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Review Article



# The Relationship among Exercise, Nutrition, and COVID-19 Severity

**Michael White MS, CSCS[1], Quentin Z Nichols, PhD[2], Juliet Moore PhD [3], Michaela Alesi MS[4], and Stella Lucia Volpe, PhD, RDN, ACSM-CEP, FACSM[1]***

[1]*Department of Human Nutrition, Foods, and Exercise, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, USA*

[2]*Sensei Wellness, Santa Monica, CA, USA*

[3]*Division of Bio kinesiology and Physical Therapy University of Southern California, Los Angeles, California, USA*

[4]*Bonafide Health, LLC p/b Pharmavite, Harrison, NY, USA*

***Corresponding author:** Stella Lucia Volpe, PhD, RDN, ACSM-CEP, FACSM, Department of Human Nutrition, Foods, and Exercise Virginia Polytechnic Institute and State University 295 West Campus Drive (MC 0430) Wallace Hall, Blacksburg, VA 24061. USA

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## Abstract

COVID-19 is a complex, multifactorial disease state that caused a global pandemic beginning in late 2019. The aim of this review is to elucidate a connection between nutrition and exercise status, and COVID-19 symptom severity. Key nutrients that support antioxidant activity and antiinflammation, as well as healthy body composition, aerobic fitness, and muscle mass may all improve COVID-19 symptom severity and recovery time. We reviewed various data on COVID-19 outcomes with exercise status and key nutrients. Improved nutrient status of vitamin D, zinc, omega-3 fatty acids, N-acetyl cysteine (NAC), and Nicotinamide adenine dinucleotide (NAD+) with exercise, may be effective in combating COVID-19 outcomes. Conclusion: Those concerned with COVID-19 symptom severity would benefit from sound nutrition and exercise habits, in conjunction with following the latest Centers for Disease Control and Prevention (CDC) guidelines.

**Keywords:** Aerobic Fitness, Antioxidants, Exercise, COVID, COVID-19, Inflammation, Muscle Mass, Nutrients, Nutrition, SARS-CoV-2, Strength

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), better known as COVID-19, was identified in the United States in late December of 2019. COVID-19 is a coronavirus generally characterized by dry cough, fatigue, fever, dyspnea, anosmia, and ageusia [1,2] By January 30, 2020, the World Health Organization (WHO) claimed COVID-19 to be of international concern following the mass outbreak of COVID-19 in China [3]. Individuals admitted to the intensive care unit (ICU) are commonly reported to have underlying conditions such as diabetes mellitus, hypertension, and cardiovascular disease [4]. COVID-19 presents a host of physical health issues, both acutely and chronically, following infection. Acutely, dyspnea associated with COVID-19 may induce acute respiratory distress syndrome (ARDS), acute cardiac injury, clinically significant arrhythmia, and neurological damage [3,5]. COVID-19 also presents long-term health issues, the condition is commonly referred to as "post-COVID syndrome" (PCS), or "Long-COVID". PCS is characterized by a wide range of physiological symptoms, such as severe fatigue, chronic headache, continued or new dyspnea, joint pain, and neurological conditions such as myalgia and attention deficit [3–6]. Following COVID-19 recovery, individuals may also experience persistent COVID-19 symptoms, known as

Post-COVID Syndrome, also coined "long-COVID", characterized by a host of physical and cognitive ailments. Pulmonary, cardiac, and vascular fibrosis are among the physical ailments associated with long-COVID, leading to decreased quality of life, as well as mortality. Acute lung damage from COVID-19 infection can lead to prolonged dyspnea, and is seen more frequently in individuals who required mechanical ventilation when they had COVID [7]. Long-COVID may also present a host of neurological symptoms, both in the central nervous (CNS) and peripheral nervous system (PNS) [7,8]. Ataxia, dizziness, chronic headache, epilepsy, and impaired cognitive function were all observed in individuals with long-COVID, stemming from neuronal brain damage due to hypoxia and infection from the COVID-19 infection [8].

The symptoms of COVID-19 have been demonstrated to be much more severe in individuals who were obese during the time of their infection [9–12]. Simonet et al. [9] reported that 75.8% of individuals admitted to the ICU who were ventilated due to COVID-19 complications had a body mass index (BMI) >30 $kg/m^2$ (which is considered obese). Palaiodomos et al. [10] examined the characteristics of 200 individuals admitted to a tertiary hospital and found that obesity was independently associated with worse health outcomes and increased mortality while these individuals were hospitalized with COVID-19 compared to those who were not obese. Healthy nutrition and physical activity habits are commonly associated with the maintenance of lower a BMI (BMI<30$kg/m^2$) [13,14]. The goal of this review is to establish the potential compounding effects of physical activity, nutrition, and supplementation to support the immune system in reducing the severity and overall effects of COVID-19 on health outcomes.

## Methodology

Online databases (PubMed, PubMed Central, Scopus, EMBRANE) were searched for relevant literature using the following key terms "Aerobic Fitness", "Antioxidants", "Cardiovascular", "COVID", "COVID-19", "Exercise", "Medical Nutrition Therapy", "Minerals", "Muscle", "Nutrients", "Nutrition", "SARS-CoV-2", and "Vitamins". Primarily human clinical data was used, with murine model data supporting potential mechanistic evidence. All the used literature was available as full-text documents through The Virginia Polytechnical Institute and State University libraries.

## Exercise & Immunity

The immune system's response to exercise has been a research area of interest. As early as the 1950s, researchers have consistently shown lymphocytosis immediately following strenuous exercise that transitions to lymphopenia during recovery [15]. It has been observed that following an acute bout of endurance exercise, the immune system is temporarily suppressed, increasing the susceptibility for developing upper respiratory tract infection (URTI) for up to two hours [16]. Researchers who have conducted epidemiologic studies have shown an increased risk of URTI during recovery from strenuous exercise in endurance athletes, which appears to be related to frequency and intensity of exercise [17,18]. The risk of URTI development follows a characteristic J-shaped curve. Moderate exercise provides reduced risk of infection compared to sedentary behaviour, while strenuous exercise increases the risk of URTI compared to being sedentary. This increased risk of URTI becomes larger with repetitive bouts of exercise [19,20]. However, recent evidence has begun to dispute the long-held belief of the "open window hypothesis" where the circulating immune cell reduction results in increased risk of infection [16]. This has been reviewed elsewhere, and exercise has been shown to provide resistance to both bacterial and viral infections within the current literature [21]. Apart from the immune cell changes, it is known that muscle tissue directly interacts with the immune system and other organs during exercise as muscle releases endogenous interleukin (IL)-6 in response to exercise [22]. This increase in circulating IL-6 concentrations during and following exercise has been shown to occur with no increase in messenger ribonucleic acid (mRNA) concentrations within blood leukocytes [23]. The chemoattractant cytokine IL-8 is also released with IL-6 in response to the contraction of muscle fibers and glycogen use [24]. These cytokines may then have interactions with circulating immune cells and other tissues to respond to energy needs, oxidative stress, and muscle damage associated with exercise. Interleukin-6 plays a two- part role in the immune response to exercise: 1) it acutely promotes the production of anti- inflammatory mediator IL-10, which upregulates IL-1 receptor antagonist (IL-1ra); and 2) it inhibits the expression of the pro-inflammatory protein, tumor necrosis factor-alpha [25]. These direct interactions from the working muscle itself lend to the long-term benefit of exercise on overall health. The "open window hypothesis", described by Nieman and Pedersen [19], is based on vigorous exercise intensity; however, this label can be interpreted in many ways. The intensity that is described to elicit this open window is high performance, elite activities such as high-level athletic training or competitions (e.g., marathons). For the average person who exercises, these levels of intensity will likely not be attained during their training. Caution should be taken when relating the open window hypothesis to non-athletes, because exercise could be discouraged during times of high infection rates, such as flu season or a pandemic like COVID-19. Diet and exercise are key protective factors that should be encouraged for promoting immunity.

### Exercise Risk & Viral Infection

The benefits of exercise for overall health and the prevention or reduced risk of cardiovascular disease, diabetes mellitus, cancer, and metabolic disorders have been well-documented [26–29]. Maintaining exercise habits has also been shown to improve the resistance to infection, with habitual moderate-intensity exercise showing protective effects for infection risk and enhancing vaccination effectiveness [30].

Moderate- and vigorous-intensity exercise elicit varying responses within the immune system. Siedlik et al. [31] performed meta-analyses examining short- and long-duration acute exercise bouts of moderate- and high-intensity. They reported that short-duration, moderate-intensity exercise had the least effect on immune cell proliferation, while long-duration, high-intensity exercise had the highest suppression of immune cell proliferation [31]. Further-

more, it appears that endurance exercise provides larger effects on immune cell number and function compared to resistance exercise in the same participants [32].

Moderate-intensity exercise has been shown to promote the effectiveness of vaccines and immune function after a single bout and has been described as the acute stress-induced immuno- enhancement hypothesis [33]. Several groups of researchers have also demonstrated that both aerobic exercises, such as cycling, and eccentric resistance training to induce muscle damage around the vaccination site, increase the response to vaccinations because exercise acts as an adjuvant therapy to improve the response to vaccines that may have low responses normally [34]. The therapeutic effect of exercise on post-injection muscle soreness is likely due increased blood flow to the muscle, which reduce post-injection metabolites and edemas responsible for the soreness [35,36].

## Exercise and COVID-19 Prophylaxis

Skeletal muscle plays a key role in the maintenance of a generalized healthy immune response via multiple mechanisms. Healthy skeletal muscle synthesizes and releases glutamine, which is utilized by macrophages, neutrophils, and lymphocytes [37–41]. Skeletal muscle also produces anti-inflammatory IL-6, which can subsequently decrease inflammation and signal for anti- inflammatory IL-10, and IL-1ra secretion [42]. Skeletal muscle weakness has been shown to negatively influence motor and respiratory function and is linked to poor immune response and metabolic stress when facing acute infections such as COVID-19. Cheval and colleagues [43] concluded that maximal grip strength may affect COVID-19 symptom severity and was negatively associated with the risk of COVID-19 hospitalization, independent of other risk factors. Muscle cross-sectional area has also been correlated with an increase in successful extubation (from ventilator use) and a decrease time spent in the ICU, as well as a decreased risk of mortality from COVID-19 [44]. Gil and colleagues [45] conducted an observational study to determine if there was an association between skeletal muscle mass and length of stay for COVID-19 hospitalization. Individuals' hand-grip strength and cross-sectional area of the vastus lateralis were assessed upon admission. Hand- grip strength and vastus lateralis cross-sectional area data were organized into tertiles, the "high" classification for both tests was the highest tertile, and the "low" classification was the lowest tertile. When the researchers compared high versus low hand-grip strength, they reported that those with stronger hand-grip strength had shorter lengths of stay and less severe COVID-19 symptoms compared to those with weaker hand-grip strength (P=0.007) [45]. The researchers also reported that those admitted to the hospital for COVID-19 with larger vastus lateralis cross-sectional area had shorter lengths of stay and less severe symptoms compared to those with smaller cross- sectional area of the vastus lateralis (P=0.016) [45]. Cheval et al. [43] investigated the relationship between muscular strength and COVID-19 hospitalization rates in adults 50 years of age and older. Individuals who were $^{3}$50 years of age of, who also tested positive for COVID-19, participated in measuring grip strength in both hands using a hand-grip dynamometer. The researchers reported that individuals who were not hospitalized had significantly stronger average hand-grip strength (34.5 ±11.8 kg) than individuals who were hospitalized for COVID-19 (31.9±11.45 kg) (P=0.027) [43]. Suh and colleagues [46] reported that individuals who had died from COVID-19, not only had acute sarcopenia, but also had myopathy due to necrotic muscle fibers. Individuals in the ICU with COVID-19 benefitted from beginning an early physical rehabilitation program to mitigate the loss of muscle mass and function [47]. These findings show the importance of skeletal muscle mass and strength for mitigating the severity of COVID-19 symptoms, emphasizing the importance of exercise and proper nutrition to maintain muscle mass.

Thoracic Computed Tomography (CT) scans were retrospectively compared among individuals hospitalized with COVID-19 to elucidate any corollary relationship between the image results and COVID-19 severity [48]. The CT scans revealed that the muscle mass of individuals admitted to the ICU for COVID-19 (29±24 Hounsfield Units) was significantly lower than the muscle mass of individuals who did not require admission to the ICU for COVID-19 (39.4±12 Hounsfield Units) (P=0.001) (Hounsfield Units are a universal unit for CT scans that indicate density). Muscle mass measured through CT scans could be a predictor for which individuals would require hospitalization in the ICU due to their COVID-19 symptoms [48]. Cardiovascular fitness is also an important aspect of exercise that effects COVID-19 prognosis. Latorre-Román and colleagues [49] performed a cross-sectional study where they examined the role of prior participation in physical activity and COVID-19 symptom severity. They reported that, performing moderate-intensity physical activity (>150 minutes per week) was protective against hospitalization for COVID-19 induced respiratory injury. Zbinden-Foncea and colleagues [50] hypothesized that those with high levels of cardiovascular fitness may have a more robust immune protection from COVID-19 compared to individuals without a high level of cardiovascular fitness. This indicates that the immune effects of cardiovascular fitness may attenuate COVID-19 symptom severity.

## Exercise following COVID-19 Recovery

Singh and colleagues [51] reported that individuals previously infected with COVID-19 who had recovered displayed a significantly lower peak aerobic capacity versus the control group who had never experienced COVID-19 infection (70% ± 11% versus 131% ± 45% of predicted peak aerobic capacity, respectively) (P<0.0001). Singh and colleagues [51] found that the decrease in peak exercise aerobic capacity stemmed from the individuals with COVID-19 having significantly lower oxygen extraction (0.49±0.1) than the oxygen extraction capabilities of individuals who never contracted COVID-19 (0.78±0.1) (P<0.0001). Aparisi [52] investigated oxygen consumption of individuals with COVID-19 who did not require hospitalization. Of those with COVID-19, the individuals who reported persistent dyspnea had significantly lower oxygen consumption compared to those who did not report persistent dyspnea (17.8 mL/kg/minute vs 22.8 mL/kg/minute, respectively) (P<0.001) [52]. Following COVID-19 recovery, different exercise modalities may be used to attenuate long- COVID symptoms and COVID-19 repercussions. Considerations for dyspnea and blood pressure during

exercise following COVID-19 infection need to be made to not overburden the cardiorespiratory system [53–55]. Exercise can stimulate the production of extracellular superoxide dismutase (EcSOD) and anti-inflammatory IL-6, both of which can reduce the oxidative stress caused by COVID-19 infection [55]. Exercise can cause attenuation of cardiac fibrosis and cardiac inflammation by increasing mitochondrial biogenesis in cardiac tissue via stimulation of the SIRT1/PGC-1α/PI3K/Akt pathway [56]. As previously mentioned, skeletal muscle contraction stimulates the secretion of glutamine, which can be utilized by macrophages, neutrophils, and lymphocytes. Skeletal muscle contraction can also increase concentrations of anti- inflammatory IL-6, IL-10, IL-1ra, suggesting the importance of exercise as part of a rehabilitative method following COVID-19 infection [42].

### Gym Cleanliness

One major barrier to exercise participation at public gyms is the cleanliness of the facility. A common conception of gyms is the lack of participation in the routine cleaning of equipment after use by patrons. Researchers have shown that gym equipment does not harbor infectious bacterial species with a routine cleaning protocol in place [57,58]. However, Goldhammer et al. [58] reported that, although bacteria are exterminated with regular twice-a-day cleaning, viruses may still be present after cleaning. Not only did virus contamination increase after cleaning, but weight equipment had significantly higher levels of viral contamination compared to aerobic equipment. Furthermore, patron cleaning of equipment is relatively low unless there are large amounts of signage and access to cleaning wipes within a gym environment [59]. Goldhammer and colleagues [58] suggested that the difference in bacteria based on equipment type is due to two factors. The first of which was an observed difference in frequency in which the aerobic equipment was being sprayed with disinfectant compared to weight training equipment. The authors also suggest that the material of the equipment played a role in the bacterial density. The smooth, stainless-steel surface of the weight training equipment provide a non-porous environment on which bacteria could thrive, whereas the aerobic exercise equipment was more porous, providing a worse environment for bacteria proliferation [59].

In spite of gym cleanliness helping with viral and bacterial transmission, emerging data would suggest that even following preventative public health guidelines, fitness centers may still to be an area where outbreaks of COVID-19 can commonly occur [60,61]. A fitness center in Minnesota followed The Minnesota Department of Health COVID-19 prevention guidelines to reduce COVID-19 transmission. These guidelines included: limiting the occupancy of the facility to 25%, requiring 6 feet of distancing between persons and equipment, frequent surface cleaning, optional mask use while exercising, and 30 minutes of cleaning and sanitization following every 90-minute reservation [61]. Despite these efforts, five employees and 18 members of the fitness center were infected with COVID-19.

## Nutrition and COVID-19 Prophylaxis

Nutrition status can affect various aspects of physiological function, including immune response to viral infection [62,63]. Nutrient intake, and subsequent nutrient status, could influence the severity and/or duration of COVID-19 symptoms.

### Vitamin D

Vitamin D is defined as both a fat-soluble vitamin and a hormone or secosteroid. Vitamin D is obtained by sunlight and by food. Murai et. al [64] reported that a single dose of 200,000 International Units (IU) of vitamin D3 did not significantly decrease the length of stay of individuals hospitalized with moderate to severe COVID-19, nor did the singular high dose administration of vitamin D3 reduce the incidence of ICU administration, mortality, or need for mechanical ventilation. Murai et al.'s [64] findings should not discount the importance of vitamin D3, but perhaps indicate the need for frequent dosing as opposed to singular dosing. When comparing the effects of 5000 IU and 1000 IU of daily oral vitamin D3 administration, Sabico and colleagues [65] reported that, individuals with mild to moderate COVID-19 symptoms who received 5,000 IU of vitamin D3, took significantly fewer days (6.2±0.8 days) to resolve their cough, compared with individuals who received 1,000 IU of vitamin D3 (9.1±0.8 days) to resolve their cough (P=0.007). Sabico and colleagues [65] also reported that individuals receiving 5,000 IU vitamin D3 recovered from their ageusia 5.5 days sooner than those receiving 1,000 IU (11.4±1.0 vs 16.9±1.7 days, respectively) (P=0.035). The data on vitamin D intake and COVID-19 symptoms is equivocal, nonetheless, individuals strive to obtain the recommended amounts of vitamin D through food and sunlight to maintain normal concentrations in the body.

### Zinc

Zinc is a required mineral that is involved in more than 300 metabolic reactions in the body. It is an important micronutrient with both immunoregulatory and anti-viral properties, providing a potential use in the treatment of COVID-19 [66]. Jothimani and colleagues [66] reported an association between individuals who were zinc deficient (serum zinc concentrations <80 µg/dL) and increased severity of COVID-19-related complications compared with individuals who had normal zinc concentrations (80-120 mcg/dL) [66,67]. Individuals with zinc deficiency displayed a higher prevalence of ARDS (18.5%), while individuals with normal zinc concentrations had a significantly lower (P=0.0063) prevalence of ARDS (0%). Jothimani and colleagues [66] also reported that individuals with COVID-19, who also had a zinc deficiency, experienced thrombotic complications at more than twice the rate of individuals with normal zinc concentrations (70.4% vs 30.0%, respectively) (P=0.009). Zinc deficiency was also associated with increased peak median IL-6 concentrations (Interquartile Range 23.8 to 158.1 pg/mL) compared to peak median IL-6 concentrations of individuals with COVID-19 and normal zinc concentrations (Interquartile Range 3.05 to 44.03 pg/mL), indicating that individuals with normal zinc concentrations secreted less anti-inflammatory IL-6, because there was a lower inflammatory burden following COVID-19 infection. (P=0.029) [66]. Furthermore, individuals with deficient zinc concentrations had longer hospital stays than those with normal zinc concentrations (7.9 vs 5.7 days, respectively, P=0.047)

[66]. Zinc may help prevent the entry of the SARS-CoV-2 virus into the cell via multiple mechanisms. Zinc supplementation has been shown to improve bronchial health in rats who were zinc deficient by improving bronchial cilia, the hair like projections on the lining of the lungs, responsible for clearance of microbes and debris from the airway [68,69]. Zinc supplementation improved the health of bronchial cilia compared to the control group, with increased number of cilia (4.6±1.08 vs 4.0±0.79, respectively, P<0.001) and length of cilia (7.68±0.66 μm vs 5.16±0.91 μm, respectively, P<0.0001), [69]. These ciliary changes led to overall improvements in removal of viruses and reduced the risk of developing secondary bacterial infections [70]. Considerations for mucociliary virus removal are highly relevant, because approximately 50% of individuals who were hospitalized and who died from COVID-19 had bacterial or fungal infections. [70, 71].

Zinc may influence gene expression via Angiotensin-Converting Enzyme-2 (ACE-2) [70]. Zinc's influence on ACE-2 is important to highlight because ACE-2 has been identified as one of the main points of entry for SARS-CoV-2 [72]. The expression of ACE-2 mRNA is at least partially regulated via Sirtuin1 (SIRT1), a genetic regulator of immune function [73-75]. Through its inhibitory effects on inflammation and oxidative stress, SIRT-1 expression effects the prognosis and outcomes of metabolic, age-related, autoimmune, and cardiovascular diseases [73-76]. Zinc inhibits SIRT-1 activity through the induction of regulatory T-cells via the deacetylation of transcription factor Foxp3 [60]. Zinc has been shown to inhibit the activity of SIRT-1 more potently than a well- established SIRT-1 inhibitor, nicotinamide, indicating zinc may reduce ACE-2 activity resulting in limited entry of Sars-CoV-2 into the cell [70]. Zinc may also be effective in reducing viral replication rates. Velthius et al. [77] examined the effects of zinc on viral replication in SARS-coronavirus (SARS-CoV) in a cell culture model. SARS- CoV cell cultures were treated with varying concentrations of zinc solution before undergoing MTS assay assessment, an assay that measures cell proliferation. In a dose-dependent manner, zinc solution reduced viral replication rates via inhibitory effects on the replication and transcription complex of SARS-CoV [77]. However, further data directly evaluating zinc supplementation effects on SARS-CoV-2 in human clinical trials is needed to understand the role zinc plays in COVID-19 immunity. Zinc plays an integral role in the recognition and response to viral pathogens in both the Toll-Like Receptor and interferon response [78]. Toll-Like Receptors function as sensors to recognize pathogens and signal for an interferon-based immune response to remove a virus [79]. During pathogen recognition, zinc ions play a regulatory role in interferon production, by reducing type 1 interferons, and interferon-stimulated genes [78]. Following pathogen recognition, zinc plays a part in the response to viral pathogens by stimulating the activity of Natural Killer Cells, and

increasing Interferon binding capacity [78,80]. The anti-viral immune response is also largely dependent on zinc, due to zinc's role in the production of lymphocytes and macrophages [80,81]. Furthermore, Read and colleagues [78] found that zinc may significantly improve the turnover of chronic and acute viral infections and help attenuate their symptoms and respective pathologies. Zinc also acts as a potent antioxidant and anti-inflammatory mineral, providing a supporting mechanism for the oxidative stress and inflammatory burden often associated with COVID-19 infection [70,78,80,81].

## Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids that have been shown to support cardiovascular health; they can lower serum triglyceride concentrations in the blood [82]. The three main types of omega-3 fatty acids are: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linoleic acid (ALA). Both EPA and DHA are derived from fish, while ALA is derived from plants [82]. Omega-3 fatty acids could also pay a role in decreasing the severity of COVID-19. In 10% to 15% of cases of COVID-19 infection, severe pneumonia develops, potentially in tandem with ARDS [83]. ARDS presents with an overabundance of immune cell proliferation and cytokine activity (referred to "cytokine storm syndrome"), generally 7 to 15 days following symptom onset, resulting in systemic inflammation and organ failure [83]. Essential polyunsaturated fatty acids, like omega-3 fatty acids, are important for the maintenance of immune function, because they regulate acute and chronic inflammation [83–85]. Omega-3 fatty acids are precursors for specialized pro-resolving lipid mediators (resolvins, protectins, maresins), and thus, could be helpful in maintaining a robust immune response, reducing both the length and severity of inflammation, and promoting tissue healing [62,83]. Omega-3 fatty acids may also influence the entry and replication of viruses [83]. Weill and colleagues [83] suggest that the countries with highest omega-3 fatty acid consumption had over four times lower relative COVID-19 death rates compared to countries with the lowest omega-3 fatty acid consumption (36 vs 175 deaths per million).

## N-Acetyl Cysteine

N-acetyl cysteine (NAC) is an antioxidant and is derived from L-cysteine (an amino acid). NAC has been used for the flu, cough and dry eyes, though there has not been strong evidence indicating it will help these conditions [86]. NAC has historically been used for as a treatment option to break up thickened mucus in the lungs and to combat acetaminophen overdose [87]. NAC may also improve general immune function, suppress viral replication, and reduce inflammation [87,88]. NAC acts as an anti-inflammatory agent by inhibiting the signalling of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), a protein complex that regulates inflammatory responses, decreasing the production of pro-inflammatory cytokines [89]. When evaluating the efficacy of NAC as a treatment option to attenuate ARDS, Soltan-Sharifi et al. [90] reported that, individuals with ARDS who received treatment of a single-day of 150 mg/kg of NAC, followed by 50 mg/kg/day of intravenous NAC for 10 days, had significantly lower clinical severity scores (18.3 ± 1) than the control group who did not receive NAC infusions (21.1 ± 2) (P<0.01) [90]. NAC has been found to be useful for attenuating the effect of ARDS and may potentially be useful in limiting or preventing lung damage caused by COVID-19 infection [88]. NAC may be beneficial in reducing the ability of the virus to enter the cell via

limiting ACE-2 receptor affinity by disrupting the disulfide bonds of mucus into thiol groups [88]. NAC can easily cross the cell membrane to be deacetylated and produce L-Cysteine, the rate-limiting amino acid in reduced glutathione synthesis [88].

### Glutathione

Glutathione is comprised of cysteine, glycine, and glutamic acid. It is found in high concentrations in most cells of the body [91]. It is a critical component to the immune system because it acts as a cofactor in the enzymatic action of antioxidants, supports healthy mitochondrial function, and neutralizes free radicals [91,92]. Due to the structure of glutathione as a tripeptide, it cannot effectively enter cells, making NAC a useful tool to replenish cellular glutathione stores [88,91]. While the recycling of glutathione increases during COVID-19 illness, it cannot effectively match the significantly higher demand for glutathione, and thus glutathione synthesis must increase, which requires L-cysteine [88,91,93]. Glutathione depletion has been implicated in worsening the pathology of disease via mechanisms related to oxidative stress and inflammation [91,94]. Several risk factors for worsened COVID-19 illness are also positive risk factors for having lower endogenous glutathione concentrations, such as being a male (due to testosterone and estrogens effects on glutathione [95], 65 years of age or older, having a chronic disease, being a smoker, and having a diet low in fruits and vegetables [94,96]. Glutathione may also have anti-viral properties such as protecting host cells via its antioxidant capabilities, boosting immune cell function, and inhibiting viral replication [94]. Glutathione may also be beneficial in reducing or attenuating the cytokine storm [91,92,94].

### Nicotinamide Adenine Dinucleotide

Nicotinamide adenine dinucleotide (NAD+) acts as an immune regulator, with both anti-viral and anti-inflammatory properties [97]. The COVID-19 induced depletion of NAD+ may pose a large risk of increasing the symptom severity, and mortality of individuals with COVID-19 [97,98]. NAD+ elicits its anti-inflammatory effects by increasing sirtuins (SIRT-1, SIRT-2, and SIRT-3 activity), which decrease the activity of the previously mentioned pro-inflammatory NF-kB pathway [74,97,99,100]. Part of NAD+'s anti-viral properties are derived from its actions on SIRT- 1, which is not only a mediator for inflammation, but also defends deoxyribonucleic acid (DNA) and RNA against viral damage during infection [74,99,100]. Another aspect of NAD+'s anti-viral properties are derived from its interaction with poly-ADP-ribose polymerases (PARPs), specifically PARP-1. PARP-1 is of particular importance with respect to COVID-19, because PARP- 1 induces cellular death as a consequence of oxidative stress [99,101–103]. Concentrations of NAD+ tend to be lower in older individuals, those with diabetes mellitus, hypertension, and obesity, which are all comorbidities affecting COVID-19 mortality rates [98,100].

### Medical Nutrition Therapy Considerations for COVID-19

For nutritional care, there are a variety of nutritional interventions that may attenuate the severity of COVID-19 symptoms and alleviate the immune response seen in individuals who contract COVID-19. A potential challenge for the nutritional management of individuals with COVID-19 is the effects of anosmia and ageusia on appetite. Nutritional strategies that may attenuate COVID- 19 immune response include maintaining adequate energy intake, with sufficient consumption of carbohydrates [104], protein and dietary fats [105], maintaining a healthy microbiome [83, 104, 106- 108]. Vitamin D supplementation may be of interest to those treating an individual with COVID- 19 depending on current vitamin D status, for vitamin D's generalized viral immune function [109,110], even though high-quality data on vitamin D supplementation for COVID-19 is still lacking [111]. Energy needs for individuals hospitalized with COVID-19 will be largely based on body weight, and/or age [105]. General guidelines for energy intake range from 20 to 30 kcal/kg body weight/day to provide ample nutrition for recovery [112]. Because COVID-19 infection may result in hospitalized bed rest and lower levels of activity, adequate dietary intake is important to help offset potential acute sarcopenia [113,114]. A protein intake of 25 to 30 grams per meal, with a daily consumption of 1 to 2 g/kg body weight of protein, is the suggested intake to maintain muscle protein synthesis to offset sarcopenia [115–117]. The amino acid content of dietary proteins has immune system benefit [118], with new emerging data suggesting that lysine may play an anti-viral factor in COVID-19 outcomes [119]. Many individuals who contract COVD-19 present with preexisting conditions such as obesity, diabetes mellitus, and hypertension [121,122], which places these individuals at greater risk for developing more severe symptoms [121]. For these individuals, extra nutritional interventions may include the development of a nutrition prescription, implementation of enteral nutrition or feeding tube, and the use of supplementation therapy to correct nutrient deficiencies [117,123].

### Nutrition Following COVID-19 Infection

Nutritional recommendations following COVID-19 infection should be made on a patient-by-basis after the nutritional screening. Prolonged bed rest from hospitalization paired with COVID-19 immune stress may result in muscle wasting, requiring an increase in dietary protein and caloric intake [124]. Vitamin D3 supplementation may be beneficial, especially for those individuals who spend a significant amount of time indoors, for its effects on immune function [64,65,108,124].

Consideration for dyspnea, ageusia and anosmia must be taken into consideration, as individuals with prolonged ageusia and anosmia may find eating food more difficult than usual

## Discussion

In accordance with the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) the COVID-19 vaccine is the most effective way to help your immune system manage and reduce the severity of COVID-19. To the author's knowledge, this is one of the first reviews examining the combined effects of physical activity, nutrition, and supplementation to support the immune system's ability to function properly. Prior to COVID-19, those who were meeting the physical activity guidelines with a

fitness membership may be at risk of sedentary behaviour due to physical distancing requirements and gym closures [125]. The habits for outdoor or home exercise may not be well established in the previously mentioned population, indicating that improvements in dietary choices and proper supplementation may be warranted. Exercise and nutrition habits exist in a reciprocal relationship with COVID-19 symptom severity. Those with adequate zinc status may have lower-length hospital stays and decreased COVID-19 complication occurrence due to zincs action on the ACE-2 receptor. Adequate intake of omega-3

fatty acids also proves to be beneficial, as they show to affect viral replication and promote the production of pro-resolving lipid mediators. NAC supplementation may also be considered for attenuating COVID-19 symptom severity by interfering with viral replication, reducing inflammatory markers, as well as improving immune function by increasing endogenous glutathione concentrations. Maintenance of caloric intake is particularly important for those hospitalized with severe COVID-19 symptoms to attenuate the often-observed acute sarcopenia in hospitalized COVID-19 individuals.

## Conclusion

Regular resistance exercise and cardiovascular exercise are beneficial habits to have if an individual is interested in reducing potential COVID-19 symptom severity. Healthy skeletal muscle can attenuate the inflammatory response caused by COVID-19 by secreting glutamine and pro- inflammatory cytokines. Vastus lateralis and thoracic skeletal muscle mass may also be used as part of a predictive screening tool for practitioners when assessing a patient's risk for developing severe COVID-19 symptoms. Cardiovascular exercise and fitness also prove to be effective in attenuating COVID-19 symptom severity. A summation of previously mentioned research in this review can be made into several lifestyle recommendations to help attenuate COVID-19 symptoms. Appropriate caloric intake coming from a diet with appropriate diet dietary protein intake (1.0 to 2.2 g/kg body weight [115,117] may help offset potential acute sarcopenia, and attenuate COVID-19 symptoms. Diets with adequate intake of nutrients such as zinc, omega 3 fatty acids, and vitamin D can improve the severity of COVID- 19 related symptoms as they all play a role in promoting general immune health. Exercise habits that include both cardiovascular exercise, and resistance exercise at a moderate intensity for 150 minutes weekly can improve COVID-19 symptom severity. The maintenance of a healthy body weight through diet and exercise will also decrease the likelihood of developing severe COVID-19 symptoms.

Regarding long-COVID, similar recommendations can be made. A healthy diet with appropriate caloric intake and adequate vitamin D concentrations may help improve the symptoms of long- COVID [126] and even improve the time to recovery. Similarly, regular exercise can also improve a patient's symptoms with long-COVID. Individual considerations must be made when returning to exercise, and previous dietary habits. Anosmia and ageusia may make consuming food difficult, and even nauseating for some individuals. Continued fatigue and dyspnea may make exercise difficult, especially at higher intensities. The COVID-19 pandemic led to the temporary closure of many gyms, recreation centers, and other indoor exercise venues. These closures may have led to the decrease in habitual physical activity for those who frequently utilized indoor exercise venues. Strategies for individuals who cannot go to an indoor exercise venue to begin, or continue physical activity include home exercise programs. Home exercise programs can be based around any combination of resistance bands, easy-to-access dumbbells, and bodyweight exercise, as well as outdoor endurance exercise.

Continued research is required to determine further influences of various nutritional, dietary supplement and/or exercise interventions on COVID-19 prevention and outcomes, because current data are somewhat limited. Research into how the COVID-19 pandemic affected habitual nutrition and physical activity habits may also help the creation of further nutrition and physical activity guidelines, because lockdowns and general public awareness to the spread of infectious disease may have changed how some individuals engage in exercise

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