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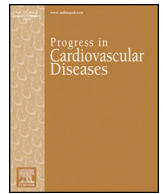
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Shelter from the cytokine storm: Healthy living is a vital preventative strategy in the COVID-19 era



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ABSTRACT

Coronavirus disease 2019 (COVID-19) continues to have a devastating effect on a global scale. COVID-19 variants continue to arise and counteract vaccination efficacy. As such, preventative health measures, such as social distancing and stay at home mandates, will continue for the foreseeable future. Evidence on those at greatest risk for poor outcomes if infected with COVID-19 has rapidly come to light. It has become clear that those with unhealthy lifestyle characteristics, chronic disease risk factors and/or a confirmed diagnosis of one or more chronic conditions are at greatest risk for hospitalization, intensive care unit admission, mechanical ventilation, and death if infected with COVID-19. The cytokine storm is a phenomenon that has been posited as a pathophysiologic response to COVID-19 infection that leads to poor outcomes. The current graphical review illustrates the association between unhealthy lifestyle characteristics and increased vulnerability to the cytokine storm as well as the physiologic mechanisms healthy living behaviors elicit and decrease risk for the cytokine storm. Through this graphical review, we will demonstrate unhealthy lifestyle characteristics, chronic disease risk factors and diagnoses, and COVID-19 outcomes are intricately linked, creating a new global syndemic. It is also clear that a primary way to uncouple this syndemic is through increasing healthy living behaviors, as illustrated in this graphical review. Moving forward, healthy living medicine should be practiced with renewed vigor to improve human resiliency to health threats posed by both chronic disease and viral infections.

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Abbreviations: ARSD, Acute respiratory distress syndrome; BMI, Body mass index; COVID-19, Coronavirus disease 2019; CRF, Cardiorespiratory fitness; IL, Interleukin; NLRP3, nod-like receptor family, pyrin domain-containing 3; PA, Physical activity; ROS, Reactive oxygen species; SNS, Sympathetic nervous system; TNF, Tumor necrosis factor; WAT, White adipose tissue.

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Introduction

Coronavirus disease 2019 (COVID-19) continues to have a devastating effect on a global scale. COVID-19 variants continue to arise and counteract vaccination efficacy. As such, preventative health measures, such as social distancing and stay at home mandates, will continue for the foreseeable future. Evidence on those at greatest risk for poor outcomes if infected with COVID-19 has rapidly come to light. Specifically, it has become clear that those with unhealthy lifestyle characteristics, chronic disease risk factors and/or a confirmed diagnosis of one or more chronic conditions are at greatest risk for hospitalization, intensive care unit admission, mechanical ventilation, and death when diagnosed with COVID-19.¹ The cytokine storm is a phenomenon that has been posited as a pathophysiologic response to COVID-19 infection that leads to poor outcomes.² The current graphical review illustrates the association between unhealthy lifestyle characteristics and increased vulnerability to the cytokine storm as well as the physiologic mechanisms healthy living behaviors elicit and decrease risk for the cytokine storm.

The unhealthy phenotype: focus on excess body mass and adiposity

Unhealthy lifestyle characteristics (i.e., sedentary lifestyle and poor nutrition) often lead to excess body mass and adiposity, commonly defined as a body mass index (BMI) at the overweight (i.e., 25.0–29.9 kg/m²) or obese (i.e., ≥30.0 kg/m²) level. Previous research has demonstrated that obesity is a clear risk factor for poor outcomes in those with COVID-19.³ The relationship between excess body mass and the immune system is complex and involves several different mechanisms. Under normal conditions, white adipose tissue (WAT) plays a key role in the hemostatic regulation of several biological systems including the immune system.⁴ This is mediated by the release of various cytokines (adipokines) with each possessing different effects both locally and systemically.⁴

In states of hyperplasia and hypertrophy of the adipocytes following a chronic positive energy balance characteristic of obesity, this process is altered, resulting in an elevated production of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-18 and TNF-alpha and a reduction in anti-inflammatory cytokines, such as adiponectin.⁵ The production and secretion of pro-inflammatory adipokines is influenced by several different mechanisms including extracellular mediators/cross talk, and intracellular adaptations, such as adipose hypertrophy and inflammation.⁵

Pathological changes to the sympathetic nervous systems (SNS) have been proposed as a driver of this dysregulation of adipose tissue and the low-grade chronic inflammatory state in obesity. It has been widely accepted that the SNS is overactive in patients with obesity, and that overactivity of the SNS may contribute to elevated markers of systemic inflammation.⁶ However, while SNS overactivity is positively associated with the magnitude of weight gain, it has been shown to occur early in response to a high-saturated fatty acids diet, even before significant weight gain occurs.⁵ Adipose tissue in individuals with obesity demonstrate impaired SNS stimulated lipolysis leading to hypertrophy and hyperplasia which may be due to desensitized adrenoreceptors in the adipose tissue and possibly denervation.⁵ Fig. 1 illustrates the link between unhealthy lifestyle characteristics, excess body mass and abnormalities in systemic inflammation. In such individuals, the stage is set for increased COVID-19 severity in the event of infection.

The cytokine storm and COVID-19

The term 'cytokine storm' refers to a broad systemic inflammatory response, involving elevated circulating cytokine profiles that occur following systemic infection. Hyperactivation and/or dysregulation of immune cell activation can occur and cause clinically significant and irreversible multi-organ damage, failure and even death.⁷ For such reason, the cytokine storm is currently being targeted by several therapeutic strategies in patients with COVID-19.

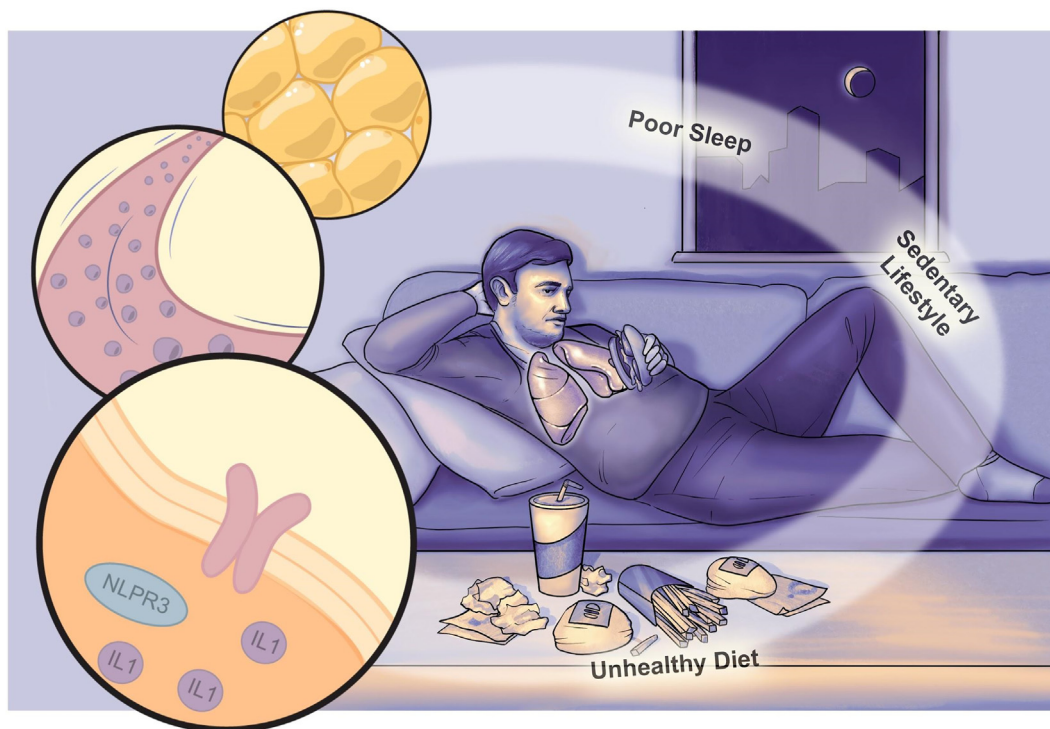


Fig. 1. The unhealthy phenotype – priming the pump for increased severity with COVID-19 infection.

Legend: The following image features an overweight (not necessarily obese) figure, shown in sedentary position eating/nearby unhealthy foods late at night to indicate poor sleep habits. A zoomed-in callout of adipose tissue is shown releasing pro-inflammatory cytokines with a single white blood cell. From there, you can see an extremely schematic view of a TLR and a relationship between NLRP3 and IL-1.

Whilst their role is complex, cytokines are a group of proteins that provide intercellular signaling and communication, which controls cell proliferation and differentiation alongside the regulation of angiogenesis as well as immune and inflammatory responses.⁸ Upon detection of a pathogen, the immune system responds with a regulated and proportional production of cytokines to remove the pathogen and restore homeostasis. An 'adequate' response requires sufficient cytokine production to eliminate the pathogen whilst avoiding a hyperinflammatory response, which occurs when cytokine production is disproportionate. Whereas the exact mechanism of a hyperactive immune response creates a conundrum for clinical staff to resolve, failures in the body's own feedback and regulatory processes which seek to prevent hyperactive immune responses are responsible for excessive cytokine production and any resultant systemic damage that often outstrips the intended benefit from a 'typical' immune response.⁷

Cytokine and/or immune system hyperactivity has been observed in previous pandemic situations, and the importance within the COVID-19 pandemic has been discussed profoundly due to broad presentation of symptoms and increased progression to acute respiratory distress syndrome (ARDS).⁹ The immunopathology of COVID-19 infection involves the innate and adaptive components of the immune system.¹⁰ Following infection, neutrophil count becomes increased and natural killer cells are reduced leading to the release of leukopenia based upon a reduced concentration of monocytes, eosinophils, and basophils.¹¹ Accordingly, reductions in lymphocytes (TCD4+ and TCD8+) coincides with upregulation of B lymphocytes and higher levels of Immunoglobulin G within plasma which typically occurs 7–10 days following infection. Pro-inflammatory cytokines such as tumor-necrosis factor (TNF)- α , interleukin (IL)-6, IL-1 β , IL-8, IL-17, IL-18 and IL-2) are also elevated abnormally.¹² Elevations here lead to crosstalk activation of the neuroendocrine-immune system, with a consequent release of glucocorticoids which impairs the immune response, leading to serious

adverse and potentially life-changing/threatening complications (e.g., multiple organ failure).¹³ These concepts are illustrated in Fig. 2.

The clinical presentation of a cytokine storm has been articulately summarized by Fajgenbaum and June⁷; within the lungs, the cytokine storm can be increasingly problematic. A cytokine-induced infiltration of neutrophils and macrophages can provoke the onset of pulmonary edema and the formation of hyaline membranes that fracture the alveolar wall leading to acute-phase physiological responses (e.g., tachypnea, dyspnea, and hypoxemia) which in-turn impacts tissue oxygenation and more broadly the ability to complete activities of daily life.¹² In the most severe cases, this can progress rapidly, requiring mechanical ventilation and can lead to the development of irreversible damage to lung architecture, requiring long term support and rehabilitation.

Of note, lifestyle components can significantly contribute to either the activation (Fig. 1) or the inhibition of the above-described pathways. The role of diet in the setting of COVID-19 infection has not been largely investigated and more research is encouraged in this field¹⁴; however, dietary saturated fatty acids and sugars can typically promote a pro-inflammatory cascade by activating the macromolecular complex NLRP3 inflammasome, whose formation was also recently discovered in lungs of patients with COVID-19,¹⁵ and responsible for the production of the pro-inflammatory cytokines IL-1 β and IL-18 (Fig. 1),¹⁶ while other dietary factors, such as unsaturated fatty acids can exert opposite anti-inflammatory effects.¹⁷ Similarly, reduced physical activity (PA) and increased sedentary behaviors have been associated with greater systemic inflammation, potentially contributing to worsening of the pro-inflammatory state in patients with COVID-19. This is also supported by the fact that promoting healthy lifestyle behaviors, such as increasing PA and reducing sedentary behaviors can improve cardiorespiratory fitness (CRF) and reduce the proinflammatory state characteristic of chronic non-communicable diseases.¹⁸

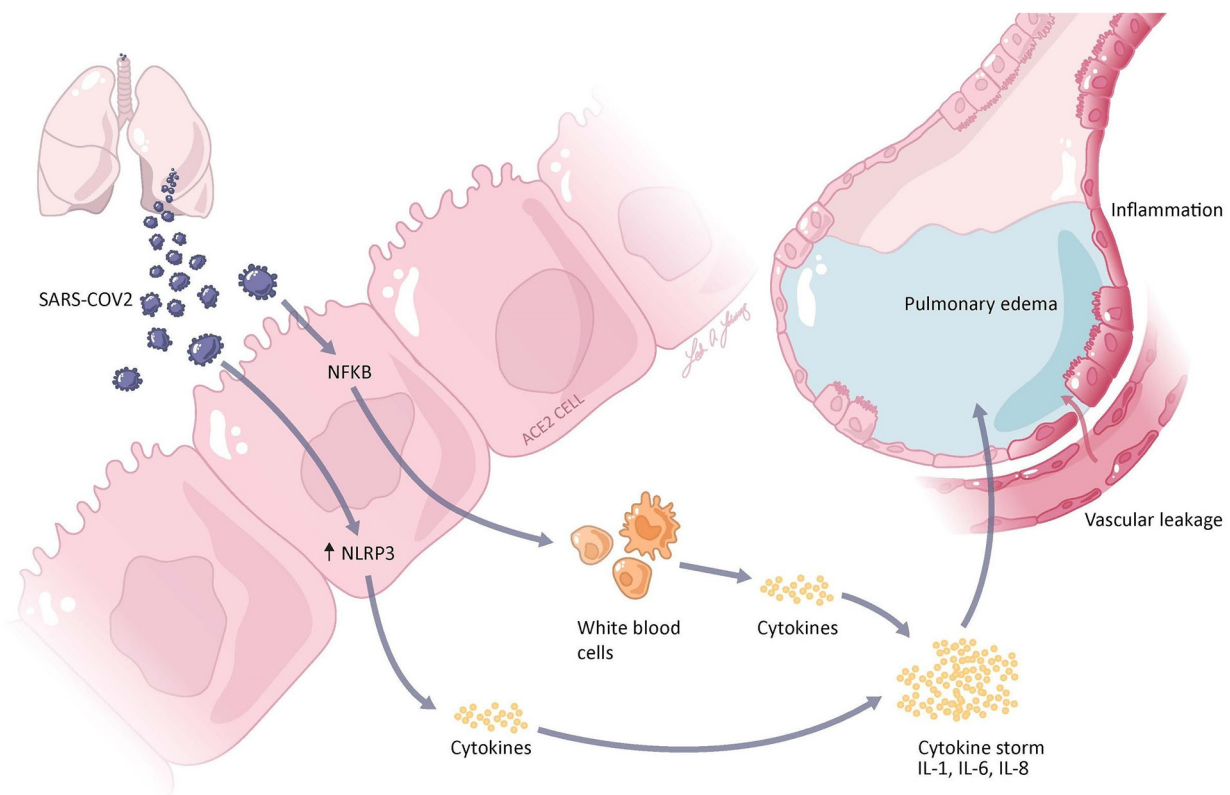


Fig. 2. The cytokine storm and COVID-19.

Legend: The Cytokine Storm and Compounding Impact of COVID-19.

No human figure will be shown, as this story will focus on the cellular level. A large amount of pro-inflammatory cytokines will be shown, building onto similar imagery from graphic 1 and leading to the cytokine storm. Inflammation response leads to compounding effects from COVID-19 in the lungs.

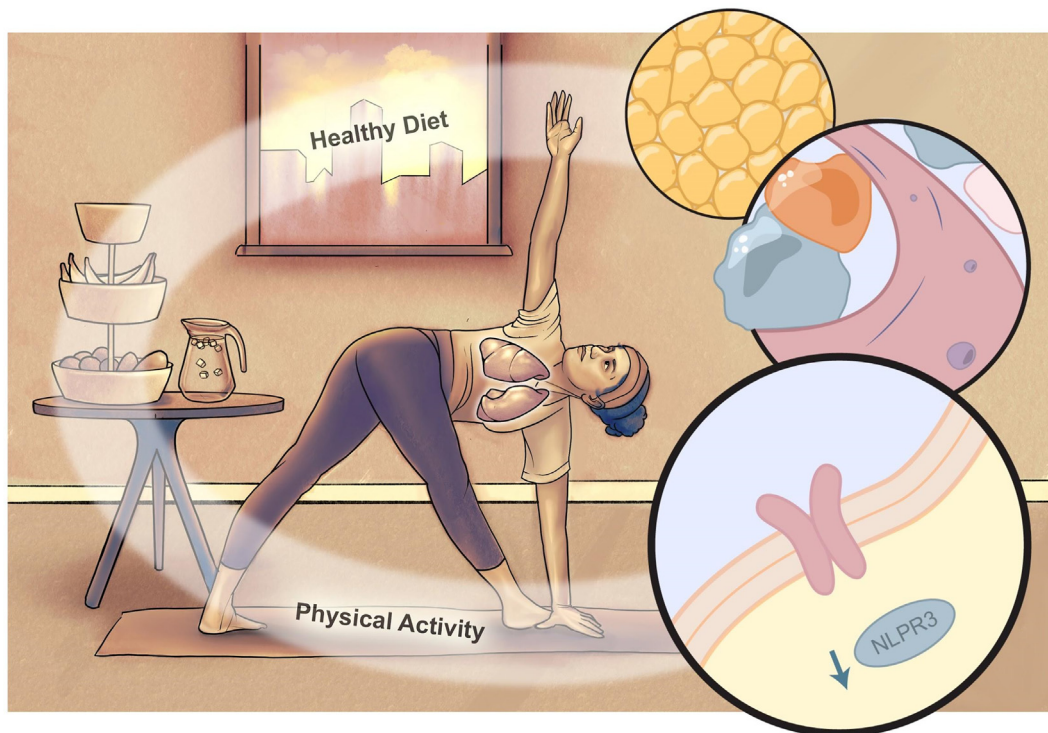


Fig. 3. The healthy phenotype – protection for the cytokine storm.

Legend: This figure is meant to juxtapose the first figure to emphasize the most important parts of the story. A healthy-weight figure is shown doing yoga during the day, with nearby healthy foods and water. Similarly, to Image 1, a zoom-in shows a lower amount of adipose tissue to prevent those pro-inflammatory cytokines from being released. We also see a larger amount of white blood cells and a lack of response at the TLR (as opposed to what is shown in Fig. 1).

The healthy phenotype – protection for the cytokine storm

Regular PA and consumption of a diet rich in fruits, vegetables, foods rich in unsaturated fatty acids, fibers, and low-fat dairy products and low saturated fatty acids and sugars are essential to ensuring long-term maintenance of a high CRF and healthy body composition.¹ Although appropriately powered randomized controlled trials investigating the effects of nutrition on COVID-19 disease severity are lacking, this phenotype is associated with enhanced immune function compared to sedentary and individuals with excess body mass, which may play an important role in reducing the severity of COVID-19 infection. Recent observational studies have indicated that individuals with a high CRF,¹⁹ higher levels of self-reported PA,³ and a normal body mass index²⁰ experienced fewer COVID-19 related hospitalizations and less severe symptomatology. While the underlying mechanisms explaining the protective effects of maintaining a healthy lifestyle and normal body composition have not been elucidated, lower chronic low-grade inflammation, higher anti-inflammatory cytokines such as interleukin (IL)-10 and IL-1 receptor antagonists partly contribute.³ Additionally, exercise induces the activation of AMP-activated protein kinase in the lungs and contributes to the reduction of inflammatory markers through the transformation of angiotensin II to angiotensin 1–7. This is particularly important given that COVID-19 binds to the angiotensin converting enzyme 2 receptor and activates the inflammasome response. It has been proposed that the degree of nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome activation modulates symptoms, such that a robust NLRP3 activation is associated with increasing severity.²¹ NLRP3 is also closely linked with cardiovascular dysfunction which has been a prominent consequence associated with COVID-19 infection. Elevated NLRP3 signaling has been noted in the presence of a high-saturated fatty acid diet but can be attenuated with PA and healthy dietary patterns along with caspase-1 activation and

IL-1 β as well as decreasing adiponectin and adiponectin receptor 1 in aortic endothelial cells of mice.²²

Another significant source of oxidative stress and inflammation results from impaired mitochondrial function due to physical inactivity and obesity. Exercise can improve mitochondrial function as it induces acute elevations of reactive oxygen species (ROS) that signal and promote adaptive mechanisms such as upregulation of super oxygen dismutase, catalase, glutathione peroxidase and increased mitochondrial biogenesis.²³ Regularly engaging in PA effectively enhances antioxidant defense systems and mitochondrial function, thereby lowering ROS levels and improving innate immunity. This is partly accomplished by enhanced activation of mitochondrial antiviral-signaling proteins which trigger the expression of factor kappa light chain enhancer of activated B cell and type I interferons, thus strengthening defenses against viruses.²⁴ These adaptations are therefore critical in the cell's ability to respond to viral stressors like COVID-19. Collectively, preliminary evidence linking the protective immunological effects of regular PA and a normal body composition against severe COVID-19 symptoms are consistent with observations in other viral infections, as illustrated in Fig. 3.

Conclusions

Prior to the global health crisis precipitated by COVID-19, the world was already entrenched in a chronic disease pandemic, which, in large part was brought about by the concurrent unhealthy lifestyle pandemic.¹ We are now aware unhealthy lifestyle characteristics, chronic disease risk factors and diagnoses, and COVID-19 outcomes are intricately linked, creating a new global syndemic.²⁵ It is also clear that a primary way to uncouple this syndemic is through increasing healthy living behaviors, as illustrated in this graphical review. Moving forward, healthy living medicine should be practiced with renewed

vigor to improve human resiliency to health threats posed by both chronic disease and viral infections.

Declaration of Competing Interest

None.

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