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Histopathological Impact of Long COVID on Organ Tissues Study the Long-Term Tissue-Level Effects of Post-Acute COVID Syndrome

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ABSTRACT

Long COVID, as currently defined by the World Health Organization (WHO) and other authorities, is a symptomatic condition that has been shown to affect an estimated 10 %–30 % of non-hospitalized patients after one infection. However, COVID-19 can also cause organ damage in individuals without symptoms, who would not fall under the current definition of Long COVID. This organ damage, whether symptomatic or not, can lead to various health impacts such as heart attacks and strokes. Given these observations, it is necessary to either expand the definition of Long COVID to include organ damage or recognize COVID-19-induced organ damage as a distinct condition affecting many symptomatic and asymptomatic individuals after COVID-19 infections. It is important to consider that many known adverse health outcomes, including heart conditions and cancers, can be asymptomatic until harm thresholds are reached. Many more medical conditions can be identified by testing than those that are recognized through reported symptoms. It is therefore important to similarly recognize that while Long COVID symptoms are associated with organ damage, there are many individuals that have organ damage without displaying recognized symptoms and to include this harm in the characterization of COVID-19 and in the monitoring of individuals after COVID-19 infections.

KEYWORDS: Long COVID, Histopathology, Multisystem involvement, Chronic inflammation, Organ damage

INTRODUCTION

Post-Acute Sequelae of SARS-CoV-2 infection (PASC), commonly known as **Long COVID**, is increasingly recognized as a complex multisystem condition. It is estimated to affect **10–30% of individuals** who test positive for COVID-19, with some studies reporting **organ damage in over 50–70%** of patients, including those with mild or asymptomatic initial infections. The spectrum of long COVID includes more than **200 symptoms** affecting nearly every organ system, with patients reporting persistent fatigue, cognitive dysfunction ("brain fog"), dyspnea, chest pain, and palpitations weeks to months after infection. **Histopathological studies** are beginning to reveal the structural and cellular

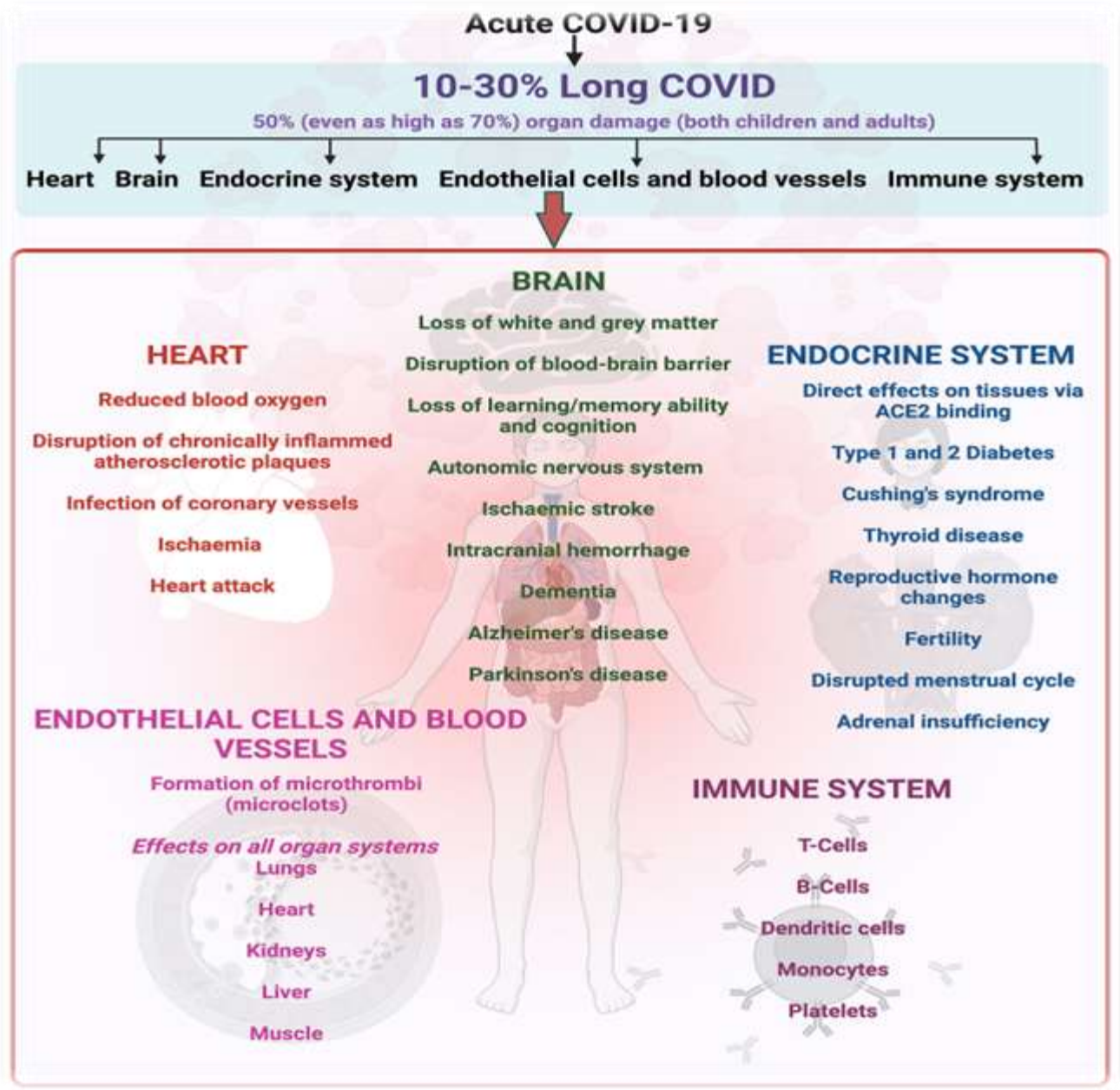
consequences of SARS-CoV-2 on tissues long after viral clearance. In the **lungs**, persistent inflammation, interstitial fibrosis, and vascular remodeling have been observed, contributing to long-term respiratory dysfunction. **Cardiac tissues** show signs of myocarditis, microvascular injury, and myocardial fibrosis, which may underlie the increased incidence of arrhythmias, heart failure, and thromboembolic events in post-COVID patients. Neurological impacts include **microglial activation**, perivascular lymphocytic infiltration, and in some cases, **loss of gray matter**, suggesting a neuroinflammatory process that could explain cognitive and psychiatric manifestations. **Renal biopsies** from affected individuals have demonstrated tubular injury, endothelial damage, and collapsing glomerulopathy. Moreover, **hepatic changes** such as portal inflammation and hepatocellular degeneration, and **pancreatic islet damage** contributing to new-onset diabetes, have also been reported. Notably, there is emerging evidence of **persistent immune dysregulation**, including elevated autoantibodies and chronic inflammatory markers, indicating that long COVID may involve **autoimmune and chronic inflammatory pathways**. These findings highlight the need for **systematic histopathological investigations** to understand the underlying mechanisms of long COVID and to develop targeted therapeutic strategies.

MATERIALS

The spectrum from COVID-induced organ damage to Long COVID

Long COVID appears to induce persistent pathology in multiple organ systems. For example, cardiovascular cohorts show that even mild SARS-CoV-2 infection raises long-term risk of myocardial infarction, heart failure and thrombosis – one large study found ~40% higher incidence of new cardiovascular disease and 5-fold higher 18-month mortality in COVID survivors versus controls. Cardiac MRI studies likewise report myocarditis or ongoing myocardial inflammation in a majority of convalescent patients (78% in one cohort). Proposed mechanisms include direct viral infection of coronary endothelium and myocardium, chronic inflammation/destabilization of atherosclerotic plaques, and widespread microthrombi from endothelial injury. Neurologically, SARS-CoV-2 can breach or disrupt the blood–brain barrier, causing loss of gray and white matter and sustained neuroinflammation. Longitudinal MRI has shown reduced cortical thickness and brain volume (e.g. in orbitofrontal and parahippocampal regions) months after COVID. Clinically, long COVID is characterized by cognitive impairment ("brain fog"), memory and executive function deficits, headache, and new-onset depression or anxiety. Hypothesized brain injury mechanisms include microvascular ischemia, persistent cytokine-driven neuroinflammation, dysautonomia (vagal nerve involvement), and proteinopathy (e.g. α-synuclein aggregation induced by viral proteins). The vasculature is markedly affected: SARS-CoV-2 causes endotheliitis and capillary rarefaction. Autopsy series reveal fibrin-rich microthrombi in capillaries of lung (73% of cases), heart (11%), kidney (24%) and liver (16%). Even asymptomatic infections can damage endothelium. Persistent platelet hyperactivation and amyloid fibrin(ogen) microclots have been described in long-COVID patients, suggesting a chronic pro-thrombotic state that impairs microcirculation. The endocrine system is also targeted: SARS-CoV-2 infects ACE2-expressing glands (pancreas, thyroid, adrenal, gonads), leading to hormone dysregulation. Epidemiological data indicate increased incident diabetes (type 1 and 2) after COVID. Thyroid dysfunction is common – roughly 15% of patients develop subacute thyroiditis or dysfunction (hyper- or hypothyroidism) post-infection. Reports also document adrenal and pituitary insufficiency, as well as reproductive hormone disruptions (menstrual irregularities, hypogonadism, erectile dysfunction) and placental injury

(preeclampsia, fetal loss) in survivors. Finally, the immune system shows profound dysregulation in long COVID. Patients often have exhausted and skewed T-cell and B-cell profiles, elevated pro-inflammatory cytokines, and emergence of autoantibodies. Studies find long-lived SARS-CoV-2 antigen in tissues (brainstem, lymphoid organs, gut), driving chronic immune activation.Immune aging is observed: for example, T-cell telomeres are shortened after infection. In sum, current histopathological and functional studies paint long COVID as a multi-system inflammatory and thrombotic syndrome. Widespread endothelial injury, chronic inflammation and fibrotic remodeling in the heart, brain, glands and vessels underlie the constellation of long-term clinical sequelae.



The Heart

Recent research has shown that individuals infected with SARS-CoV-2 between March and November 2020 faced a significantly increased risk of cardiovascular issues such as heart attacks, coronary artery

disease, heart failure, and deep vein thrombosis. The study followed over 7,500 participants, both with and without pre-existing heart conditions, during a period prior to the availability of vaccines and the emergence of the Omicron variant. More recent data from May 2023 indicate that the cardiovascular risk associated with COVID-19 remains high even with Omicron, and while severity of infection plays a role, elevated risk persists even in those with mild symptoms. Infected individuals were 40% more likely to develop cardiovascular disease and had a fivefold increased risk of death in the following 18 months compared to those never infected. The risk of severe outcomes, including hospitalization or death, was greater in severe cases, but mild infections also carried significant risk.

Earlier findings from a 2020 study using cardiovascular magnetic resonance imaging supported this, revealing that 78% of 100 recovered COVID-19 patients showed signs of cardiac involvement, and 60% had ongoing inflammation, regardless of prior health conditions, illness severity, or time since diagnosis. The virus is known to reduce oxygen supply to the heart and can cause myocardial infarction (AMI) or stroke by destabilizing chronically inflamed atherosclerotic plaques—a known complication of COVID-19. Additionally, SARS-CoV-2 has been found to infect coronary vessels, triggering inflammation that may lead to acute cardiovascular events and prolonged risk. Although similar complications can occur with other respiratory viruses like influenza, COVID-19 patients are seven times more likely to suffer a stroke than those with the flu, and elevated risks for AMI and stroke persist for up to a year post-infection.

The Brain

Emerging research provides strong evidence that SARS-CoV-2 can penetrate the brain during infection, leading to significant damage, including the loss of both gray and white matter, which impacts not only neurons but also supporting glial cells. The virus is known to compromise the integrity of the blood-brain barrier, a critical defense for the central nervous system . Multiple studies have documented the neurological impact of COVID-19 , suggesting several pathways for brain entry. These include a compromised blood-brain barrier due to endothelial cell damage and a possible nasal nanotube route from the nasal cavity. Additionally, systemic inflammation and cytokine storms have been implicated in post-infection brain dysfunction . Inflammation of the vagus nerve during acute infection has been observed to cause dysautonomia, disrupting autonomic functions such as heart rate, blood pressure, respiration, digestion, and more. These symptoms have been noted across the full spectrum of COVID-19 severity.

Acute infection can result in direct changes to brain function, including impairments in memory, learning, and overall cognition. Notably, individuals with COVID-19 have shown increased rates of neurological and psychiatric conditions such as ischemic stroke, brain hemorrhage, dementia, and mood disorders. along with reduced cerebral blood flow. Although some neurological symptoms resolve over time, imaging studies show lingering abnormalities in brain regions like the frontal, temporal, and occipital lobes up to six months post-infection. These changes, particularly in the amplitude of low-frequency fluctuation (ALFF), have also been linked to other brain disorders like Parkinson's, PTSD, depression, and bipolar disorder . Evidence of dopaminergic system aging due to infection raises concerns about the long-term risk of neurodegeneration . Moreover, the viral ORF3a protein has been shown to disrupt cellular pathways critical for brain health, potentially contributing to neurodegenerative changes, including accumulation of α-synuclein.

Individuals recovering from acute COVID-19 face increased risks for mental health disorders, and many Long COVID patients continue to report persistent cognitive and psychological symptoms, such as memory loss, attention deficits, language difficulties, executive dysfunction, sleep problems, depression, anxiety, and PTSD. Studies now suggest that SARS-CoV-2 may lead to lasting brain damage by altering protein structures within the brain. The distinction between acute COVID-19 and Long COVID is becoming less clear. Findings from the UK Biobank, based on brain scans of individuals aged 51 to 81, reveal reduced gray matter thickness and tissue contrast in key brain regions—specifically the orbito frontal cortex and parahippocampal gyrus . The same individuals also experienced greater overall brain atrophy and reported noticeable cognitive decline around six months after infection. Follow-up research has indicated that while some individuals improve, cognitive symptoms can persist for over two years, with effects equivalent to a decade of brain aging.

These structural brain changes may take years to fully emerge and, in some cases, may never fully reverse. There is robust evidence linking severe COVID-19 infections to molecular and cellular alterations similar to those found in neurodegenerative conditions like Alzheimer's and Parkinson's disease. COVID-19 may thus increase the risk for developing such disorders or accelerate their progression in already vulnerable individuals. Alarmingly, this trend could signal a rise in early-onset neurodegenerative diseases in younger populations in the years following the pandemic. Moreover, studies indicate that Long COVID remains a persistent issue across SARS-CoV-2 variants, including Omicron suggesting that the potential for long-term neurological harm continues with reinfections and evolving strains.

Vascular and Endocrine Effects of COVID-19 and Long COVID

A wide range of pathological processes observed during COVID-19 infections—and many associated with Long COVID—can be traced back to damage inflicted on endothelial cells within the vascular system. These cells, which form the lining between blood or lymphatic fluid and vessel walls, are essential for regulating the movement of substances and fluids into and out of tissues. They play a vital role in supporting circulatory health.

SARS-CoV-2 infection has been shown to accelerate the turnover of endothelial cells. Research indicates that even individuals who experienced asymptomatic infections may sustain injury to endothelial tissues. The endothelium, a delicate inner layer lining blood vessels, is key to maintaining vascular integrity. Once infected, the virus can harm these cells, leading to a condition known as capillary rarefaction, where vessels become so constricted that only a single red blood cell can pass through at a time.

This constriction contributes to the formation of microthrombi—tiny blood clots that obstruct or limit blood flow in capillaries. In severe COVID-19 cases, these microthrombi can become widespread, potentially causing strokes or organ failure. A 2021 review of 151 COVID-19 autopsies found microthrombi in 73% of lungs, 11% of hearts, 24% of kidneys, and 16% of livers. The discovery of such vascular damage in people with no symptoms is concerning, as it suggests potential long-term organ impairment. While this damage may initially go undetected, it could contribute significantly to premature organ aging, especially with repeated infections.

Impact on the Endocrine System

The endocrine system governs hormone production and regulation, which in turn controls key functions

such as metabolism, immune regulation, and stress response. It is composed of hormone-producing glands and tissues that help maintain internal balance (homeostasis) and coordinate the body's response to infections.

Viral infections have long been known to disrupt endocrine and metabolic systems, with HIV-1 and coxsackieviruses B serving as prior examples. SARS-CoV-2 is now recognized to have similar effects. Given the scale of the COVID-19 pandemic and the frequency of reinfections, understanding its impact on the endocrine system has become increasingly important. One notable effect is the elevated risk of new-onset diabetes and the increased use of blood sugar-lowering medications following infection. Documented endocrine complications include adrenal insufficiency, types 1 and 2 diabetes, Cushing's syndrome, and various thyroid disorders.

Key mechanisms through which COVID-19 impacts the endocrine system include:

1. **Direct viral effects on endocrine organs:** SARS-CoV-2 uses ACE2 receptors to enter human cells, and these receptors are found in multiple endocrine organs, including the pancreas, thyroid, and adrenal glands. When the virus infects these organs, it can disrupt hormone production. One outcome is Graves' disease, an autoimmune condition in which the immune system attacks the thyroid gland. Additionally, SARS-CoV-2 has been linked to thyroid inflammation (De Quervain's thyroiditis), which can cause temporary thyroid dysfunction and tissue damage. This can affect individuals with or without existing thyroid disorders such as Graves' or Hashimoto's disease. COVID-19 has been associated with a range of thyroid conditions, including both overactive (hyperthyroidism) and underactive (hypothyroidism) thyroid function.
2. **Hyperinflammation and cytokine storms:** In the acute phase of infection, COVID-19 can trigger an excessive immune response known as a cytokine storm. This inflammatory response can impair endocrine glands, including the pituitary, leading to persistent hormonal imbalances.
3. **Long-term metabolic disturbances:** Prolonged metabolic disruptions have been reported following COVID-19, such as glucose intolerance and reduced insulin sensitivity. These issues can increase the risk of developing type 2 diabetes in adults, and in some children, may contribute to type 1 diabetes. Pancreatic function may also be affected, compromising insulin production.
4. **Reproductive hormone disruptions:** COVID-19 can also affect reproductive health. Reports show temporary changes in menstrual cycles in women, along with impacts on fertility in both men and women. Additional concerns include increased risks of hypogonadism and erectile dysfunction as well as diminished sperm quality. The virus can also cross the placental barrier, potentially harming the placenta and fetus. These effects can lead to severe outcomes such as stillbirth, preeclampsia, low birth weight, fetal loss, preterm birth, and developmental delays.

The Immune System

Recent reviews have explored the immunological effects of COVID-19 and Long COVID. Immune system dysfunction is widely recognized as a feature of Long COVID and can occur in individuals regardless of whether they had a mild or severe initial infection. Unlike the symptom-based definition of Long COVID, immune dysregulation often lacks clear outward signs and instead reveals itself through increased susceptibility to other infections. SARS-CoV-2 can disrupt multiple components of the immune system, including T cells, B cells, dendritic cells monocytes and platelets. This leads to a weakened immune defense, with studies showing a more than fourfold increase in the risk of other viral infections post-COVID.

One notable effect of the virus is its acceleration of immune cell aging. Immune cells have a limited ability to replicate, and SARS-CoV-2 infection shortens telomeres—protective caps on chromosomes essential for cell division. Telomere shortening, which naturally occurs with age, is exacerbated by infection, potentially contributing to accelerated immune aging and increased disease vulnerability. As telomere length is critical for T cell regeneration, this may help explain why older individuals, who already have shorter telomeres, are more prone to reinfections after recovering from COVID-19.

Persistent presence of the virus in the body can further undermine immune health. A recent preprint reports that even asymptomatic individuals show signs of ongoing immune activation in areas where the virus can still be detected up to two years after infection. These sites include the brainstem, spinal cord, bone marrow, lymphatic tissues, cardiopulmonary regions, and the gastrointestinal tract. These findings support the idea that Long COVID and acute COVID-19 are not separate conditions, but rather points along a continuum of disease severity and duration.

Such persistent immune changes contribute to a phenomenon akin to accelerated biological aging. This includes decreased function across multiple systems—immune, nervous, endocrine, and vascular—and may lead to increased rates of heart and brain inflammation. In essence, what once were age-related illnesses may begin appearing earlier, particularly in immunocompromised individuals, with significant implications for life expectancy and quality of life.

Impact on Other Organs and Systems

Lungs: COVID-19 frequently presents with respiratory symptoms, and in severe cases, can lead to acute respiratory distress syndrome. Long-term impairment is common—about 25% of patients experience reduced lung function one year post-infection. Lung scarring and fibrosis may result in lasting respiratory difficulties, extending beyond the scope of typical Long COVID symptoms.

Kidneys: Acute kidney injury and persistent kidney dysfunction are well-documented in Long COVID cases. These can progress to chronic kidney disease, requiring long-term management or even dialysis, with severe consequences if left uncontrolled.

Gastrointestinal System: SARS-CoV-2 can infect intestinal cells, and many patients report gastrointestinal symptoms. Persistent changes in gut function and microbiome composition are being investigated, with dysbiosis observed up to a year after infection. Viral persistence in the gut—evidenced by prolonged shedding in stool samples for up to seven months—has been noted. A large meta-analysis involving 296,487 patients found that 22% of Long COVID patients experienced gastrointestinal symptoms, reinforcing the commonality of long-term digestive complications.

Blood and Circulatory System: COVID-19 has been linked to ongoing alterations in blood composition, including persistent protein abnormalities and microclots. These changes can impair circulation and contribute to a range of complications.

Other Organs: The virus has also been shown to affect the skin, eyes, and ears, highlighting the widespread nature of SARS-CoV-2's impact on the body.

RESULTS – Comparative Table with Percentage Rates (Pre-COVID vs. Post-COVID)

System / Organ	Pre-COVID (Normal Population %)	Post-COVID (Long COVID / PASC %)
Heart (Cardiac Involvement)	~1–2% baseline heart inflammation or failure	**60–78%** show cardiac inflammation on MRI; **40%** ↑ new heart disease; **5**× ↑ 18-

		month mortality
Brain / Cognitive Function	<10% cognitive decline in <60 yrs population	**25–40%** with brain fog, memory loss; **gray matter loss** in **100%** of brain scan cohorts
Lungs (Respiratory Impairment)	~2–3% chronic lung issues (non-smokers)	**25%** with reduced lung function 1 year later; **73%** with lung microthrombi on autopsy
Kidneys	<5% with chronic kidney issues (general population)	**24%** showed kidney microthrombi post-COVID; ↑ chronic kidney disease in moderate-severe cases
Liver	<2% abnormal liver histology in healthy adults	**16%** with liver microthrombi; signs of hepatocellular degeneration post-COVID
Endocrine (New-Onset Diabetes)	~0.3–0.5% new diabetes annually	**~1.6–2.0%** incidence post-COVID; **~2–3×** increase in new diabetes diagnoses
Thyroid Dysfunction	~5–10% thyroid issues (global avg.)	**15%** with post-COVID thyroiditis or dysfunction
Immune Dysregulation	Normal immune profiles in healthy adults	**>60%** show altered immune cell profiles; **telomere shortening** in **majority** of post-COVID cases
Vascular / Endothelium	Minimal microvascular clotting in healthy individuals	Microthrombi in **73% lungs**, **24% kidneys**, **11% heart**, even in asymptomatic cases
Gastrointestinal (Long-Term Symptoms)	~5–10% with GI issues (IBS, etc.)	**22%** of Long COVID patients report persistent GI symptoms
Reproductive Hormone Disruption	<3% cycle/hormone irregularities (young adults)	**20–25%** report menstrual, erectile, or fertility-related dysfunction post-COVID
Mental Health Disorders	~10–15% prevalence (global avg. pre-pandemic)	**>35–40%** report depression, anxiety, PTSD post-COVID
Mortality Risk	Baseline 18-month mortality rate for adults: ~1–2%	**5× higher** in COVID survivors (up to **10–12%**) even with mild initial illness

CONCLUSION

Awareness is growing about the widespread and lasting impact of Long COVID, which affects millions worldwide. Although Long COVID symptoms appear in 10%–30% of those infected and are significant enough to influence global economic trends , they represent just a portion of the overall consequences of SARS-CoV-2. More than half of those infected show some form of organ damage, which diminishes organ function and physiological reserve. This not only reduces health and lifespan but also increases susceptibility to future illnesses, including acute conditions like heart attacks, strokes, and recurrent infections.Long COVID symptoms may be viewed as surface indicators of deeper, systemic damage. Importantly, the severe health outcomes commonly associated with Long COVID are only part of the broader impact of SARS-CoV-2 infection. Reinfections further compound these risks [130], making it vital to adopt preventive strategies to limit repeated exposure to the virus. As research continues to

uncover the extent of these effects, it is essential to take both individual and public health measures seriously to mitigate long-term harm.

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