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# A REVIEW ON EPIDEMIOLOGICAL AND PATHOPHYSOLOGICAL DETERMINANTS OF LONG COVID

**Soheli Chowdhury[(1)]*, Majeedul H. Chowdhury[(2)]***

[1]Department of Natural Sciences, Hostos Community College, The City University of New York (CUNY), NY 10451, USA –tel +1 347 3371253. ORCID iD: 0009-0003-9719-5755
[2]Department of Biology, Touro University, Flatbush Campus, NY 11230, USA –tel +1 347 3371279. ORCID iD 0009-0002-8915-8420
*schowdhury@hostos.cuny.edu
*majeedul.chowdhury@touro.edu

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## ABSTRACT

Long COVID is a condition that emerges following SARS-CoV-2 infection and persists for at least three months, with recurrent symptoms of varying intensity. Approximately 10% of COVID-19 patients do not experience full recovery from the initial infection. Women and individuals who experienced severe COVID-19 are at a higher risk of developing Long-COVID, as are certain ethnic groups and adults aged 50–59, who show higher prevalence rates. Initially, the virus replicates primarily in the upper respiratory tract, where there is high expression of angiotensin-converting enzyme-2. As infection progresses, it can spread to other organs. Many Long COVID symptoms appear to result from an overactive immune response rather than direct viral effects on tissues. Some studies suggest that dormant viruses may become reactivated, potentially contributing to increased autoantibody levels and worsening disease severity. Proposed mechanisms in Long COVID pathophysiology include dysfunctional mitochondrial metabolism, prion involvement, amyloid formation, and genetic factors. This review synthesizes current knowledge on the characteristics of long COVID, drawing on an analysis of available online literature.

**Keywords:** Long COVID, SARS-CoV-2, ACE-2, Antibody, Autoimmunity

## Introduction

Long COVID, also known as "post-COVID conditions" (CDC, 2024), is a chronic condition that develops following infection with the SARS-CoV-2 virus, which causes COVID-19. This condition is characterized by a prolonged period of recurring symptoms and a worsening of the illness, affecting multiple organ systems in the body. Defining a loosely understood medical condition like Long COVID has been an uphill task. Still, as research progresses, patient groups, clinicians, and researchers, in collaboration with government agencies, have come up with diverse definitions to fit the term.

Most people who exhibit the SARS-CoV-2 virus proceed to make a full recovery. Still, millions of people have experienced a progressive state of disease that persists for months, and organ damage that occurs months after the acute face of the COVID-19 virus infection. Long COVID has gross social, economic, and medical impacts worldwide. The prevalence of the condition dramatically varies, and the CDC estimates that 10-35 % of the people infected with COVID-19 experience Long COVID [1]. According to the U.S. Census Bureau and the National Center for Health Statistics, the Household Pulse Survey indicated that by March 5 to April 1, 2024, 17.6% of U.S. adults had experienced Long COVID at one time, and 6.9% of the adults in the U.S. currently suffer from the Long COVID [2].

According to the World Health Organization (WHO), Center for Disease Control and Prevention (CDC), and National Institute for Health and Care Excellence (NICE), the term post-Covid/long COVID can be defined as a post-acute phase that lasts the first 2-3 weeks after COVID-19 infection and is characterized mainly by respiratory symptoms; other symptoms and signs may persist or appear after 1 month. Although most patients resolve them within 12 weeks, a small proportion continues to be symptomatic for an extended period and can be termed post-COVID/ Long COVID [3].

Long COVID exhibits a myriad of possible symptoms and conditions that are likely to affect any organ system. The most common symptoms are respiratory and extreme myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Patients with Long COVID may also experience shortness of breath, memory lapses, lightheadedness, sleep disorders, and loss of taste and smell. Others may experience singular or several diagnosable illnesses like hypoxemia and interstitial lung disease, arrhythmias, migraine, chronic kidney disease, dysautonomia, connective tissue disease, vascular- and clotting abnormalities, among others.

Long COVID can occur after infections with any degree of severity or asymptomatic infections and do not require laboratory confirmation. To date, there are no SARS-CoV-2 infection tests with significant sensitivity, and due to false negatives from PCR and antigen tests, most patients with Long COVID receive negative results. Antibody tests can show the presence of past COVID-19 virus infection, but the levels of antibodies usually fluctuate and disperse with time. Administration of the COVID-19 vaccine complicates antibody tests and causes positive results.

In this review paper, Long COVID will be analyzed based on recent studies across the scientific and theoretical spectrum. Some of the areas of Long COVID to be looked at encapsulate but not limited to the following areas: prevalence and epidemiology; organ, tissue, and organelles damage; overactive immune system and autoantibody; prion involvement; amyloidogenesis; genetic mechanism; and Long COVID disease hypotheses.

*PREVALENCE OF LONG COVID*

According to the U.S. death certificate data in the National Vital Statistics System (NVSS),-Long COVID was an underlying cause of 3,544 deaths between January 2020 and June 2022[11]. The percentage of COVID-19 deaths with Long COVID peaked in June 2021 (1.2%) and in April 2022 (3.8%)[11].

Long COVID is a critical global threat medically, socially, and economically. Its prevalence is inaccurate, and the variation in the estimates is due to a lack of

clear and precise diagnostic biomarkers or a unique diagnostic method that distinguishes the Long COVID from the other conditions[4]. In many studies, prevalence is measured based on how the condition is defined based on the presence and severity of the signs and symptoms, record of previous SARS-CoV-2 infections, laboratory and imaging results, background occurrences of its known symptoms, and timing inclusive of several other factors[5].

Over 800 million people in the world have been infected by the SARS-COV-2 virus, and an estimated 10-20% of this number is at risk of suffering from Long COVID. The risk of sequelae is estimated at two years for hospitalized and no-hospitalized individuals, which is an all-time high[3]. By 2023, a prevalence of 10 % places the estimated 65 million people globally who have already shown signs and symptoms of Long COVID[6]. European Observatory on Health and Policies reports that, between 2020 and 2021, 25% of patients with COVID-19 have had prolonged symptoms, including breathing problems, fatigue, and impaired cognitive functions, and 10% of them still experience these symptoms after three months[7]. According to the U.S. Census Bureau, 6.9% of U.S. citizens are affected by Long COVID. Globally, 144.7 million individuals experienced at least three symptom clusters of Long COVID, including cognitive malfunction, fatigue, and persistent respiratory syndrome, three months post-SARS-CoV-2 virus infection in 2020 and 2021[8] .

Long COVID is more common in women than in men [1, 8] . Data shows that women are affected by long-term COVID at about twice the rate of men, whether considering three months or twelve months after the onset of COVID-19, as well as the need for general hospital ward or ICU care [8]. Even the three typical symptoms, such as fatigue, respiratory, and cognitive, individually or as a combination of 2-3 symptoms, are also higher in women[9]

An intriguing observation is that older adults are less likely to have Long COVID than younger adults. Nearly three times as many adults ages 50-59 currently have Long COVID than those ages 80 and older [9].

A higher prevalence of Long COVID has been reported in people of Hispanic and Latino ethnic backgrounds. Nearly 9% of Hispanic adults currently have Long COVID, higher than non-Hispanic White (7.5%) and Black (6.8%) adults and over twice the percentage of non-Hispanic Asian adults (3.7%)[9]. Socioeconomic risk factors entail low incomes and the inability to rest in the early weeks of developing COVID-19[10]. Recent publications report of Long COVID prevalence varied among states of the USA, with a range of 4-5% in Hawaii, Maryland, and Virginia to 10 -11 % in Kentucky, Alabama, Tennessee, and South Dakota [9].

The idea that chronic stress contributes to health inequalities by socioeconomic status (SES) through physiological wear and tear, or allostatic load (AL), has garnered attention. Although current empirical evidence linking SES to cortisol, the primary stress hormone, and AL is weak, future research should standardize methods for measuring SES, chronic stress, and cortisol to better understand this relationship[77]. Further epidemiological studies are needed to determine if the higher prevalence of Long COVID in adults aged 50-59, women, and people of Hispanic and Latino ethnicity is due to the impact of SES and stress on AL. If this is the case, strategies could be developed first to manage SES and stress, and subsequently mitigate the impact of Long COVID on these groups.

*EPIDEMIOLOGY OF LONG COVID*

Based on the WHO reports in Europe alone, over 17 million individuals directly experienced the effects of Long COVID in the first twenty-four months of the COVID-19 global menace. Referencing the CDC data from the Household Pulse Survey, one out of 13 adults has Long COVID symptoms three months after acute SARS-CoV-2 infection. According to O'Mahoney et al.[5], 45% of patients with COVID-19 had one or more symptoms of long COVID at four months during follow-up visits, regardless of their hospitalization status. In another case-control study conducted from January through to April 2021in the U.K., the prevalence of relentless signs and

symptoms of long COVID related to COVID-19 was placed at an estimated 5%[12]. In a Chinese cohort study, two years after acute COVID-19, 19.8% of hospitalized patients with mild infections still experience symptoms associated with long COVID[13]. In a Swedish-based Cohort study, 30% of patients who survived severe COVID-19 infection were still symptomatic at four months after hospitalization, and 80% of the patients diagnosed with long COVID had symptoms at four months and reported the condition still affecting them twenty-four months later [14].

Other epidemiology factors such as association among variants, vaccination status, and long COVID conditions were studied. Prevalence of long COVID at 6-months shows a similar relation for the Delta, Wildtype, and the Omicron variants for unvaccinated population[15]. Significant evidence shows a reduction in probability among the vaccinated people infected by the Omicron variant compared to the unvaccinated population who suffered from the Wildtype variant. The same study discovered a non-relation between the prevalence of long COVID and the number of doses of the vaccine. Another study supported reduced odds of long COVID incidence with the Omicron variant compared to the delta type depending on an individual's age and time elapsed since the last vaccination[16]. A significant research reported that the unvaccinated population infected by the Wildtype variant had a considerable number of long COVID symptoms compared to those unvaccinated patients infected by the delta or alpha variants after six months of severe SARS-CoV-2 infection[17].

## Long Covid Modus Operandi

*ORGAN AND TISSUE DAMAGE IN LONG COVID*

Many long COVID patients experience symptoms across multiple organs. Long COVID encapsulates a variety of outcomes with evolving onset conditions that entail cardiovascular, thrombotic, and cerebrovascular conditions, chronic fatigue syndrome, type 2 diabetes mellitus, and dysautonomia[6]. One prospective study of low-risk individuals, looking at the heart, lungs, liver, kidneys, pancreas, and spleen, noted that 70% of 201 patients had damage to at least one organ, and 29% had multi-organ damage[6]. Most damage observed in various tissues has been attributed to the immune-mediated response and inflammation rather than direct infection of cells by the virus.

Disruption of the heart and circulatory system can lead to endothelial dysfunction and subsequent downstream effects, as well as an increased risk of deep vein thrombosis[18,19], pulmonary embolism, and bleeding events. Microclots and hyperactivated platelets have been detected in both acute COVID-19 and Long COVID, contributing to thrombosis[20].

Months after the acute phase infection, many Long COVID positive patients show abnormal electroencephalographic (EEG) activity reflecting "brain fog" and mild cognitive impairments. Compelling evidence has been put forward that cognitive deficits due to COVID-19 and Alzheimer's disease and related dementia (ADRD) are driven by overlapping pathologies and neurophysiological abnormalities. It is proposed that similar EEG abnormalities in Long COVID and ADRD are due to parallel neuroinflammation, astrocyte reactivity, hypoxia, and neurovascular injury[79].

The predominant site of virus replication in the early stage of infection is the upper respiratory tract, characterized by a high level of angiotensin-converting enzyme-2 (ACE-2) expression. That might justify the initial symptoms of respiratory distress in patients[21]. However, the highest levels ACE-2 expression were found in the intestine, colon, kidney, and heart muscle, further complicating the understanding of the organ system.

Frere et al. [22] conducted a study using a hamster model to investigate the long-term effects of SARS-CoV-2 infection on various tissues. They found that the hamster lungs were initially the most affected organ, with limited involvement in other organs. However, 31 days after infection, they observed powerful peribronchiolar metaplasia and tubular atrophy in the kidneys. The virus also caused persistent inflammation

in the olfactory bulb and epithelium. Interestingly, similar changes were found in human autopsy samples from COVID-19 survivors. The authors[22] suggest that hamsters could be valuable for further research on the mechanisms and treatments of Long COVID.

*ORGANELLES DAMAGE IN LONG COVID.*

Two cell organelles, mitochondria and lysosomes, play a direct role in the pathology of the SARS-CoV-2 virus, which progresses to Long COVID. COVID-19 can impair the function of mitochondria in vital organs, such as the heart, brain, kidneys, liver, and lungs, with lasting effects on the entire organism even after the virus is eliminated[23]. The invading process is targeted by many single-stranded RNA viruses in other diseases as well, which are known for altering the physiological pathways in favor of viral reproduction[24,25]. Hijacking ATP production enables viruses to take over a viable source of energy from the host to sustain their own needs for replication[21]. The infected mitochondria in COVID victims are markedly thin[26] with abnormally swollen cristae[27]. Mitochondria lose their membrane potential during this state, and dysfunctional mitochondrial metabolism might result. Additionally, altered fatty acid metabolism and dysfunctional mitochondrion-dependent lipid metabolism have been observed[28,29]. Many patients with Long COVID complaints about their crushing fatigue even after a light physical activity. This symptom of exhaustion, or post-exertional malaise (PEM), is a hallmark of Long COVID. The fatigue status, as noted in many Long COVID studies, could be attributed to low ATP production from mitochondrial dysfunction, leading to low levels of ATP[30]. To better understand the resting skeletal muscle metabolism during PEM, metabolites in skeletal muscle and in venous blood were studied. It was found the key metabolites of the tricarboxylic acid cycle were lower in skeletal muscle and blood in Long COVID patients, but did not change during post-exertional malaise. The ratio of citric acid to lactate in skeletal muscle was lower in Long COVID patients, indicative of a shift away from oxidative metabolism in patients. Skeletal muscle creatine concentrations were lower in patients with Long COVID, likely contributing to the lower oxidative phosphorylation capacity in patients[30]. Potential therapeutic strategies targeting mitochondrial function, including pharmacological interventions, lifestyle modifications, exercise, and dietary approaches have been discussed, and emphasis has been given on the need for further research and collaborative efforts to advance our understanding and management of Long COVID[81].

Another cell organelle, the lysosome, is involved in the pathology of COVID-19 and continues in Long COVID[31]. Through its catabolic process, lysosomes in health destroy damaged cell organelles, proteins, and invading microbes, including viruses, by creating autophagosomes, which merge with lysosomes to clear debris from the cell, called autophagy[31,32]. However, autophagy can promote the replication of RNA viruses by inhibiting the body's natural antivirus immune responses[32] or by promoting infectivity by releasing vesicles containing the virus[33,34]. Studies have identified a protein in SARS-CoV-2, called ORF3a (open reading frame 3a), that disrupts the fusion of autophagosomes with lysosomes[31-33]. This disruption leads to incomplete autophagy, allowing intact viruses to remain inside the lysosome. Eventually, the virus travels through the Golgi apparatus and trans-Golgi network, where viral envelope proteins receive additional post-translational modifications before exiting the cell in significant numbers through lysosomal exocytosis[35]. It's worth noting that other viruses in the coronavirus family, such as SARS-CoV and MERS-CoV, similarly prevent the fusion of autophagosomes with lysosomes[31,36].

Only a few studies have been conducted on cell's nucleus to find the DNA damage in SARS-CoV-2 viral infection, which persists in Long COVID. Surprisingly, SARS-CoV-2, a single-strand RNA virus, can damage host DNA by creating reactive oxygen species. This can result in single or double-stranded breaks, intra or intercross links, and base modification[37]. A similar finding was reported in 50 COVID patients compared to matched healthy patients. The Alkaline Single-Cell Gel Electrophoresis Technique (Comet Assay)

was conducted to assess the level of DNA damage in lymphocytes, indicating that damage is consistently higher in COVID patients and doubles in patients with severe symptoms[38].

*POTENTIAL PRION INVOLVEMENT IN LONG COVID*

Prions are protein infectious particles that cause fatal brain diseases, like Parkinson's disease and Alzheimer's disease. Prion disorders exhibit incubation periods, neuronal loss, and induce abnormal folding of specific normal cellular proteins. These agents may also induce memory, personality, and movement abnormalities, as well as depression, confusion, and disorientation. Some of these behavioral changes have been reported in COVID-19, and include mitochondrial damage caused by SARS-CoV-2 and subsequent production of reactive oxygen species. It has been surmised Long COVID may involve the induction of spontaneous prion emergence, especially in individuals susceptible to its origin[39].

*AMYLOIDOGENESIS IN LONG COVID*

When studying Long COVID and COVID-19 symptoms, amyloidogenicity of the SARS-CoV-s spike protein (S-protein) should be taken into account, because of their similarities with amyloid-diseases, viz. type 2 diabetes mellitus, fibrinolytic disturbances, and neurologic and cardiac problems. Investigation *in vitro* of the amyloidogenicity of the SARS-CoV-2 S-protein provided data that proposes a molecular mechanism for potential amyloidogenesis of its S-protein in humans facilitated by endoproteolysis[40].

*GENETIC MECHANISMS IN LONG COVID*

Using combinatorial analysis, 73 unique genes were identified in a long COVID population, and a mechanism of action hypotheses has been formed for each gene's role in the development of long COVID. Researchers surmised that long COVID patients with genetic variants that predispose them to metabolic dysfunction and insulin resistance are more likely to suffer from long term pathological sequelae of long COVID, and would have increased rates of new-onset type 2 diabetes mellitus compared to the non-long COVID population[41].

Studies have demonstrated that at least 20% of individuals infected with SARS-CoV-2 remain asymptomatic. A significant association of a common *HLA* class I allele, *HLA-B*15:01*, with asymptomatic infection with SARS-CoV-2 has been demonstrated, where HLA-B*15:01$^+$ T cells from pre-pandemic samples were reactive to an immunodominant SARS-CoV-2 peptide that shares high sequence similarity with peptides from seasonal coronaviruses, HKU1-CoV and OC43-CoV[42].

*OVERACTIVE IMMUNE SYSTEM AND AUTOANTIBODY IN LONG COVID*

Many of the manifestations of acute COVID-19 are caused by overactivation of the immune system rather than the direct effects of the virus on host tissue. In individuals with Long COVID who had mild acute COVID-19 found T cell alterations, including exhausted T cells[43], reduced CD4+ and CD8+ effector memory cell numbers,[43,44] and elevated PD-1 (programmed cell death-1is a protein expressed on T cells that can affect the survival of memory cells and regulate their function), expression on central memory cells, persisting for at least 13 months[44]. Studies have also reported highly activated innate immune cells, a lack of naive T and B cells, and elevated expression of interferon-β (IFNβ) and interferon- λ1 (IFNλ1), persisting for at least 8 months[45]. Depleted T and B cell numbers are strongly associated with persistent SARS-CoV-2 shedding, which may further contribute to the chronic immune activation in Long COVID[46].

Multiple studies have found elevated levels of autoantibodies in Long COVID, such as anti-nuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), and antiphospholipid antibodies[47-49] including autoantibodies to ACE-2[50]. The binding of high-affinity viral spike protein with ACE-2 is a key factor in generating autoantibodies to ACE-2. The COVID-19 virus binds to the ACE-2 via a receptor binding domain (RBD) from the spike protein to invade the host cells[51]. In acute cases, a cytokine storm - a distinct immunopathological feature of COVID-19, which releases different inflammatory molecules, interleukins, and chemokines worsens

the illness course and the prognosis[52-54]. As the cytokine storm intensifies, high levels of inflammatory molecules, such as serum amyloid A (SAA, marker of high inflammation), von Willebrand factor (VWF), interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha (TNF-α) are increased drastically[54]. Such autoimmune responses contribute to worsening disease conditions and stimulate persistent symptoms with lasting inflammation effects. In another study of hospitalized COVID-19 patients with differing severity, autoantibodies to ACE-2 presence were identified in different isotypes, including IgG, IgM, and IgA, or a combination in 10% of the patients, which were recorded in high concentrations[55]. Anti-ACE2 autoantibodies play a role in innate immunity by regulating hypertension, diuresis, sodium cell balance, and the Renin-Angiotensin-Aldosterone system. Autoantibodies to Annexin A1, a major neutrophil protein with anti-inflammatory action, were detected in high concentration for patients with COVID-19 with IgG isotypes or IgM or IgA or a combination of the three in about 20% of the patients, and it was proved that they were related to disease severity and long-lasting symptoms. The study tested a hemophilic patient suffering from Long COVID symptoms for over twelve months, and Annexin was discovered in voluminous concentrations throughout the follow-up[56,80]. New autoantibodies to interferon have also been discovered in Long COVID victims, speculating that it could be linked to disease prognosis and severity. These antibodies may act as regulators in a mechanism to control excess interferon.

Autoantibodies may remain active for weeks or months and progressively decrease as time goes by as the antigen inducements disappear. In Long COVID cases, autoimmunity complications progress to chronic autoimmune diseases[57]. In some cases, the autoantibodies turn drastic to chronic symptoms and remain persistent. With the scenarios, above explained, viral infectious of COVID-19 and autoimmunity are playing "Double Down" as the pathogen itself or its metabolites complexed with self-proteins, body cells, and blood cell surface proteins which generate autoantibodies via molecular mimicry and epitope spreading[56]. High levels of other autoantibodies that target the tissue such as connective tissue, extracellular matrix components, vascular endothelium, coagulation factors and platelets, and organ systems, including the lung, central nervous system, skin, and gastrointestinal tract have been found in some patients with Long COVID[6].

Autoantibodies can also be generated from dormant viruses. Humans can carry many dormant viruses, such as the Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Varicella Zoster Virus (VZV), Herpes Simplex Virus (HSV), and Hepatitis C Virus (HCV). These viruses can remain in the body after the initial infection without causing symptoms for the entire life. However, in some cases, they may reactivate when the host's immune system is weakened, leading to changes in gene expression, protein production, and immune regulation[58]. Reactivation of EBV, HSV, and HCV are reported[58-60] in post-COVID conditions and tied with rheumatoid arthritis, type 1 diabetes mellitus, Alzheimer's disease, cancer, which might explain the chronic condition after Covid 19 infection and continues during Long COVID conditions[58].

A similar study found elevated anti-ribonucleoprotein and anti-SS autoantibodies (a type of autoantibody that is associated with many autoimmune diseases after viral infections, e.g., Epstein-Barr virus, cytomegalovirus) are associated with the development of rheumatological diagnosis[61-63]. Several cases of new-onset autoimmune diseases post-COVID have been reported, including vasculitis[64,65], arthritis[66], systemic lupus erythematosus (SLE) [67], and myositis[68] in patients with no prior history of autoimmunity, irrespective of acute phase severity[69-71]. Further research will determine the extent of autoimmunity caused by the reactivation of latent viruses in long-term COVID-19 patients.

Some studies focused on the enzyme caspases, a family of intracellular cysteine-dependent aspartate-specific proteases that primarily mediate both apoptosis and inflammation. Study in mice infected with SARS-CoV-2 and blocking the enzyme called

caspase 11, resulted in lower inflammation and tissue injury and fewer blood clots in mice lungs. The human version of caspase 4 was highly expressed in COVID-19 patients hospitalized in the ICU – confirming the link to severe disease[72,73]. Another study found a correlation between elevated cytokine levels and caspases 3,8, and 9 in the seminal fluid of long COVID patients compared to control patients[74].

*LONG COVID DISEASE HYPOTHESES BASED ON AUTOIMMUNITY*

Understanding how COVID-19 progresses to Long COVID has been an uphill task for researchers. To decipher the underlying mechanisms, several animal models, including mice, hamsters, ferrets, and monkeys, were used during the pandemic to study SARS-CoV-2 transmission, infection dynamics, and therapeutic interventions. As in most diseases, no one animal model seems to reproduce Long COVID as it occurs in humans entirely, but some studies conducted on mice have yielded exciting results.

Acute SARS-CoV-2 infection triggers the generation of diverse and functional autoantibodies. Iwasaki et al.[75] reported that immunoglobulin G (IgG) samples from Long COVID patients reacted with human pons tissue, and were cross-reactive with mouse sciatic nerves, spinal cord, and meninges, which correlated with Long COVID patient-reported headache and disorientation. Passive transfer of these autoantibodies from Long COVID patients to mice led to increased sensitivity and pain, mirroring patient-reported symptoms, and also, loss of balance and coordination, reflecting donor-reported dizziness[75].

Based on this and other seminal work on Long COVID, Iwasaki et al. [75] has proposed that the main disease hypotheses for the root causes of Long COVID include: 1.Viral persistence (infectious virus or its remnants hidden away in tissue and causing chronic inflammation); 2. Autoimmunity is triggered by the infection (body's own disease-fighting B and T cells triggering an immune response and subsequent inflammation in a process called autoimmunity); 3. Reactivation of latent viruses (dormant viruses reactivating and/or dysbiosis of the microbiome, disturbing body's homeostasis and causing inflammation and throwing off body's homeostasis); and 4. Inflammation-triggered chronic changes leading to tissue dysfunction and damage (macroscopic and microscopic tissue damage resulting from the initial COVID-19 infection viz., lungs, brains, and endothelial tissues[76].

## Conclusion

In previous research, we examined the environmental and social factors affecting COVID-19 transmission and mortality rates in both developing and developed countries, drawing on examples from each global region[78]. These factors are also essential in understanding the complexities of Long COVID, a still poorly defined condition arising after infection with the SARS-CoV-2 virus.

The likelihood of developing Long COVID is influenced by risk factors such as advanced age (particularly in the 50–59 age group), female gender, and hospitalization during the initial infection, and pre-existing conditions. SARS-CoV-2 infection triggers robust innate and adaptive immune responses, which can heighten inflammation and lead to cytokine storms. Such excessive immune responses may contribute to severe, persistent disease, with risks of morbidity and mortality. Additionally, autoimmune complications are significant, with various autoantibodies implicated in Long COVID progression; targeting these autoantibodies may offer therapeutic benefits for some patients.

The SARS-CoV-2 pandemic may now be in our rearview mirror, yet its aftermath continues to impact us through the lingering effect of Long COVID. This pandemic was not the last challenge humanity will face; indeed more emerging viral infectious diseases lie in wait, poised to disrupt global public health. Studying Long COVID is crucial for developing effective diagnostic tools and treatments to reduce its incidence. High-quality, peer-reviewed research is needed to deepen our scientific understanding of Long COVID's prevalence, incidence, and treatment,

ultimately establishing universally defined clinical criteria for this condition.

## Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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