1419. https://doi.org/10.1093/bbb/zbad115.
108. Quan H, Koltai E, Suzuki K, et al. Exercise, redox system and neurodegenerative diseases. *Biochimica et biophysica acta Molecular basis of disease*. 2020;1866(10):165778. https://doi.org/10.1016/j.bbadis.2020.165778.
109. Liu C, Liang X, Sit CHP. Physical activity and mental health in children and adolescents with neurodevelopmental disorders: a systematic review and meta-analysis. *JAMA Pediatr*. 2024;178(3):247–257. https://doi.org/10.1001/jamapediatrics.2023.6251.
110. Willison AG, Pawlitzki M, Lunn MP, et al. SARS-CoV-2 vaccination and neuroimmunological disease: a review. *JAMA Neurol*. 2024;81(2):179–186. https://doi.org/10.1001/jamaneurol.2023.5208.
111. Wong MK, Brooks DJ, Ikejezie J, et al. COVID-19 mortality and progress toward vaccinating older adults - world health organization, worldwide, 2020-2022. *MMWR Morbid Mortal Week Rep*. 2023;72(5):113–118. https://doi.org/10.15585/mmwr.mm7205a1.
112. Herrera-Esposito D, de Los Campos G. Age-specific rate of severe and critical SARS-CoV-2 infections estimated with multi-country seroprevalence studies. *BMC Infect Dis*. 2022;22(1):311. https://doi.org/10.1186/s12879-022-07262-0.
113. Richterman A, Meyerowitz EA, Cevik M. Indirect protection by reducing transmission: ending the pandemic with severe acute respiratory syndrome coronavirus 2 vaccination. *Open Forum Infect Dis*. 2022;9(2):ofab259. https://doi.org/10.1093/ofid/ofab259.
114. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. *Age Ageing*. 2021;50(2):279–283. https://doi.org/10.1093/ageing/afaa274.
115. Andrew MK, McElhaney JE. Age and frailty in COVID-19 vaccine development. *Lancet (London, England)*. 2021;396(10267):1942–1944. https://doi.org/10.1016/s0140-6736(20)32481-8.
116. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. *Nat Med*. 2023;29(2):334–343. https://doi.org/10.1038/s41591-022-02156-9.

117. Chen Y, Klein SL, Garibaldi BT, et al. Aging in COVID-19: vulnerability, immunity and intervention. *Ageing Res Rev*. 2021;65:101205. https://doi.org/10.1016/j.arr.2020.101205.
118. Saadeh M, Calderón-Larrañaga A, Vetrano DL, et al. Associations of pre-pandemic levels of physical function and physical activity with COVID-19-like symptoms during the outbreak. *Aging Clin Exp Res*. 2022;34(1):235–247. https://doi.org/10.1007/s40520-021-02006-7.
119. Zhang J, Yu Y, Petrovic M, et al. Impact of the COVID-19 pandemic and corresponding control measures on long-term care facilities: a systematic review and meta-analysis. *Age Ageing*. 2023;52(1). https://doi.org/10.1093/ageing/afac308.
120. Calderón-Larrañaga A, Dekhtyar S, Vetrano DL, et al. COVID-19: risk accumulation among biologically and socially vulnerable older populations. *Ageing Res Rev*. 2020;63:101149. https://doi.org/10.1016/j.arr.2020.101149.
121. Zazzara MB, Penfold RS, Roberts AL, et al. Probable delirium is a presenting symptom of COVID-19 in frail, older adults: a cohort study of 322 hospitalised and 535 community-based older adults. *Age Ageing*. 2021;50(1):40–48. https://doi.org/10.1093/ageing/afaa223.
122. Boulis M, Boulis M, Cosgrove M, He K. Characteristics and treatments of coronavirus disease 2019 patients presenting with persistent hiccups: a scoping review. *Clin Neuropharmacol*. 2023. https://doi.org/10.1097/wnf.0000000000000554.
123. Tiseo G, Yahav D, Paul M, et al. What have we learned from the first to the second wave of COVID-19 pandemic? An international survey from the ESCMID study group for infection in the elderly (ESGIE) group. *Eur J Clin Microbiol Infect Dis : Off Publ Europ Soc Clin Microbiol*. 2022;41(2):281–288. https://doi.org/10.1007/s10096-021-04377-1.
124. Grund S, Bauer JM. Malnutrition and sarcopenia in COVID-19 survivors. *Clin Geriatr Med*. 2022;38(3):559–564. https://doi.org/10.1016/j.cger.2022.04.001.
125. Riesgo H, Castro A, Del Amo S, et al. Prevalence of risk of malnutrition and risk of sarcopenia in a reference hospital for COVID-19: relationship with mortality. *Ann Nutr Metabol*. 2021;77(6):324–329. https://doi.org/10.1159/000519485.
126. Dumitrascu F, Branje KE, Hladkowicz ES, et al. Association of frailty with outcomes in individuals with COVID-19: a living review and meta-analysis. *J Am Geriatr Soc*. 2021;69(9):2419–2429. https://doi.org/10.1111/jgs.17299.
127. Ferrara MC, Zarcone C, Tassistro E, et al. Frailty and long-COVID: is COVID-19 responsible for a transition in frailty status among older adults who survived hospitalization for COVID-19? *Aging Clin Exp Res*. 2023;35(2):455–461. https://doi.org/10.1007/s40520-022-02308-4.
128. Damanti S, Cristel G, Ramirez GA, et al. Influence of reduced muscle mass and quality on ventilator weaning and complications during intensive care unit stay in COVID-19 patients. *Clin Nutr*. 2022;41(12):2965–2972. https://doi.org/10.1016/j.clnu.2021.08.004.
129. Kim JW, Yoon JS, Kim EJ, et al. Prognostic implication of baseline sarcopenia for length of hospital stay and survival in patients with coronavirus disease 2019. *J Gerontol Series A, Biol Sci Med Sci*. 2021;76(8):e110–e116. https://doi.org/10.1093/gerona/glab085.
130. Gil S, Jacob Filho W, Shinjo SK, et al. Muscle strength and muscle mass as predictors of hospital length of stay in patients with moderate to severe COVID-19: a prospective observational study. *J Cachex Sarcop Muscle*. 2021;12(6):1871–1878. https://doi.org/10.1002/jcsm.12789.
131. Ahmadiani ES, Ariyanfar S, Soroush M, Razeghi Jahromi S. Role of sarcopenia risk in predicting COVID-19 severity and length of hospital stay in older adults: a prospective cohort study. *Br J Nutr*. 2023;129(11):1888–1896. https://doi.org/10.1017/s000711452200215x.
132. Martí-Pastor A, Moreno-Perez O, Lobato-Martínez E, et al. Association between clinical frailty scale (CFS) and clinical presentation and outcomes in older inpatients with COVID-19. *BMC Geriatr*. 2023;23(1):1. https://doi.org/10.1186/s12877-022-03642-y.
133. Silva E, Schmitt ACB, de Godoy CG, et al. Risk factors for the impairment of ambulation in older people hospitalized with COVID-19: a retrospective cohort study. *Int J Environ Res Publ Health*. 2023;20(22). https://doi.org/10.3390/ijerph20227057.
134. Covino M, Russo A, Salini S, et al. Frailty assessment in the emergency department for risk stratification of COVID-19 patients aged ≥80 years. *J Am Med Dir Assoc*. 2021;22(9):1845–1852.e1. https://doi.org/10.1016/j.jamda.2021.07.005.
135. Yakti FAZ, Abusalah L, Ganji V. Sarcopenia and mortality in critically ill COVID-19 patients. *Life*. 2023;14(1). https://doi.org/10.3390/life14010024.
136. Zhang XM, Jiao J, Cao J, et al. Frailty as a predictor of mortality among patients with COVID-19: a systematic review and meta-analysis. *BMC Geriatr*. 2021;21(1):186. https://doi.org/10.1186/s12877-021-02138-5.
137. Yang Y, Luo K, Jiang Y, et al. The impact of frailty on COVID-19 outcomes: a systematic review and meta-analysis of 16 cohort studies. *J Nutr Health Aging*. 2021;25(5):702–709. https://doi.org/10.1007/s12603-021-1611-9.
138. Subramaniam A, Anstey C, Curtis JR, et al. Characteristics and outcomes of patients with frailty admitted to ICU with coronavirus disease 2019: an individual patient data meta-analysis. *Critical Care Explorat*. 2022;4(1):e0616. https://doi.org/10.1097/cce.0000000000000616.
139. Hughes JM, Bartle JT, Choate AL, et al. Walking all over COVID-19: the rapid development of STRIDE in your room, an innovative approach to enhance a hospital-based walking program during the pandemic. *Geriatrics*. 2021;6(4). https://doi.org/10.3390/geriatrics6040109.
140. Fernandez F, Vazquez-Muñoz M, Canals A, et al. Intrahospital supervised exercise training improves survival rate among hypertensive patients with COVID-19. *J Appl Physio (Bethesda, Md : 1985)*. 2023;134(3):678–684. https://doi.org/10.1152/japplphysiol.00544.2022.
141. Sedaghati P, Derakhshan KF, Ahmadabadi S, Moghaddam SRR. Effects of corrective and breathing exercises on respiratory function of older adults with a history of COVID-19 infection: a randomized controlled trial. *BMC Complem Med Therap*. 2023;23(1):199. https://doi.org/10.1186/s12906-023-04031-7.
142. Davis HE, McCorkell L, Vogel JM, Topol EJ. Author correction: long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(6):408. https://doi.org/10.1038/s41579-023-00896-0.
143. Kim Y, Bae S, Chang HH, Kim SW. Characteristics of long COVID and the impact of COVID-19 vaccination on long COVID 2 years following COVID-19 infection: prospective cohort study. *Sci Rep*. 2024;14(1):854. https://doi.org/10.1038/s41598-023-50024-4.
144. Fung KW, Baye F, Baik SH, et al. Prevalence and characteristics of long COVID in elderly patients: an observational cohort study of over 2 million adults in the US. *PLoS Med*. 2023;20(4):e1004194. https://doi.org/10.1371/journal.pmed.1004194.
145. Daitch V, Yelin D, Awwad M, et al. Characteristics of long-COVID among older adults: a cross-sectional study. *Int J Infect Dis : IJID : Off Publ Int Soc Infect Dis*. 2022;125:287–293. https://doi.org/10.1016/j.ijid.2022.09.035.
146. Tosato M, Carfì A, Martis I, et al. Prevalence and predictors of persistence of COVID-19 symptoms in older adults: a single-center study. *J Am Med Dir Assoc*. 2021;22(9):1840–1844. https://doi.org/10.1016/j.jamda.2021.07.003.
147. Martone AM, Tosato M, Ciciarello F, et al. Sarcopenia as potential biological substrate of long COVID-19 syndrome: prevalence, clinical features, and risk factors. *J Cachex Sarcop Muscle*. 2022;13(4):1974–1982. https://doi.org/10.1002/jcsm.12931.
148. Ramírez-Vélez R, Legarra-Gorgoñon G, Oscoz-Ochandorena S, et al. Reduced muscle strength in patients with long-COVID-19 syndrome is mediated by limb muscle mass. *J Appl Physiol (Bethesda, Md : 1985)*. 2023;134(1):50–58. https://doi.org/10.1152/japplphysiol.00599.2022.
149. Lauria A, Carfì A, Benvenuto F, et al. Neuropsychological measures of post-COVID-19 cognitive status. *Front Psychol*. 2023;14:1136667. https://doi.org/10.3389/fpsyg.2023.1136667.
150. Asadi-Pooya AA, Akbari A, Emami A, et al. Long COVID syndrome-associated brain fog. *J Med Virol*. 2022;94(3):979–984. https://doi.org/10.1002/jmv.27404.
151. Ramírez-Vélez R, Oscoz-Ochandorena S, García-Alonso Y, et al. Maximal oxidative capacity during exercise is associated with muscle power output in patients with long coronavirus disease 2019 (COVID-19) syndrome. A moderation analysis. *Clin Nutr ESPEN*. 2023;58:253–262. https://doi.org/10.1016/j.clnesp.2023.10.009.
152. Priya SP, Sunil PM, Varma S, et al. Direct, indirect, post-infection damages induced by coronavirus in the human body: an overview. *Virusdisease*. 2022;33(4):429–444. https://doi.org/10.1007/s13337-022-00793-9.
153. Santoro L, Falsetti L, Zaccone V, et al. Impaired endothelial function in convalescent phase of COVID-19: a 3 month follow up observational prospective study. *J Clin Med*. 2022;11(7). https://doi.org/10.3390/jcm11071774.
154. Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. *Acta Pharmacol Sin*. 2023;44(4):695–709. https://doi.org/10.1038/s41401-022-00998-0.
155. Udina C, Ars J, Morandi A, et al. Rehabilitation in adult post-COVID-19 patients in post-acute care with therapeutic exercise. *J Frailt Aging*. 2021;10(3):297–300. https://doi.org/10.14283/jfa.2021.1.
156. Tosato M, Ciciarello F, Zazzara MB, et al. Nutraceuticals and dietary supplements for older adults with long COVID-19. *Clin Geriatr Med*. 2022;38(3):565–591. https://doi.org/10.1016/j.cger.2022.04.004.
157. Tosato M, Calvani R, Picca A, et al. Effects of l-Arginine plus vitamin C supplementation on physical performance, endothelial function, and persistent fatigue in adults with long COVID: a single-blind randomized controlled trial. *Nutrients*. 2022;14(23). https://doi.org/10.3390/nu14234984.
158. Galluzzo V, Zazzara MB, Ciciarello F, et al. Fatigue in Covid-19 survivors: the potential impact of a nutritional supplement on muscle strength and function. *Clin Nutr ESPEN*. 2022;51:215–221. https://doi.org/10.1016/j.clnesp.2022.08.029.
159. De Roza JG, Ng DWL, Wang C, et al. Impact of perceived safety and barriers on physical activity levels in community-dwelling older adults during the COVID-19 pandemic in Singapore: a cross-sectional mixed methods study. *J Aging Phys Activ*. 2023;31(1):89–95. https://doi.org/10.1123/japa.2021-0184.
160. Chambonniere C, Lambert C, Tardieu M, et al. Physical activity and sedentary behavior of elderly populations during confinement: results from the FRENCH COVID-19 ONAPS survey. *Exp Aging Res*. 2021;47(5):401–413. https://doi.org/10.1080/0361073x.2021.1908750.
161. Tanaka T, Son BK, Iijima K. Poor health behaviors among housebound Japanese community-dwelling older adults due to prolonged self-restraint during the first COVID-19 pandemic: a cross-sectional survey. *J Frailt Aging*. 2023;12(1):86–90. https://doi.org/10.14283/jfa.2022.20.
162. Mak VP, White K, Wilkens LR, et al. The impact of COVID-19 on cancer screening and treatment in older adults: the multiethnic cohort study. *eLife*. 2023. https://doi.org/10.7554/eLife.86562, 12.
163. Zhu J, Di Gessa G, Zaninotto P. Changes in health behaviours during the COVID-19 pandemic and effect on weight and obesity among older people in England. *Sci Rep*. 2023;13(1):14661. https://doi.org/10.1038/s41598-023-41391-z.
164. Trabelsi K, Ammar A, Masmoudi L, et al. Sleep quality and physical activity as predictors of mental wellbeing variance in older adults during COVID-19 lockdown: ECLB COVID-19 international online survey. *Int J Environ Res Publ Health*. 2021;18(8). https://doi.org/10.3390/ijerph18084329.
165. Li Y, Hou T, Cheng M, et al. Anxiety prevalence and its association with physical activity in patients with non-communicable diseases during COVID-19 lockdown: a cross-sectional study in Shanghai, China. *BMC Public Health*. 2023;23(1):317. https://doi.org/10.1186/s12889-022-14369-1.

166. Creese B, Khan Z, Henley W, et al. Loneliness, physical activity, and mental health during COVID-19: a longitudinal analysis of depression and anxiety in adults over the age of 50 between 2015 and 2020. *Int Psychogeriatr*. 2021;33(5):505–514. https://doi.org/10.1017/s1041610220004135.
167. Beauchamp MK, Joshi D, McMillan J, et al. Assessment of functional mobility after COVID-19 in adults aged 50 years or older in the Canadian longitudinal study on aging. *JAMA Netw Open*. 2022;5(1):e2146168. https://doi.org/10.1001/jamanetworkopen.2021.46168.
168. Sacre JW, Holmes-Truscott E, Salim A, et al. Impact of the COVID-19 pandemic and lockdown restrictions on psychosocial and behavioural outcomes among Australian adults with type 2 diabetes: findings from the PREDICT cohort study. *Diabet Med : J British Diabet Assoc*. 2021;38(9):e14611. https://doi.org/10.1111/dme.14611.
169. Nascimento RJD, Barbosa Filho VC, Rech CR, et al. Changes in health-related quality of life and physical activity among older adults in the first-wave COVID-19 outbreak: a longitudinal analysis. *J Aging Phys Activ*. 2022;30(3):389–396. https://doi.org/10.1123/japa.2021-0104.
170. Supriya R, Gao Y, Gu Y, Baker JS. Role of exercise intensity on Th1/Th2 immune modulations during the COVID-19 pandemic. *Front Immunol*. 2021;12:761382. https://doi.org/10.3389/fimmu.2021.761382.
171. Doro MR, de Araújo IP, Santana JO, et al. Has COVID-19 lowered physical activity practice while boosting online searches for professional exercise information? *Europ J Translat Myol*. 2023;33(2). https://doi.org/10.4081/ejtm.2023.11343.
172. Otaki N, Yokoro M, Yano M, et al. Social contact impacts physical activity and sedentary behavior among older adults in Japan due to COVID-19. *BMC Geriatr*. 2022;22(1):491. https://doi.org/10.1186/s12877-022-03188-z.
173. Kawamura K, Kamiya M, Suzumura S, et al. Impact of the coronavirus disease 2019 outbreak on activity and exercise levels among older patients. *J Nutr Health Aging*. 2021;25(7):921–925. https://doi.org/10.1007/s12603-021-1648-9.
174. Aragão-Santos JC, Pantoja-Cardoso A, Dos-Santos AC, et al. Effects of twenty-eight months of detraining imposed by the COVID-19 pandemic on the functional fitness of older women experienced in concurrent and functional training. *Arch Gerontol Geriatr*. 2023;111:105005. https://doi.org/10.1016/j.archger.2023.105005.
175. Elliott J, Munford L, Ahmed S, et al. The impact of COVID-19 lockdowns on physical activity amongst older adults: evidence from longitudinal data in the UK. *BMC Public Health*. 2022;22(1):1802. https://doi.org/10.1186/s12889-022-14156-y.
176. Kim S, Yoon H, Morton P, Jang Y. Longitudinal links between behavioral activation coping strategies and depressive symptoms of U.S. adults living alone during the COVID-19 pandemic. *PLoS One*. 2022;17(5):e0267948. https://doi.org/10.1371/journal.pone.0267948.
177. Rosenberg M, Eckstrom E. Factors that promote resilience for older adults and their informal caregivers during the COVID-19 pandemic. *Aging Ment Health*. 2023;27(10):2011–2018. https://doi.org/10.1080/13607863.2023.2176819.
178. Pleguezuelos E, Sánchez-Nuño S, Del Carmen A, et al. Effect of different types of supervised exercise programs on cardiorespiratory and muscular fitness, pain, fatigue, mental health and inflammatory and oxidative stress biomarkers in older patients with post-COVID-19 sequelae "EJerSA-COVID-19": a randomized controlled trial. *BMC Geriatr*. 2023;23(1):865. https://doi.org/10.1186/s12877-023-04544-3.
179. Blumen HM, Ayers E, Wang C, et al. Randomized controlled trial of social ballroom dancing and treadmill walking: preliminary findings on executive function and neuroplasticity from dementia-at-risk older adults. *J Aging Phys Activ*. 2023;31(4):589–599. https://doi.org/10.1123/japa.2022-0176.
180. Li ML, Kor PP, Sui YF, Liu JY. Health maintenance through home-based interventions for community-dwelling older people with sarcopenia during and after the COVID-19 pandemic: a systematic review and meta-analysis. *Exp Gerontol*. 2023;174:112128. https://doi.org/10.1016/j.exger.2023.112128.
181. Daniele de Araújo Silva J, Cândido Mendes Maranhão D, Machado Ferreira Tenório de Oliveira L, Luiz Torres Pirauá A. Comparison between the effects of virtual supervision and minimal supervision in a 12-week home-based physical exercise program on mental health and quality of life of older adults: secondary analysis from a randomized clinical trial. *Geriatr Gerontol Int*. 2023;23(11):864–870. https://doi.org/10.1111/ggi.14673.
182. Lee DA, Callisaya ML, Haines TP, Hill KD. Program evaluation and refinement of the "Safe Functional Home Exercise" program for improving physical activity in older people with dementia who receive home care. *Healthcare (Basel, Switzerland)*. 2024;(2):12. https://doi.org/10.3390/healthcare12020166.
183. Soto-Bagaria L, Eis S, Pérez LM, et al. Mobile applications to prescribe physical exercise in frail older adults: review of the available tools in app stores. *Age Ageing*. 2023;52(12). https://doi.org/10.1093/ageing/afad227.
184. Galway SC, Laird MHD, Dagenais M, Gammage KL. Navigating a new normal: perceptions and experiences of an online exercise program for older adults during COVID-19. *J Aging Phys Activ*. 2023;31(5):743–755. https://doi.org/10.1123/japa.2022-0118.
185. Granet J, Peyrusqué E, Ruiz F, et al. Web-based physical activity interventions are feasible and beneficial solutions to prevent physical and mental health declines in community-dwelling older adults during isolation periods. *J Gerontol Series A, Biol Sci Med Sci*. 2023;78(3):535–544. https://doi.org/10.1093/gerona/glac127.
186. Lee OE, Lee H, Park A, Choi NG. My precious friend: human-robot interactions in home care for socially isolated older adults. *Clin Gerontol*. 2024;47(1):161–170. https://doi.org/10.1080/07317115.2022.2156829.
187. Li Y, Cui M, Pang Y, et al. Association of physical activity with socio-economic status and chronic disease in older adults in China: cross-sectional findings from the survey of CLASS 2020 after the outbreak of COVID-19. *BMC Public Health*. 2024;24(1):37. https://doi.org/10.1186/s12889-023-17492-9.
188. Buffel T, Yarker S, Phillipson C, et al. Locked down by inequality: older people and the COVID-19 pandemic. *Urban Stud*. 2023;60(8):1465–1482. https://doi.org/10.1177/00420980211041018.
189. Hasson R, Sallis JF, Coleman N, et al. COVID-19: implications for physical activity, health disparities, and health equity. *Am J Lifestyle Med*. 2022;16(4):420–433. https://doi.org/10.1177/15598276211029222.
190. Izquierdo M, Duque G, Morley JE. Physical activity guidelines for older people: knowledge gaps and future directions. *Lancet Health longev*. 2021;2(6):e380–e383. https://doi.org/10.1016/s2666-7568(21)00079-9.
191. Poon ET, Sun F, Tse AC, et al. Effectiveness of tele-exercise training on physical fitness, functional capacity, and health-related quality of life in non-hospitalized individuals with COVID-19: the COFIT-HK study. *J Exer Sci Fitness*. 2024;22(2):134–139. https://doi.org/10.1016/j.jesf.2024.01.003.
192. U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans*. second ed. Washington, DC: U.S. Department of Health and Human Services; 2018. Retrieved from https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf.
193. Ammar A, Brach M, Trabelsi K, et al. Effects of COVID-19 home confinement on eating behaviour and physical activity: results of the ECLB-COVID19 international online survey. *Nutrients*. 2020;12(6). https://doi.org/10.3390/nu12061583.
194. Bertrand L, Shaw KA, Ko J, et al. The impact of the coronavirus disease 2019 (COVID-19) pandemic on university students' dietary intake, physical activity, and sedentary behaviour. *Appl Physiol Nutr Metabol = Physiol Appl Nutrit Metabol*. 2021;46(3):265–272. https://doi.org/10.1139/apnm-2020-0990.
195. Rodríguez-Larrad A, Mañas A, Labayen I, et al. Impact of COVID-19 confinement on physical activity and sedentary behaviour in Spanish university students: role of gender. *Int J Environ Res Publ Health*. 2021;18(2). https://doi.org/10.3390/ijerph18020369.
196. Sidebottom C, Ullevig S, Cheever K, Zhang T. Effects of COVID-19 pandemic and quarantine period on physical activity and dietary habits of college-aged students. *Sports Med Health Sci*. 2021;3(4):228–235. https://doi.org/10.1016/j.smhs.2021.08.005.
197. Talapko J, Perić I, Vulić P, et al. Mental health and physical activity in health-related university students during the COVID-19 pandemic. *Healthcare (Basel, Switzerland)*. 2021;9(7). https://doi.org/10.3390/healthcare9070801.
198. Burnatowska E, Surma S, Olszanecka-Glinianowicz M. Relationship between mental health and emotional eating during the COVID-19 pandemic: a systematic review. *Nutrients*. 2022;(19):14. https://doi.org/10.3390/nu14193989.
199. Torres L, Caciula MC, Tomoiaga AS, Gugu-Gramatopol C. Correlations between mental health, physical activity, and body composition in American college students after the COVID-19 pandemic lockdown. *Int J Environ Res Publ Health*. 2023;20(22). https://doi.org/10.3390/ijerph20227045.
200. Khan MA, Menon P, Govender R, et al. Systematic review of the effects of pandemic confinements on body weight and their determinants. *Br J Nutr*. 2022;127(2):298–317. https://doi.org/10.1017/s0007114521000921.
201. Tison GH, Barrios J, Avram R, et al. Worldwide physical activity trends since COVID-19 onset. *Lancet Global Health*. 2022;10(10):e1381–e1382. https://doi.org/10.1016/s2214-109x(22)00361-8.
202. Gallo LA, Gallo TF, Young SL, et al. The impact of isolation measures due to COVID-19 on energy intake and physical activity levels in Australian university students. *Nutrients*. 2020;12(6). https://doi.org/10.3390/nu12061865.
203. Jodczyk AM, Gruba G, Sikora Z, et al. PaLS study: how has the COVID-19 pandemic influenced physical activity and nutrition? Observations a year after the outbreak of the pandemic. *Int J Environ Res Publ Health*. 2021;18(18). https://doi.org/10.3390/ijerph18189632.
204. Ripley-Gonzalez JW, Zhou N, Zeng T, et al. The long-term impact of the COVID-19 pandemic on physical fitness in young adults: a historical control study. *Sci Rep*. 2023;13(1):15430. https://doi.org/10.1038/s41598-023-42710-0.
205. Kriaučionienė V, Grincaitė M, Raskilienė A, Petkevičienė J. Changes in nutrition, physical activity, and body weight among Lithuanian students during and after the COVID-19 pandemic. *Nutrients*. 2023;15(18). https://doi.org/10.3390/nu15184091.
206. Arundell L, Salmon J, Timperio A, et al. Physical activity and active recreation before and during COVID-19: the our life at home study. *J Sci Med Sport*. 2022;25(3):235–241. https://doi.org/10.1016/j.jsams.2021.10.004.
207. Gómez Chacón R, Nuñez Sánchez JM, Gálvez Ruiz P. Effects of physical activity and COVID-19 on healthy student strengths in the university system: implications for post-pandemic management. *Europ J Invest Health Psychol Educ*. 2024;14(1):243–255. https://doi.org/10.3390/ejihpe14010016.
208. Atakan MM, Li Y, Koşar ŞN, et al. Evidence-based effects of high-intensity interval training on exercise capacity and health: a review with historical perspective. *Int J Environ Res Publ Health*. 2021;18(13). https://doi.org/10.3390/ijerph18137201.
209. Bhurka A, Shukla Yu. Effect of aerobic exercise versus resistance training on anxiety and physical fitness among post COVID young adults-A comparative interventional study. *Int J Health Sci*. and Research. 2023;13:11. https://doi.org/10.52403/ijhsr.20231110.
210. Yon AL, Reel JJ, Chen-Edinboro LP, et al. Influences of the COVID-19 pandemic on intuitive exercise and physical activity among college students. *Behav Sci*. 2022;12(3). https://doi.org/10.3390/bs12030072.
211. Xia W, Huang CH, Guo Y, et al. The physical fitness level of college students before and after web-based physical education during the COVID-19 pandemic. *Front Pediatr*. 2021;9:726712. https://doi.org/10.3389/fped.2021.726712.
212. Channa A, Popescu N, Skibinska J, Burget R. The rise of wearable devices during the COVID-19 pandemic: a systematic review. *Sensors (Basel, Switzerland)*. 2021;21(17). https://doi.org/10.3390/s21175787.

213. Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. *Diabetes Metabol Syndr*. 2021;15(3):869–875. https://doi.org/10.1016/j.dsx.2021.04.007.
214. Koc HC, Xiao J, Liu W, et al. Long COVID and its management. *Int J Biol Sci*. 2022; 18(12):4768–4780. https://doi.org/10.7150/ijbs.75056.
215. Crook H, Raza S, Nowell J, et al. Long covid-mechanisms, risk factors, and management. *BMJ (Clinical research ed)*. 2021;374:n1648. https://doi.org/10.1136/bmj.n1648.
216. Wu K, Van Name J, Xi L. Cardiovascular abnormalities of long-COVID syndrome: pathogenic basis and potential strategy for treatment and rehabilitation. *Sports Med Health Sci*. 2024;6(3):221–231. https://doi.org/10.1016/j.smhs.2024.03.009.
217. Stavrou VT, Kyriaki A, Vavougios GD, et al. Athletes with mild post-COVID-19 symptoms experience increased respiratory and metabolic demands: α cross-sectional study. *Sports Med Health Sci*. 2023;5(2):106–111. https://doi.org/10.1016/j.smhs.2022.10.004.
218. Cattadori G, Di Marco S, Baravelli M, et al. Exercise training in Post-COVID-19 patients: the need for a multifactorial protocol for a multifactorial pathophysiology. *J Clin Med*. 2022;11(8). https://doi.org/10.3390/jcm11082228.
219. Vasiliadis AV, Boka V. Safe return to exercise after COVID-19 infection. *Sultan Qaboos Univ Med J*. 2021;21(3):373–377. https://doi.org/10.18295/squmj.8.2021.124.
220. Metzl JD, McElheny K, Robinson JN, et al. Considerations for return to exercise following mild-to-moderate COVID-19 in the recreational athlete. *HSS J : the Musculoskel J Hospit Spec Surg*. 2020;16(Suppl 1):102–107. https://doi.org/10.1007/s11420-020-09777-1.
221. Ladlow P, Barker-Davies R, Hill O, et al. Use of symptom-guided physical activity and exercise rehabilitation for COVID-19 and other postviral conditions. *BMJ Milit Health*. 2024;170(6):510–515. https://doi.org/10.1136/military-2023-002399.
222. Singh SJ, Daynes E, McAuley HJC, et al. Balancing the value and risk of exercise-based therapy post-COVID-19: a narrative review. *Eur Respir Rev : Off J Europ Respirat Soc*. 2023;32(170). https://doi.org/10.1183/16000617.0110-2023.
223. Anderson E, Durstine JL. Physical activity, exercise, and chronic diseases: a brief review. *Sports Med Health Sci*. 2019;1(1):3–10. https://doi.org/10.1016/j.smhs.2019.08.006.
224. Jimeno-Almazán A, Pallarés JG, Buendía-Romero Á, et al. Post-COVID-19 syndrome and the potential benefits of exercise. *Int J Environ Res Publ Health*. 2021; 18(10). https://doi.org/10.3390/ijerph18105329.
225. Cavigli L, Fusi C, Focardi M, et al. Post-acute sequelae of COVID-19: the potential role of exercise therapy in treating patients and athletes returning to play. *J Clin Med*. 2022;12(1). https://doi.org/10.3390/jcm12010288.
226. Cheng X, Cao M, Yeung WF, Cheung DST. The effectiveness of exercise in alleviating long COVID symptoms: a systematic review and meta-analysis. *Worldviews Evidence-Based Nurs*. 2024;21(5):561–574. https://doi.org/10.1111/wvn.12743.
227. Tryfonos A, Pourhamidi K, Jörnåker G, et al. Functional limitations and exercise intolerance in patients with Post-COVID condition: a randomized crossover clinical trial. *JAMA Netw Open*. 2024;7(4):e244386. https://doi.org/10.1001/jamanetworkopen.2024.4386.
228. Edward JA, Peruri A, Rudofker E, et al. Characteristics and treatment of exercise intolerance in patients with long COVID. *J Cardpulm Rehabil Prev*. 2023;43(6): 400–406. https://doi.org/10.1097/hcr.0000000000000821.
229. Jamieson A, Al Saikhan L, Alghamdi L, et al. Mechanisms underlying exercise intolerance in long COVID: an accumulation of multisystem dysfunction. *Physiol Rep*. 2024;12(3):e15940. https://doi.org/10.14814/phy2.15940.
230. Zhao HM, Xie YX, Wang C. Recommendations for respiratory rehabilitation in adults with coronavirus disease 2019. *Chin Med J*. 2020;133(13):1595–1602. https://doi.org/10.1097/cm9.0000000000000848.
231. Jimeno-Almazán A, Buendía-Romero Á, Martínez-Cava A, et al. Effects of a concurrent training, respiratory muscle exercise, and self-management recommendations on recovery from post-COVID-19 conditions: the RECOVE trial. *J Appl Physiol (Bethesda, Md : 1985)*. 2023;134(1):95–104. https://doi.org/10.1152/japplphysiol.00489.2022.
232. Zheng C, Chen XK, Sit CH, et al. Effect of physical exercise-based rehabilitation on long COVID: a systematic review and meta-analysis. *Med Sci Sports Exerc*. 2024;56 (1):143–154. https://doi.org/10.1249/mss.0000000000003280.
233. Salman D, Vishnubala D, Le Feuvre P, et al. Returning to physical activity after covid-19. *BMJ (Clinical research ed)*. 2021;372:m4721. https://doi.org/10.1136/bmj.m4721.
234. American College of Sports Medicine. In: Liguori G, Feito Y, Fountaine C, Brad R, Edition Eleventh, eds. *Acsm's Guidelines for Exercise Testing and Prescription*. Philadelphia: Wolters Kluwer; 2022.
235. Gloeckl R, Zwick RH, Fürlinger U, et al. Practical recommendations for exercise training in patients with long COVID with or without post-exertional malaise: a best practice proposal. *Sports Med Open*. 2024;10(1):47. https://doi.org/10.1186/s40798-024-00695-8.