

Fatigue in the COVID-19 pandemic



Beyond diseases and syndromes, there are some other conditions, such as fatigue, which are frequently reported by older people and represent unmet clinical needs. In particular, fatigue is one of the most reported symptoms both during and after COVID-19 infection. Fatigue cannot be completely explained by a single disease or unique pathogenetic mechanism. The most promising mechanisms underlying the condition include inflammation, mitochondrial dysfunction, sleep alterations, autonomic nervous system abnormalities, and poor nutritional status.¹ All these mechanisms are also a common thread of COVID-19 infection (table) and many recovered patients, the so-called long haulers, face long-term physical, cognitive, and psychological symptoms, including fatigue, which represents one of the most persistent and debilitating post-COVID-19 symptoms.² Some convalescent patients might face long-lasting respiratory complications, mainly due to the COVID-19 fibrotic lung damage resulting in increased morbidity, long-term disability, and even death. Fatigue might be due to the excessive respiratory effort related to respiratory complications (ie, dyspnoea, pneumonia, and acute respiratory distress syndrome). However, the lack of a gold standard for assessment of fatigue, as well as the subjective nature of the symptom, make it a condition that is poorly considered. Fatigue is observed in many medical conditions, including cancer, neurodegenerative disorders, rheumatological disease, and heart failure, but can also be an isolated symptom with unknown underlying causes, as in the case of chronic fatigue syndrome.¹ In older people, but also in the context of COVID-19 infection, it is often difficult to differentiate fatigue from mood disorders, depression, and sleepiness, which frequently occur simultaneously.^{2,3} COVID-19 is characterised by increased production of pro-inflammatory cytokines, which can result in the so-called cytokine storm, determining the most severe forms of the disease.⁴ Myalgias, muscle loss, and weakness are frequently observed in patients with COVID-19 and might persist for several months after infection, which can be partly explained by direct virus entry into muscle cells via the angiotensin-converting enzyme 2 receptor, determining local inflammation.⁵ This augmented inflammatory response might lead to mitochondrial dysfunction, further exacerbating muscle

loss. Chronic low-grade inflammation and mitochondrial dysfunction are observed in some chronic conditions that are characterised by the presence of fatigue⁶ and have been evoked as hallmarks of ageing, playing a major role in the aetiopathogenesis of sarcopenia.⁷ Since mitochondria are the hub of energy production, energy shortage related to mitochondrial dysfunction (but also resulting from inflammatory processes) might result in decreased stamina and increased fatigue.⁶

COVID-19 infection might also be characterised by loss of taste and smell, leading to anorexia, which is an important contributor to malnutrition (ie, undernutrition). Additionally, the high catabolic response to COVID-19 infection, leading to weight loss and muscle decline, might further contribute to the manifestation of fatigue. Loss of muscle mass and strength is a whole-body process that also affects respiratory muscles.⁸ Hence, respiratory function might be further compromised by the acute muscle wasting seen during COVID-19 infection or in individuals with a sarcopenic or dysphagic background. Furthermore, reduced force of contraction of respiratory muscles can lead to so-called respiratory fatigue⁹ and might result in a reduced ability for expulsive airway clearance tasks, such as coughing and sneezing, contributing to an increased risk of pneumonia and other respiratory

	Fatigue in older people	Post-COVID-19 fatigue
Inflammation	Low-grade systemic inflammation (ie, inflammaging)	Abnormal release of pro-inflammatory cytokines (ie, cytokine storm)
Mitochondrial dysfunction	Hallmark of ageing; defective immune response to viral infections (ie, immunosenescence)	Increased inflammatory or oxidative state
Autonomic nervous system abnormalities	Modifications of cardiac function	Cardiovascular damage
Poor nutritional status	Anorexia of ageing; undernutrition	Anorexia (ie, loss of taste and smell, loss of appetite); weight loss and cachexia; high catabolic conditions
Obesity and physical inactivity	Inflammation; metabolic and endocrine alterations; reduced mobility	Inflammation; immobilisation; lifestyle changes (ie, sedentary behaviour)
Sarcopenia	Sarcopenia of ageing; sarcopenia of respiratory muscles	Muscle wasting; sarcopenia of respiratory muscle
Sleep alterations	Daytime sleepiness; poor nocturnal sleep quality; sleep apnoea; depression; mood disorders	Social isolation; psychological distress; anxiety; obstructive sleep apnoea; daytime sleepiness
Respiratory complications	Chronic obstructive pulmonary disease	Dyspnoea; acute respiratory distress syndrome; lung fibrotic damage

Table: Potential determinants of fatigue in older people and in the context of COVID-19 pandemic

infections, and thus creating a vicious circle. Obesity, which has been evoked as one of the key risk factors associated with poor COVID-19 outcomes,¹⁰ has been repeatedly associated with fatigue; the release of pro-inflammatory cytokines and adipokines by adipose tissue has been described as the mechanism that mediates this finding.³ Inflammatory mediators can pass the blood–brain barrier and can be transmitted as stress signals, leading to autonomic nervous system abnormalities, including fatigue. Recently, SARS-CoV-2 variants characterised by and increased transmission capacity have emerged, with a consequent net decrease in the mean age of infected people who can also experience fatigue despite their young age.

Fatigue can thus be envisioned as a disorder of energy balance and availability, a sort of alert that mimics the exhaustion of the metabolic reserves of an individual (ie, frailty). In fact, some frailty instruments include, more or less explicitly, the concept of fatigue. The long-term negative effects of the pandemic might negatively affect the accumulation of the biological reserves of an individual. In other words, in the near future, we could see a high prevalence of frailty in people who survive the pandemic.

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