

COVID-19-associated neurological and psychological manifestations

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Abstract

Long COVID is an infection-associated chronic condition that typically occurs within 3 months of acute COVID-19 infection in which symptoms are intermittently or continuously present for at least 3 months. Long COVID is estimated to affect between 80 and 400 million people globally, with an incidence of 5–20% in the community and up to 50% among hospitalized patients following acute SARS-CoV-2 infection. Common neuropsychiatric and mental health symptoms of long COVID include memory deficits, executive dysfunction, anxiety, depression, recurring headaches, sleep disturbances, neuropathies, problems with taste and smell, and dizziness that accompanies erratic heart rates and severe post-exertional malaise. Underlying pathophysiological mechanisms includes SARS-CoV-2 viral persistence, herpesvirus reactivation, microbiota dysbiosis, autoimmunity, clotting and endothelial abnormalities, and chronic immune activation. Owing to the variability in the clinical presentation, management must be tailored based on a patient's presenting symptoms.

Sections

[Introduction](#)[Epidemiology](#)[Mechanisms/pathophysiology](#)[Diagnosis, screening and prevention](#)[Management](#)[Quality of life](#)[Outlook](#)

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, officially declared by the World Health Organization (WHO) in March 2020, was initially recognized for its acute respiratory manifestations; however, accumulating scientific evidence, spurred on by patient advocacy efforts, highlighted a subset of individuals who experience prolonged and debilitating symptoms that persist for months to years beyond the acute phase of infection. Although the pandemic was officially declared ended in May 2023, the public health ramifications of long COVID will reverberate for decades in individual lives and society. Long COVID, occasionally referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), is an infection-associated chronic condition (IACC) that manifests as a complex multisystem disease state with profound implications for clinical care, public health and our understanding of viral pathogenesis and persistence.

Although most persons infected with SARS-CoV-2 recover fully, many individuals report chronic symptoms across multiple organ systems, irrespective of initial disease severity. Some of these symptoms include alterations in neurological and psychological function, such as persistent headaches, sleep disturbances and 'brain fog'. Within the first couple of months of the pandemic, people with lived experience of persistent symptoms began to connect through social media calling themselves 'long-haulers'. By mid 2020, this term 'long COVID' entered public use to describe this persistent disease¹.

The first official definition of long COVID came in December 2020 from the National Institute for Health and Care Excellence (NICE), a UK-based independent public body that provides national guidance and advice to improve health and social care in England. The NICE definition described long COVID symptoms persisting past 12 weeks not better explained by another diagnosis as 'post-COVID-19 syndrome' or 'long COVID'². More recent guidelines, namely, the 2024 National Academies of Sciences, Engineering, and Medicine (NASEM) definition, reversed the 'diagnosis of exclusion' aspect of this and other definitions to acknowledge exacerbation of pre-existing diseases or

de novo appearance of new diseases as a manifestation of long COVID. The WHO defines long COVID as a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis, with common symptoms including fatigue, shortness of breath and cognitive dysfunction, which generally impact everyday functioning³. According to the WHO clinical case definition, these symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness, and they may fluctuate or relapse over time³. Other definitions have built upon these early descriptions, with areas of active research continuing to refine language to aid future understanding and discovery.

This Primer consolidates the available scientific knowledge on long COVID based on the 2024 NASEM definition, exploring its epidemiology, mechanisms and pathophysiology, diagnosis, screening and prevention, management, quality of life and outlook. We specifically based this Primer on the NASEM definition of long COVID as it is clear, inclusive and grounded in extensive scientific review, ensuring its utility for patients, clinicians, public health agencies and researchers.

Epidemiology

Prevalence of long COVID

Conservative estimates are that at least 54 million to as many as 400 million people have long COVID (or PASC) globally^{4–7}, with an incidence of 5–20% in the community^{8–10} and as high as 50% or greater in patients who were hospitalized for acute COVID-19, if the co-attribution of critical illness post-intensive care syndrome and IACC is included¹¹. The prevalence of long COVID seems to be lower in vaccinated individuals. Indeed, in one study in Western Australia, the prevalence of long COVID was 18.2% in a highly vaccinated population, in which more than 90% of vaccine-eligible individuals had been vaccinated, with a higher absolute relative risk (aRR) of long COVID in those with two or fewer COVID-19 vaccine doses than in those with four or more doses (aRR 1.4, 95% CI 1.2–1.8) and those with three doses (aRR 1.3, 95% CI 1.1–1.5)¹². Of note, this Australian study did not include unvaccinated individuals; however, other studies can offer comparisons. In a US-based study, the prevalence of long COVID in a vaccinated population was 21.6% versus a prevalence of 25.6% in unvaccinated individuals¹³, whereas in the UK, vaccinated individuals had a lower odds of long COVID symptoms with the first dose of vaccine reducing the odds by 12.8% and the second dose initially reducing the odds by 8.8% with a subsequent decrease of 0.8% per week (–1.2% to –0.4% per week; $P < 0.001$)¹⁴. Although research is limited, long COVID can occur in children and adolescents (Box 1).

Prevalence of neuropsychiatric manifestations of COVID-19

Neuropsychiatric manifestations are observed acutely and chronically with COVID-19 and contribute to the disability caused by SARS-CoV-2 infection¹⁵. Neurological manifestations can involve the central nervous system (CNS) or the peripheral nervous system in both the acute infection and the chronic state. Acute symptoms commonly include headache, photophobia (sensitivity to light), sleep disturbances, anosmia (loss of smell) or ageusia (loss of taste)^{16,17}. Rarer and more severe manifestations can include encephalitis, which typically presents in the acute period, but in rare cases can present weeks later with seizures and altered consciousness. Neurological complications have been reported in up to 80% of patients hospitalized with acute COVID-19 (ref. 18). In patients requiring prolonged critical care, critical illness myopathies and sensorimotor axonal neuropathies

Box 1 | Children and adolescents

SARS-CoV-2 infection in children results in a spectrum of acute illnesses, from mild disease²¹⁸ to the multisystem inflammatory syndrome in children^{219–222} or COVID-19 (ref. 223) similar to what is described in the adult population. Following an acute illness, long COVID can develop with a wide range of symptoms, including fatigue, shortness of breath, cognitive dysfunction, joint pain and insomnia^{224–228}. Some studies have also found pulmonary dysfunction²²⁹ and brain hypometabolism^{230,231}. A large systematic review found a prevalence of long COVID in children of 25%, with mood changes, fatigue and sleep disorders as the most common symptoms, although other studies have found a higher risk of persistent dyspnoea, anosmia, ageusia and fever²³².

A large 3-year prospective follow-up study in Italy found that 7.1% of adolescents with SARS-CoV-2 infection were subsequently diagnosed with long COVID. Risk factors for long COVID were older age (>12 years), female sex, comorbidities and infection with the original variants²³³. Collaboration between healthcare providers, families, schools and community is crucial for optimizing long COVID outcomes in children. More resources to understand and treat long COVID in children and adolescents are needed.

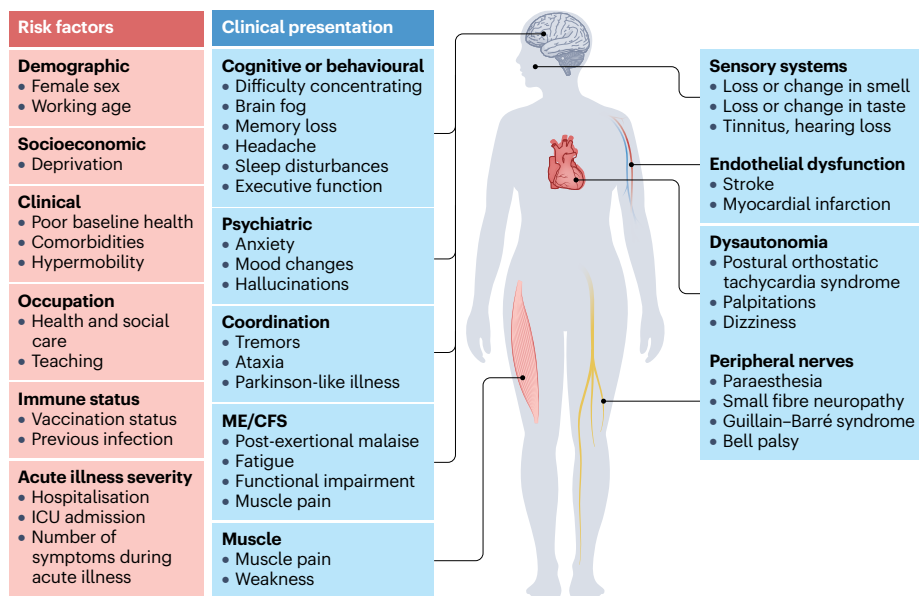


Fig. 1 | Risk factors and clinical manifestations of neurocognitive and psychiatric manifestations of COVID-19. Risk factors for neurological and psychological long COVID relate to premorbid and predisposing risk factors including demographic, socioeconomic, clinical, occupation, immune status and acute illness severity. The clinical presentation of long COVID is heterogeneous and may involve clinical symptoms across a variety of organ systems and symptom domains. ICU, intensive care unit; ME/CFS, myalgic encephalitis/chronic fatigue syndrome.

have been observed¹⁷. Guillain-Barré syndrome (GBS) is a rare but well-documented disease associated with acute SARS-CoV-2 infection, with a pooled prevalence of 15 cases per 100,000 SARS-CoV-2 infections¹⁹.

More than 200 symptoms of long COVID have been reported, including neuropsychiatric manifestations. These include poor concentration, cognitive dysfunction (brain fog), headache, dizziness, fatigue, anxiety, depressive disorders, muscle weakness, dysautonomia, tinnitus, paraesthesias, sleep disorders and loss of smell and taste^{20–22}. Cognitive impairment is consistently reported as one of the most common components of long COVID (see below). As the pathophysiology of many symptoms is poorly understood, it is not possible to clearly delineate those with a neurological aetiology. For example, breathlessness or dizziness may indicate dysautonomia (including postural orthostatic tachycardia syndrome) or problems with lung or vestibular function, respectively, and post-exertional malaise (PEM) may be muscular in origin²³. Although studies are often heterogeneous and have limitations relating to selection bias (in surveys or hospital-based studies), fatigue, cognitive impairment, breathlessness and muscle pain are consistently among the most commonly experienced symptoms of long COVID^{24,25} (Fig. 1). Of note, some symptoms of long COVID, such as fatigue, PEM, brain fog and dysautonomia, overlap with symptoms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Indeed, about half of patients with long COVID meet diagnostic criteria for ME/CFS¹¹.

While long COVID may represent the more severe chronic effects of COVID-19, reports of population-level effects on cognitive dysfunction following COVID-19 are concerning. Indeed, one large-scale community-based study showed a significant downward shift in the distribution of global cognitive scores²⁶, with the greatest cognitive impairment among those with prolonged symptoms, those hospitalized or admitted into critical care, and those infected in the early phase of the pandemic (original, Alpha variant infection). The prevalence of cognitive scores below two standard deviations was increased twofold to fourfold in these groups. Memory, reasoning and executive

function (planning) domain-specific tasks seemed to have been the most affected domains²⁶.

Other studies have shown a higher risk of incident neurological or psychiatric diagnoses, anxiety disorder, mood disorder, psychotic disorder, sleep disorder, cognitive deficit, dementia, epilepsy or seizures, ischaemic stroke, intracranial haemorrhage and myoneural junction or muscle disease following SARS-CoV-2 infection. These data suggest that COVID-19 can both cause long COVID and increase the risk of end-organ complications^{27,28}.

Risk factors for long COVID

Several studies have now shown that increased age, female sex, lower socioeconomic status, occupation (healthcare workers and teachers), more severe acute infection, and pre-existing comorbidities at the time of infection increase the risk of long COVID^{8,29,30} (Fig. 1). Moreover, COVID-19 vaccination has been associated with a 15–50% lower risk of long COVID¹⁴, although the effect on neurological symptoms specifically is unclear. In addition to reducing the incidence of long COVID, vaccination may also reduce the risk of persistent symptoms³¹, impacting recovery. One study suggested a reduction in the risk of headache and loss of smell and taste following first and second vaccine doses but did not show an effect on poor concentration and memory¹⁴. Some studies have suggested that the incidence of long COVID may be reduced with the Omicron variant and subvariants of SARS-CoV-2; however, whether this is an intrinsic characteristic of the variants or a result of widespread vaccination and population immunity when Omicron spread is unclear¹⁰. Moreover, there was no reduced risk of post-COVID complications with Omicron in one large-scale study²⁷. Prior immunity via infection was associated with a modest 28% reduction in the risk of long COVID at re-infection in a large community-based study³².

Trajectories of neurocognitive and psychiatric symptoms following COVID-19

Although several studies have investigated recovery following long COVID, the rate of recovery is unclear given the heterogeneity of

study design, patient selection, variant inclusion, patients lost to follow-up, vaccination status, duration of follow up and fluctuating or relapsing–remitting nature of long COVID²⁹. Longitudinal studies of long COVID symptoms suggest that patients with neurocognitive symptoms, neuropsychiatric symptoms, PEM and fatigue poorly recover^{33,34}. In one population-based study, while recovery from acute COVID was generally rapid in the first 3 months following infection, 22% of the cohort reported long COVID at 6 months, which reduced to 17% at 2 years after infection, indicating a poor rate of full recovery after the initial 6 months³⁴. Overall recovery rates for long COVID remain highly variable, generally ranging from ~5% to 30% for full symptom resolution within 6 to 12 months after infection³⁴. While the prevalence of long COVID did not decline markedly over the 2 years after infection, qualitative improvement in symptoms was reported by the majority³⁴. Poor recovery correlated with advanced age³⁴. One meta-analysis including more than 1.5 million patients from 46 different countries with COVID-19 showed improvement in most neurological symptoms over 12 months, with reoccurrence of symptoms at 6 and 9 months after COVID-19, and persistently high prevalence of fatigue and anosmia or hyposmia at 12 months³⁵.

Studies examining the correlation between different symptoms among patients suggest that neurological symptoms tend to form part of the more severe multisystem cluster of long COVID that is associated

with significant functional impairment and incomplete recovery³³. While dysautonomia, including postural orthostatic tachycardia syndrome (POTS), a disorder of the autonomic nervous system, characterized by dizziness, fatigue, brain fog and a rapid heart rate upon moving from a lying to a standing position, has been poorly studied in these groups due to the lack of clinical diagnoses in many patients, some studies suggest that recovery from this may also be poor²⁸.

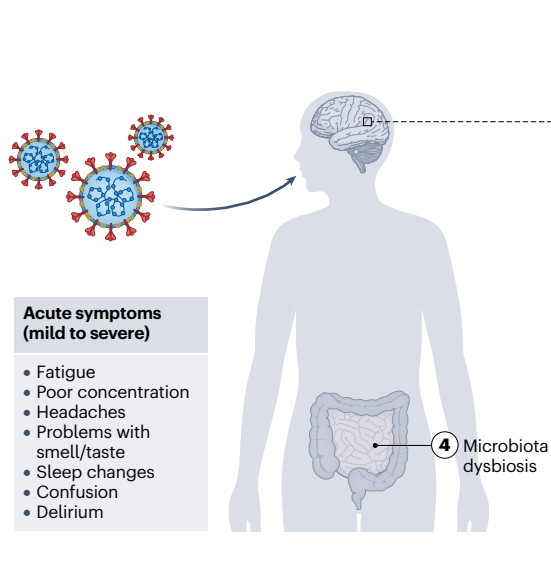
Large-scale studies examining adults and Veterans have shown increased risk of cognitive deficits, stroke, headache, dementia, dysautonomia, psychotic disorders, epilepsy or seizures even 2 years after infection^{27,28}. In children, the risk of cognitive dysfunction was seen up to 3 months after infection, and the risk of intracranial haemorrhage and nerve, nerve root and plexus disorder remained high even 2 years after infection²⁷. Notably, risks of neurological complications were not lower with the Omicron variant compared with previous variants²⁷.

Mechanisms/pathophysiology

General mechanisms of long COVID

Various pathophysiological mechanisms for neuropsychiatric long COVID have been suggested, including SARS-CoV-2 viral persistence, herpesvirus reactivation, microbiota dysbiosis, autoimmunity, clotting and endothelial abnormalities, and chronic immune activation (Fig. 2).

Acute SARS-CoV-2 infection



Pathobiological mechanisms of long COVID

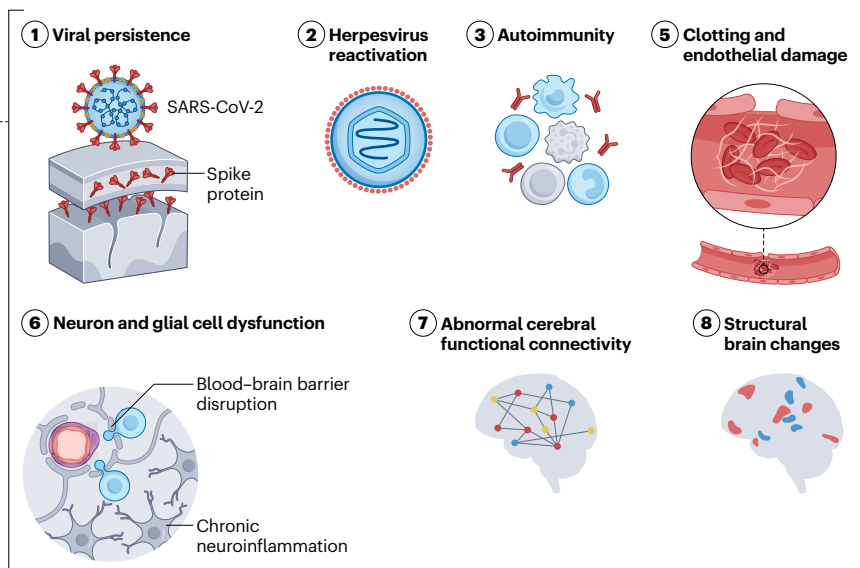


Fig. 2 | Proposed pathobiological mechanisms of long COVID. Some pathophysiological factors have been associated with neurological and psychiatric symptoms of long COVID, including viral persistence, herpesvirus reactivation, microbiota dysbiosis, autoimmunity, chronic inflammation, clotting and endothelial dysfunction. (1) Persistent SARS-CoV-2 antigen, RNA and spike protein have been found in the central nervous system (CNS), including skull marrow, meninges and parenchyma, months or years after the initial infection. (2) SARS-CoV-2 infection may reactivate herpesvirus in some individuals. Antibodies against Epstein–Barr virus have also been identified after long COVID onset, and are associated with fatigue. (3) Autoreactive T and B cells can be stimulated by viral infection. Autoantibodies against CNS antigens can be found in those with neurological long COVID. (4) Changes in the gut microbiome can be detected in patients with long COVID, including reducing butyrate-producing bacteria (which are linked with brain health). (5) Dysregulated coagulation can result from different factors, including viral

persistence, inflammation, autoimmunity and endothelial injury. These features may cause and prolong blood–brain barrier impairment. Individuals with long COVID can have fibrinolytic microclots (which are resistant to fibrinolysis) and dysfunctional platelets, potentially causing tissue hypoxia. (6) Disrupted neuron–glia homeostasis results in impaired hippocampal neurogenesis, reduction of myelinated axons and neurotoxic astrocyte reactivity. Moreover, chronic neuroinflammation can occur in long COVID; that is, systemic and CNS cytokines and chemokines can cause white matter-reactive microglia, reduced hippocampal neurogenesis, oligodendrocyte loss and reduced myelination. (7) Functional connectivity analyses with resting-state functional MRI has demonstrated altered brain networks in patients with long COVID, with changes in the normal pattern of integration and segregation of brain regions. (8) Some neuroimaging studies have demonstrated cortical atrophy after SARS-CoV-2 infection, whereas others have described microstructural white matter alterations even after mild acute infection.

Immune reaction probably contributes by causing collateral damage from exaggerated or misdirected host antiviral immune mechanisms or those resulting from autoimmune responses.

Viral persistence. Evidence for persistent viral antigen and RNA, months or years after the initial infection, has been found in autopsy and biopsy samples from multiple tissues, including the CNS including the cervical spinal cord, brainstem and olfactory nerve³⁶. However, whether this persistence reflects replicating virus remains unclear. Persistent viral RNA can stimulate the innate immune system to continue to produce antiviral cytokines and cytotoxic functions, and persistent viral antigens can continuously stimulate adaptive immune cells, resulting in elevated antibodies against SARS-CoV-2 antigens and T cell exhaustion^{37,38}. Notably, the spike protein from SARS-CoV-2 accumulates in the skull marrow, brain meninges and parenchyma as found in post-mortem tissues of individuals who recovered from COVID-19 and died of non-COVID-19-related causes³⁹. Spike protein accumulation is associated with neutrophil extracellular traps, suggesting that viral proteins could trigger inflammation within the CNS. Viral persistence may also deplete circulating serotonin levels via viral RNA-induced type I interferons, possibly affecting memory⁴⁰. In a clinical trial, ilarazotide treatment⁴¹ was associated with faster clearance of spike protein from blood samples and sooner return to usual activities as compared with placebo, which suggests a potential role as adjuvant therapy for long COVID. However, the limited number of controlled studies comparing patients with COVID-19 with and without long COVID, along with the inclusion of non-COVID-19-related post-acute infection syndromes such as chronic post-influenza conditions in studies in general, challenges the conclusive causal associations.

Herpesvirus reactivation. By adulthood, humans harbour multiple herpesviruses in a latent state⁴². SARS-CoV-2 infection reactivates these herpesviruses in a subset of individuals, although the underlying mechanisms are not well understood. Epstein-Barr virus (EBV) viraemia during acute SARS-CoV-2 infection is a risk factor for long COVID, including memory changes, and is associated with self-reported fatigue and excess sputum production⁴³. Antibodies indicative of herpesvirus reactivation have been demonstrated for varying amounts of time: anti-EBV antibodies have been demonstrated several months after long COVID onset⁴⁴ whereas anti-EBV and anti-varicella-zoster virus antibodies have been found more than a year³⁸ after long COVID onset. EBV-reactive IgG is associated with fatigue⁴⁴ and T helper 2 cell responses³⁸, and persistent complement activation⁴⁵. Interestingly, EBV reactivation and a similar pattern of immunological dysregulation have been found in patients with ME/CFS⁴⁶.

Microbiota dysbiosis. The role of microbiota in other IACCs has been suspected for decades. In support of a role in long COVID, one prospective study in patients hospitalized for COVID-19 showed significant changes in the gut microbiome of those who developed long COVID⁴⁷. Notably, bacteria that produce short-chain fatty acids (SCFAs) such as butyrate (which is associated with brain health) were depleted at the 6-month mark in those with long COVID⁴⁷ and in patients with ME/CFS⁴⁸. Similar reductions of SCFA-producing bacteria are also observed in individuals with Parkinson disease⁴⁹ or multiple sclerosis⁵⁰. Moreover, a randomized placebo-controlled double-blind phase II clinical trial of symbiotic therapy (consisting of prebiotics and probiotics) showed positive outcomes for many long COVID symptoms, including fatigue, memory loss, concentration difficulties and insomnia⁵¹.

Autoimmunity. Viral infections have long been associated with autoimmune diseases, including multiple sclerosis and systemic lupus erythematosus. In autoimmune diseases, bystander activation and molecular mimicry can stimulate autoreactive T and B cells during a viral infection. High-throughput screening for autoantibodies did not reveal a more frequent autoantibody reactivity in participants with long COVID or control individuals^{38,52}. However, the role of T cells and the patterns of tissue-reactive antibodies in mediating disease pathologies remain undetermined. Targeted autoantibody analyses have revealed a correlation between autoantibodies to CNS antigens and neurological long COVID⁵³⁻⁵⁵. In recent studies, passive transfer of purified IgG from patients with long COVID and chronic pain induced disease phenotypes, including pain and loss of balance, and caused damage to intraepidermal nerve fibres in recipient mice^{56,57}. Existing therapies that deplete B cells (monoclonal antibodies against CD20) or reduce IgG in the circulation (FcRn inhibitors) may be promising therapeutic interventions for patients with these autoantibodies. Not surprisingly, the removal of autoantibodies from the circulation via immunoadsorption (extracorporeal adsorption) in patients with post-COVID ME/CFS improved various symptoms including fatigue, pain, and cognitive and autonomic dysfunction⁵⁸.

Clotting and endothelial damage. Cerebrovascular and thrombotic events triggered by SARS-CoV-2 infection can interrupt blood flow, compromise blood-brain barrier function, and exacerbate neuroinflammation. An autopsy study including people who died shortly after an acute infection with COVID-19 revealed multifocal vascular damage, vascular leakage, platelet aggregation, microthrombi, lymphocyte infiltrates and complement activation, with all markers of vascular injury being more common in the hindbrain⁵⁹. Moreover, similar changes have been found in patients with long COVID, namely, increased platelet activation, fibrinoid microclots⁶⁰, persistent complement activation and platelet-monocyte aggregates⁴⁵ in plasma.

Chronic inflammation. Inflammatory cytokines produced systemically or within the CNS can affect neurocognitive function in several neurological disorders, including potentially long COVID. Immune-mediated neurotoxicity in long COVID involves several mediators such as IL-6, TNF, IFN γ , IL-1 β , CSCL8, CCL5, CXCL1 and CCL11 (refs. 61,62). Mice with mild acute COVID-19 infected in the lung with minimal interstitial infiltrates without evidence of alveolar damage developed a sustained elevation in inflammatory cytokines in serum and cerebrospinal fluid (CSF) at 7 weeks after infection, with an increase in white matter-reactive microglia, reduced hippocampal neurogenesis, oligodendrocyte loss in subcortical white matter (cingulum of the corpus callosum) and reduced myelination⁶³. Moreover, CCL11, which is linked to age-dependent neurocognitive decline⁶⁴, was elevated in CSF, and injection of this chemokine alone recapitulated the microglial reactivity in the hippocampus. MRI analysis also demonstrated a widespread elevation in the mean diffusivity and extracellular free water in the white matter of individuals after SARS-CoV-2 infection compared with matched control individuals who were sampled from the same cohort prior to the pandemic, suggesting activated immune responses⁶⁵. Ultra-high field (7 T) quantitative susceptibility mapping of the brain in survivors of acute COVID-19 after hospitalization, found increased susceptibility in the inferior medullary reticular formation and the raphe pallidus and obscurus. In these regions, patients who had higher tissue susceptibility had worse acute disease severity, higher acute inflammatory markers and significantly worse functional recovery after acute infection⁶⁶.

Effects of SARS-CoV-2 in the brain

SARS-CoV-2 has effects on multiple components of the CNS and peripheral nervous system including glia, endothelium, axons and neural networks, which translate to post-acute and chronic neurological and psychological clinical manifestations of long COVID.

Glia. SARS-CoV-2 causes alterations to neuron–glia homeostasis through different pathophysiological mechanisms in mice and humans^{63,67–69}, including microgliosis⁶⁷, astrocyte infection^{69–71}, astrogliosis⁶⁸, a decrease in oligodendrocytes⁶³, axonal injury, promotion of cell fusion (including fusion between neurons and glia)⁶⁸, and abnormal neuron–glia communication⁷². Dysfunctional astrocytes can compromise blood–brain barrier integrity⁷³, impair neuronal metabolism and decrease neuronal viability^{69,70}, and reactive microglia can reduce oligodendrocyte numbers and myelination⁶³. Collectively, these processes lead to reduced hippocampal neurogenesis^{63,67}, reduced neuronal function and abnormal axonal transmission^{63,72}, impairing overall brain function and cognition⁶⁷ in mouse models.

Moreover, SARS-CoV-2 triggers a chronic neuroinflammatory process associated with elevated levels of chemokines in the CSF (including CCL11) and white matter-reactive microglia in mice and humans⁶³. In accordance with these data, individuals who had COVID-19 (who mostly did not require hospitalization) who had persistent cognitive impairment exhibited increased levels of CCL11 in the CSF⁶³ compared with those without cognitive impairment. Moreover, infusion of the SARS-CoV-2 spike protein into the brain of mice induced reversible cognitive dysfunction resembling human long COVID⁶⁷. In this study memory impairment was related to late hippocampal microgliosis and synaptic phagocytosis mediated by activation of Toll-like receptor 4 (TLR4). The complementary genotyping analysis of individuals who were mildly infected by SARS-CoV-2 revealed an association between homozygous genotype GG TLR4-2604G>A (rs10759931) and a higher risk of developing cognitive dysfunction after COVID-19 (ref. 67).

Endothelium. Neurovascular complications and coagulopathies in SARS-CoV-2 infection are associated with an increased risk of stroke during the acute infection^{74–76} and for up to 12 months after the acute period⁷⁷. Abnormal coagulation has also been implicated in the pathophysiology of long COVID⁷⁸. Different mechanisms can contribute to dysregulated coagulation, including viral persistence, endothelial injury, persistent inflammation, chronic hypoxia and autoimmunity⁶⁰. These factors may perpetuate endotheliopathy with microvascular injury and blood–brain barrier breakdown^{60,79}. In support of a role for endothelial injury in long COVID, individuals with long COVID have higher levels of fibrin amyloid (fibrinaloids) microclots, platelet dysfunction⁸⁰, altered levels of markers of haemolysis (decreased haemopexin, ICAM1 and S100-A8/A9, as well as increased thrombospondin 1 and von Willebrand factor), endothelial activation, persistent complement dysfunction, and monocyte–platelet aggregates compared with healthy controls⁴⁵. SARS-CoV-2 triggers the formation of fibrinaloid microclots, which are resistant to fibrinolysis, that can block capillaries and cause tissue hypoxia⁶⁰, compromising tissue function during both the acute infection and chronically. Although the whole brain is highly susceptible to hypoxaemia due to high metabolic demand⁷⁹, some regions, such as the hippocampi, are more critically affected by hypoxaemia than other regions⁷⁸, which could explain the chronic memory impairment that occurs with long COVID.

Axonal conduction, neural networks, plasticity and learning.

SARS-CoV-2 can also interfere with axonal conduction, neuronal networks and plasticity. Axonal conduction can be directly impaired by SARS-CoV-2 neurotropism and the suggested retrograde transport of viral particles^{81,82}, as supported by the high levels of neurofilaments found in patients with COVID-19, which reflects axonal damage⁸³. Also, astrocyte infection through spike protein and neuropilin 1 interaction^{69,84} can lead to impaired neuronal metabolism and altered biogenesis of neurotransmitters as astrocytes respond to the acute infection by remodelling energy metabolism, further impairing axonal conduction and reducing neural viability⁶⁹. Endothelial damage can also slow axonal conduction due to hypoxia, especially within the cerebellar cortex, which is highly vulnerable to hypoxia⁸⁵.

Effects of SARS-CoV-2 on axonal conduction can also be found in the peripheral nervous system, as cases of GBS were reported during the initial outbreak, causing disease with a predominant axonal phenotype, involvement of cranial nerves and severe autonomic changes^{86,87}.

SARS-CoV-2 can also disrupt brain networks by inducing changes in the grey matter^{69,88} and white matter^{89,90}. Cortical atrophy was identified in patients with COVID-19 who did not need hospitalization, but who also showed cognitive impairment^{69,88}, fatigue and anxiety⁶⁹. Moreover, white matter analyses revealed connectivity changes⁸⁹ in a subnetwork comprising the parietal sensory cortex, amygdala and pallidum⁹⁰, in addition to reduced integration and increased segregation within olfactory-related brain areas in cohorts of individuals with persistent olfactory dysfunction following COVID-19 (refs. 90,91). SARS-CoV-2 infection also reduces brainstem reflexes in patients with severe pneumonia^{92,93}.

Patients with long COVID and cognitive impairment show reduced GABA_Aergic and cholinergic transmission and glutamatergic excitability in the primary motor cortex, thus dampening long-term potentiation (LTP)-like cortical plasticity^{94–96}. These changes may ultimately lead to the development of brain fog with impaired cognitive processing speed, long-term visuospatial and verbal memory abnormalities persisting in some individuals for more than 1 year^{97,98}. These changes in plasticity may also be caused by glial involvement (see above), as microglia have been implicated in regulation of LTP-like plasticity^{99,100}.

Open issues: can SARS-CoV-2 prime neurodegeneration?

The anatomical pathways involved in SARS-CoV-2 invasion parallel the prion-like model of α -synuclein spreading, including the olfactory bulb¹⁰¹ and the brainstem nuclei^{81,82,102}. Accordingly, SARS-CoV-2 antigens can be detected in the dorsal medulla and the substantia nigra in humans, in both dopaminergic and non-dopaminergic neurons¹⁰³. However, evidence of neuroinvasion remains limited and debated¹⁰⁴. Moreover, microglia activation in the brainstem shows an anatomically segregated pattern of neuroinflammation, with a ventral-to-dorsal gradient and more severe microgliosis close to the locus coeruleus¹⁰³. With this finding, it is also noteworthy that dysfunction of the locus coeruleus–noradrenaline pathway has been suggested to prime the onset of Alzheimer disease onset¹⁰⁵. Additionally, patients with COVID-19 have upregulation of genes involved in the innate antiviral response, neuroinflammation, microglial activation and neurodegeneration¹⁰⁶.

In addition to viral neurotropism, microglia activation and gene expression, the proposed cortical excitability changes induced by SARS-CoV-2 infection closely resemble those associated with Parkinson disease and correlate with cognitive impairment⁹⁴. Overall, these findings may lead to COVID-19 being considered a ‘perfect storm’ for neurodegeneration^{107,108}. In support of this scenario, individuals

with de novo Parkinson disease following SARS-CoV-2 infection have been reported, with a tremor-dominant phenotype and a satisfactory response to dopaminergic treatment¹⁰⁹. In parallel, amyloid deposition has been found in patients 1 year after SARS-CoV-2 infection¹¹⁰, supporting the theory that spike and nucleocapsid protein can drive α -synuclein aggregation and fast amyloid fibril formation¹¹¹.

Despite the global effort to clarify COVID-19 pathophysiology, some issues remain unclear. For example, differences in the effects of pre-Omicron variants and post-Omicron variants on long COVID are still controversial. Direct neurotropism has been attributed to pre-Omicron variants, whereas pro-inflammatory changes have been associated with neurological manifestations during subsequent outbreaks^{81,82,102,105}. Accordingly, neurological phenotypes have progressively changed, also as a result of a less severe primary disease. For instance, the manifestations of GBS secondary to SARS-CoV-2 infection increasingly resemble those associated with other infections (such as isolated bulbar palsy after acute infection)⁸⁷.

Diagnosis, screening and prevention

Diagnosis

Chronic post-viral syndromes similar to long COVID have been described for decades (for example, ME/CFS). The timing and visibility of COVID-19 may have facilitated long COVID recognition compared with the recognition of other post-viral syndromes (such as ME/CFS caused by other infections). Long COVID is a clinical diagnosis that relies on a recent history of confirmed or suspected SARS-CoV-2 infection that was followed by persistent or relapsing COVID-19-attributed symptoms.

The duration of symptoms required for diagnosis of long COVID remains controversial. The US Centers for Disease Control considers symptoms lasting beyond 3 months to represent long COVID¹¹², whereas the WHO states that symptoms should be present for 3 months following the initial illness, with symptoms present for at least 2 months¹¹³. An updated definition of long COVID by the NASEM requires symptoms for at least 3 months after the initial infection which are relapsing and remitting, or progressive, and affect one or more organ systems^{114,115}. Of these different definitions, the NASEM definition was the most comprehensively derived and is the product of a multiphase process of systematic data gathering and formal review by a large committee of scientists who engaged over 1,300 participants including patients, caregivers, public health and healthcare professionals, researchers, and policy and advocacy professionals. This NASEM definition, published in 2024, is the most up-to-date clinical definition of this disease state and a template from which investigators can derive a research definition that best fits their given study objectives.

Long COVID is a heterogeneous condition³³. As the condition is newly identified, it is not possible to require or exclude any symptom from those included in the diagnosis. Fundamental to making the diagnosis is the elimination of other causes¹¹⁶. This process may require measurement of common blood analytes (such as electrolytes, blood counts, and hepatic and renal function), inflammatory markers (such as C-reactive protein, erythrocyte sedimentation rate and ferritin), and symptom-specific testing to rule out differential diagnoses (such as thyroid disease, vitamin deficiencies and autoimmune disease) or contributing illnesses (such as diabetes mellitus). However, in general, individuals with long COVID have blood test results that are largely within the normal range. Additional physiological testing (such as electrocardiography, echocardiography and imaging) is recommended to rule out life-threatening aetiologies that might be associated with long COVID symptoms (such as arrhythmia and heart failure), but results

from these tests are often normal. Given the broad range of symptoms and the overlap with other common illnesses, diagnosing long COVID remains challenging for clinicians and can often be frustrating for patients. Self advocacy and health literacy may have an important role in diagnosis^{117,118}. The diagnosis remains highly individualized and there is no common set of measurements that can be easily implemented for diagnosis. Several groups have attempted to aid long COVID diagnosis by better defining symptoms, organ involvement and subphenotypes.

Phenotypes of long COVID

Although many clinicians favour classifying long COVID based on patients' clinical presentation (such as fatigue-predominant or neurocognitive-predominant), approaches such as machine learning can be used to more objectively associate symptoms into subphenotypes of long COVID^{119–124}. For example, one analysis suggested three phenotypes of long COVID based on symptom severity, with the most severe cluster associated with nicotine use, higher BMI, diabetes mellitus, chronic pain and symptom severity at COVID-19 onset¹²³. Other studies have identified three or four subphenotypes based on symptom clusters, or four subphenotypes based specifically on fatigue-related symptoms^{119,120,122,124}. A longitudinal analysis of patients with long COVID found seven subphenotypes based on symptoms and their temporal attributes¹²¹. Finally, large-scale phenotyping of patients with long COVID revealed mechanistic subphenotypes, largely based on inflammatory pathways¹²⁵. If replicated, these proposed subphenotypes could guide earlier diagnosis, disease stratification, resource mobilization and future therapeutic trials. For now, however, classification remains largely based on clinician assessment.

Future biomarkers

Biomarkers might aid future diagnoses of long COVID. Some blood biomarkers that have been suggested for the diagnosis of long COVID are immune cells, immunoglobulins, cytokines, chemokines, complement proteins, vascular endothelial proteins, the acute phase response and coagulation pathway mediators, and/or metabolites^{126,127}. A potential advantage of blood biomarkers is that they may reflect specific organ involvement and the time course of the illness. Several promising blood biomarkers have been validated in large population cohorts^{38,40,128,129}.

Cellular changes could provide future diagnostic value. For example, higher levels of circulating endothelial cells can be found in the blood of patients with long COVID, as these cells are shed during vascular injury and/or transformation¹³⁰. Moreover, immune cells undergo several changes in long COVID, such as alterations in circulating myeloid and lymphocyte populations, some of which are associated with exaggerated humoral responses to SARS-CoV-2 infection³⁸. T cells are also altered, with increased CD4⁺ T cells and exhausted CD8⁺ T cells³⁷. Natural killer cells transition from an active state in COVID-19 to a resting state in long COVID, with the latter associated with constitutive cytokine release¹³¹. However, these cell-based assays are not easily available and have not been tested in large populations, limiting their diagnostic utility.

Physiological assays of long COVID include assessment of arterial stiffness measured with non-invasive pulse wave velocity^{132,133}, endothelial dysfunction measured with flow-mediated dilation¹³⁴, and non-invasive measures of tidal breathing parameters with plethysmography¹³⁵. Chest imaging with CT has identified dozens of different findings, categorized into interstitial or fibrotic, or pleural airway and other parenchymal abnormalities¹³⁶, while pulmonary vascular density is chronically reduced¹³⁷. PET-CT has revealed cerebral

and brainstem hypometabolism^{138,139} and MRI has demonstrated abnormalities in the frontal, subcortical and thalamic regions, as well as the basal ganglia, in patients with long COVID compared with healthy controls^{140,141}.

Although blood biomarkers, physiological measurements and imaging hold promise for aiding the diagnosis and characterization of long COVID, these techniques lack standardized protocols and require longitudinal studies to understand the dynamic nature of biomarker changes over time.

Future diagnosis

The synchronicity of the inciting infection, when millions of people worldwide had COVID-19 and testing was widely available, contributed to the rapid recognition of long COVID as an emerging post-acute condition. However, diagnosis of long COVID may be more difficult in the future, as the rate of testing for SARS-CoV-2 infection has decreased dramatically and clinicians are still without disease-specific biomarkers. The most important aspect of diagnosis will be tying unexplained symptoms to acute COVID-19. To do this, measuring blood antibodies or cellular immune responses to the nucleocapsid protein could indicate a recent SARS-CoV-2 infection¹⁴², even in vaccinated individuals. However, the use of these tests, especially antibody assays, remains controversial owing to rapid waning of antibodies in many individuals¹⁴³. As previously mentioned, viral persistence may underlie long COVID³⁶, suggesting that testing for SARS-CoV-2 RNA or antigens may hold promise for future diagnosis. Although tissue-based testing is unlikely to be feasible at scale, blood biomarkers are under development, but their interpretation and clinical utility are still unknown¹⁴⁴.

Screening

Published recommendations and guidelines for long COVID screening are available; however, their development was practical rather than evidence-based^{2,145}. Evidence-based recommendations from the European Society of Clinical Microbiology and Infectious Diseases group recommends considering routine blood tests, chest imaging (chest plain radiography or chest CT) and pulmonary function tests for patients with persistent respiratory symptoms at 3 months¹⁴⁶.

Table 1 | Comprehensive guidelines for the management of long COVID symptoms

No.	Name	Ref.
1	World Health Organization (WHO). Clinical management of COVID-19: living guideline, 18 August 2023	113
2	National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. NICE guideline NG188	2
3	Cochrane Rehabilitation. Rehabilitation and COVID-19: systematic review by Cochrane Rehabilitation	208
4	Global COVID-19 Neuro Research Coalition. Evaluation and treatment approaches for neurological post-acute sequelae of COVID-19: a consensus statement and scoping review from the Global COVID-19 Neuro Research Coalition	209
5	American Academy of Physical Medicine and Rehabilitation (AAPM&R). Long COVID guidance statements: mental health, neurological symptoms, cognitive symptoms, fatigue	210
6	National Academies of Sciences, Engineering, and Medicine (NAEM). A long COVID definition: a chronic systemic disease state with profound consequences	114

Unfortunately, these recommendations do not address long COVID subphenotypes as individuals with different subphenotypes can present with different combinations of symptoms and organ involvement. A straightforward symptom screen using validated measures tailored to the symptoms the patient is presenting with administered by a knowledgeable provider a few months following COVID-19 is the most reasonable screening approach.

Prevention

Avoiding SARS-CoV-2 infection is the only way to prevent long COVID. Although public health precautions such as widespread accessible testing and isolation requirements have largely ended, structural changes such as improving ventilation and air filtration could still be beneficial in reducing SARS-CoV-2 infection^{147,148}. On an individual level, wearing a face mask (surgical or N95) to protect against infection might prevent acquisition of SARS-CoV-2 infection and thus resultant long COVID¹⁴⁹.

Growing evidence suggests that long COVID is more likely to develop in individuals who experienced more severe COVID-19, those with repeated infections¹⁵⁰, those who had underlying comorbidities prior to COVID-19, and those who were unvaccinated at the time of SARS-CoV-2 infection^{7,151}. More recently, some studies have demonstrated a benefit of early antiviral treatment^{152,153}; however, other studies did not find this benefit^{154,155}, and no randomized trials have focused specifically on long COVID prevention. Despite this lack of direct supporting data, COVID-19 vaccination may be important in mitigating the risk of long COVID^{14,156–158}.

Management

Given that COVID-19 and its long-term sequelae are multisystem and multi-organ ailments, their management must be multidisciplinary, with involvement of all specialists dealing with the presenting symptoms and affected end-organs. The main end-organs suffering from impaired function, especially in the initial phase, are within the respiratory and cardiovascular systems. Some of these symptoms may be moderated through the elements of the nervous system, such as the autonomic system, examples being orthostatic intolerance or dyspnoea (in some cases). However, owing to the complex interplay of potential causes, which may include genuine cardiac, vascular and/or lung problems, the diagnostic work-up and management of these symptoms are typically carried out within cardiology, vascular and respiratory medicine services. Similar is the case with chronic pain, which, despite potentially involving the peripheral nervous system, is typically managed within specialized pain services. In such conditions, mental health and neurorehabilitation professionals, as well as neurologists, typically have a consulting role when required. Hence, here we focus on symptoms that predominantly or almost exclusively belong to the brain and behaviour domain, such as fatigue, cognitive impairments and mood problems.

Despite epidemiological data on the high prevalence of long COVID as well as the health and societal burden it causes, there are not enough studies to provide good evidence-based support for the practical management of this disorder. Concerns have already been raised in the scientific community regarding this issue¹⁵⁹. Although several quite extensive and authoritative guidelines for managing long COVID have been published (Table 1), they were developed mainly from expert opinion and consensus statements based on the treatment of other neurological and mental health conditions with similar symptoms.

Table 2 | Summary of selected recently completed registered clinical trials for pharmacological management of long COVID

NCT number	Intervention	Study design	Main results	Ref.
NCT05618587	Lithium aspartate	RCT in 52 patients; dose-finding study in 3 patients	Lithium aspartate for 3 weeks led to no significant improvements in fatigue or cognitive dysfunction scores; in the dose-finding study, open-label lithium aspartate at a higher dose was associated with greater reductions in fatigue and cognitive dysfunction scores than a lower dose	211
NCT05047952	Vortioxetine	Post-hoc analysis of RCT in 200 patients; 147 patients randomized 1:1 to daily treatment with either vortioxetine or placebo	Significant effects on cognitive function were found in the treatment group for the time, treatment, and treatment × time × CRP × TG–HDL × BMI interaction	212
NCT04871815	Sodium pyruvate nasal spray	2-week study in 22 individuals with long COVID	Treatment with sodium pyruvate nasal spray reduced severity of headaches, coughing/sneezing, increased oxygen saturation levels, and improved breathing	213
NCT04997395	MediCabilis Cannabis sativa 50	Single-arm open-label feasibility trial of the safety and tolerability of MediCabilis CBD oil; 12 participants (11 women, 1 man) treated orally for 21 weeks	Participants adhered to the treatment protocol, reported no serious adverse events and completed 90% of patient-reported outcomes and daily self-reports	214
NCT05152849	AXA1125	Single-centre (UK) double-blind, randomized controlled phase IIa pilot study; 60 participants screened and 41 randomized 1:1 to either AXA1125 (n=21) or placebo (n=20)	Changes in skeletal muscle phosphocreatine recovery time constant and 6MWT did not significantly differ between the treatment and placebo groups; treatment with AXA1125 was associated with significantly reduced Chalder Fatigue Questionnaire fatigue score on day 28 compared with placebo	215
NCT04604704	Low-dose naltrexone and supplementation with NAD ⁺ iontophoresis patches	Pilot study evaluating fatigue symptoms and quality of life in 36 patients with persistent moderate–severe fatigue after COVID-19	Study detected a significant increase from baseline in SF-36 survey scores after 12 weeks of treatment, suggesting improvement in quality of life; participants scored significantly lower on the Chalder fatigue scale after 12 weeks of treatment	216
NCT05576662	Oral NMV–r versus PBO–r	102 patients randomized 2:1 to treatment with oral NMV–r or with PBO–r for 15 days	A 15-day course of NMV–r in a population of patients with PASC was considered safe but did not offer a significant benefit for improving PASC symptoms (fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, and cardiovascular symptoms) at 10 weeks in a mostly vaccinated cohort with prolonged symptom duration	217
NCT05472090	TNX-102 SL	–	Not published	NA
NCT05592418	Ampligen	–	Not published	NA
NCT04944121	RSLV-132	–	Not published	NA
NCT05633407	Efgartigimod	–	Not published	NA

The trials listed represent a subset of registered clinical trials. 6MWT, six minute walk test; CBD, cannabidiol; CRP, C-reactive protein; NA, not applicable; NMV-r, nirmatrelvir–ritonavir; PASC, post-acute sequelae of SARS-CoV-2 infection; PBO-r, placebo–ritonavir; RCT, randomized controlled trial; SF-36, 36-item Short Form Health Survey; TG–HDL, triglyceride to HDL ratio.

Generally, owing to the variability in the clinical presentation of the neurological and neuropsychiatric manifestations of long COVID, management approaches must be tailored to focus on the presenting symptoms in each patient. Although many of the most common symptoms of long COVID are subjective, an objective diagnosis should be made based on the most recent clinical definitions and guidelines.

Pharmacological management

Studies of new treatments for long COVID should focus on particular organ systems and specific symptoms of long COVID¹⁶⁰. Although many studies are ongoing, only a few have been completed (Supplementary Table 1); therefore, there is little evidence for definite recommendations, and more clinical trials are still needed. Most studies focusing on neurological manifestations of long COVID have investigated the treatment cognitive impairments, including brain fog and fatigue although, few studies have been completed (Table 2 and Supplementary Table 1).

There are many systematic and other reviews as well as guidelines published for assessing the efficacy of different approaches to the treatment of long COVID symptoms. Despite all these studies, only a few potential treatment options for long COVID are available with some evidence base^{160–162}.

All guidelines for long COVID recommend that specific symptoms are referred to a specialist for treatment according to management guidelines for that condition. For example, stroke should be managed by a stroke specialist during the acute and chronic stages and for secondary prevention. Similarly, brain fog and other cognitive disorders, headaches and sleep disorders should be treated according to relevant guidelines and specialist advice^{160–162}. Specific recommendations are not available for fatigue and myalgia.

Gender and ethnic differences are not well represented in the approach to long COVID characteristics and management; however, there is some emerging evidence that Black and Hispanic individuals when compared with white and non-Hispanic individuals report less

access to testing^{163,164}. Although there are planned studies on this subject, larger, and socially more inclusive and diverse studies are needed.

Non-pharmacological management

Some manifestations of long COVID (such as fatigue, PEM, cognitive impairment, anxiety and depression) are treated via non-pharmacological approaches. The most promising non-pharmacological approaches include psychological therapies with behavioural interventions, physiotherapy with occupational therapy, and non-invasive brain stimulation (NIBS).

Fatigue and post-exertional malaise. Fatigue and PEM are the most frequently reported long COVID symptoms³³. Although these symptoms often occur together, they are separate phenomena that require specific management approaches. Fatigue is the subjective sensation of lack of physical and/or mental energy not related to or in disproportion with previous and/or ongoing levels of activity, whereas PEM is the worsening of long COVID symptoms after physical and/or cognitive exertion, including overexertion¹⁶⁵. Although the exact biological mechanisms underlying PEM are unclear, some studies have suggested that with physical activity, systemic oxygen extraction and oxidative phosphorylation capacities are exceeded, mediated by dysfunction in mitochondria and microcirculation, which is maintained by latent immune activation¹⁶⁶. Impaired metabolism leads to the accumulation of lactate, reactive oxygen species or prostaglandins following physical exertion, which further potentiate systemic immune activation¹⁶⁶.

For rehabilitation management of PEM in adults with long COVID, education and skills training on energy conservation techniques, such as pacing, are important. Pacing is an activity and energy management technique consisting of balancing activities and rests contingent on symptoms¹⁶⁷. However, interventions for rehabilitation based on fixed incremental increases in the time spent being physically active or graded exercise, which is often suggested to people with ME/CFS, should not be offered to people experiencing PEM, or if used it should be overseen by a specialist ME/CFS physiotherapist and include regular review¹⁶⁸. An evaluation by a physical medicine and rehabilitation physician or an occupational or physical therapist in the provision and training in the use of assistive products and environmental modifications (for example, a bath grab bar, raised toilet seat, etc.) may also be useful for people experiencing moderate to severe PEM.

For both fatigue and PEM, behavioural management techniques (rest breaks, cognitive behavioural therapy (CBT) and mindfulness-based stress reduction programmes), as well as educational and self-management programmes (such as relaxation, avoiding multitasking and improved sleep hygiene), are recommended by the major guidelines (Table 1). In addition, physical activity programmes (such as aerobic exercise, strengthening exercises, hydrotherapy, yoga and tai chi) are also of considerable importance for in the management of fatigue.

However, almost all the recommendations in existing guidelines are based on expert consensus and other conditions with similar symptoms to long COVID. Randomized clinical trials involving people with long COVID are scarce. A reasonably sized study ($n = 114$) involving people with severe post-COVID-19 fatigue found a significant benefit of CBT compared with routine care¹⁶⁹. Interestingly, two reasonably sized randomized placebo-controlled studies found beneficial effects of transcranial direct current stimulation (tDCS), a form of NIBS, on post-COVID-19 fatigue. In one study including 47 patients (23 in the active treatment group and 24 in the sham treatment group), tDCS of

the left dorsolateral prefrontal cortex¹⁷⁰ improved subjective measures of fatigue, and in another study including 70 patients with long-COVID-related fatigue, high-density tDCS of the left motor cortex improved subjective measures of fatigue, anxiety and quality of life¹⁷¹.

Other alternative medical regimens have been studied for the management of fatigue, although they have limited supporting evidence. Hyperbaric oxygen therapy led to improved subjective symptoms of fatigue in a small case series¹⁷². Moreover, a randomized trial investigating 2 weeks of aromatherapy (including thyme, orange, clove bud and frankincense) also showed benefit in improving energy levels in a small group of female patients compared with placebo¹⁷³.

Psychological sequelae. Mental health issues are also often reported in patients with long COVID. The guidelines for the treatment of post-COVID-19 mental health problems typically suggest psychological support, mindfulness training, CBT, peer support groups and physical exercise training (Table 1). However, as is the case for pharmacological management, these recommendations are based on the treatment of similar mental health disorders. A strong evidence base is still lacking, with only a handful of studies exploring effectiveness in long COVID.

Several behavioural and psychological interventions have been assessed in individuals with long COVID. For example, 8 weeks of a self-guided online grief-specific CBT intervention significantly lowered symptom levels in people with persistent post-COVID-19 complex bereavement disorder (a condition characterized by persistent and intense grief symptoms associated with significant distress and disturbance of daily functioning following the death of loved one to COVID-19), PTSD, and/or depression compared with people on a waiting list for routine evaluation¹⁷⁴. In addition, in a small study that included people with post-COVID-19 cognitive symptoms, a 4-week neuromeditation programme, including sound and light therapy and coach-guided meditation, significantly improved symptoms of anxiety, depression and sleep disruption compared with no treatment¹⁷⁵. Moreover, another moderately powered study in people with post-COVID-19 chronic fatigue found that tDCS of the left dorsolateral prefrontal cortex significantly reduced depression scores measured using the Beck Depression Inventory in comparison with a sham stimulation procedure¹⁷⁰.

Brain fog and cognitive impairments. Similar to other symptoms of long COVID, current guidelines for the management of brain fog and other cognitive symptoms are also based on expert consensus and derived from experience with other conditions. For example, post-COVID guidelines from the WHO provide a conditional recommendation for combining education, skills training on self-management strategies and cognitive exercises¹⁷⁶. Generally, the so-called cognitive remediation approaches, which include cognitive training, cognitive rehabilitation and cognitive stimulation, are recommended. These approaches are effective in reducing cognitive decline in people with normal ageing, in people with mild cognitive impairment^{177,178} and people with several neuropsychiatric conditions¹⁷⁹.

In addition, a moderately sized case-control proof-of-concept study showed a beneficial effect of a 2-month cognitive remediation therapy programme on global cognitive functioning, verbal fluency and executive functions, in individuals with post-COVID-19 cognitive impairments at 1 month after hospital discharge¹⁸⁰. Moreover, a small randomized, placebo-controlled study found beneficial effects of a 4-week neuromeditation programme, including sound and light therapy and coach-guided meditation, on both subjective cognitive

symptoms and performance on computerized cognitive tasks in people with post-COVID cognitive symptoms¹⁷⁵. In addition, a randomized, sham-controlled, double-blind trial, showed significant beneficial effects of 40 daily sessions of hyperbaric oxygen therapy on global cognitive functioning, attention and executive functions, in patients with post-COVID-19 cognitive symptoms for at least 3 months after confirmed infection¹⁸¹. Interestingly, energy level and sleep were also improved in this study. Despite these studies, whether benefits of cognitive remediation approaches transfer to everyday living is unknown^{182,183}, making their potential benefit for people with long COVID uncertain.

Quality of life

Long COVID is predominantly a multisymptom and multisystem health condition with varying disease patterns and durations^{29,184}. In some patients, symptoms are constant with some worsening or steadily improving, but in many patients symptoms fluctuate or have a relapsing–remitting pattern²⁹, often triggered by physical exertion, cognitive effort, stress, social activities or work¹⁸⁵. Patients often gradually become familiar with the triggers that cause symptom worsening, but the triggers are unknown in some individuals. This has serious implications for patients' quality of life¹⁸⁶ (Fig. 3), accessibility and ability to work and care for self and others¹⁸⁷, particularly with the lack of work flexibility that tends to be more pronounced in under-privileged groups.

Effects of long COVID on employment

Long COVID is associated with unemployment or part-time employment^{188,189}, and can have a negative impact on labour markets^{190,191}. The effects of long COVID on work can be long-lasting, leading to loss of job and income¹⁹². Moreover, upon returning to work, people with long COVID can face difficulties from employers and lack of support from welfare systems⁹. The episodic nature of disability, which includes 'ups and downs', 'crashes', 'troughs' and 'valleys'¹⁹³, can result in people returning to work but then feeling unable to continue with the same activity level, potentially leaving them in a gradually worsening condition and relationship with their employer.

Inequalities in long COVID can also exacerbate and be exacerbated by adverse effects on employment. Long COVID occurs more commonly in those who are socioeconomically disadvantaged¹⁹⁴. Moreover, some evidence suggests reduced likelihood of recovery in women with the lowest education and greatest deprivation levels¹⁹⁵. Some studies have found that long COVID is more prevalent in individuals from minority ethnic groups and those with migrant backgrounds in Western countries^{163,196,197}. The prevalence of long COVID also varies by type of occupation with those with 'frontline' jobs (such as healthcare, social care, transport and education) having a greater risk of long COVID^{189,194}. Some evidence shows that the risk of long COVID is significantly higher in those with underlying pre-existing long-term conditions¹⁸⁹. These differences can result in intersectional disadvantages in disease management and progression. Indeed, in London, individuals from minority ethnic groups and with multimorbidity have been found to be less likely to receive care and support for long COVID¹⁹⁸.

Whether individuals with long COVID are aware that they have long COVID is driven by several factors shaped by socioeconomic inequalities such as health and health system literacy, self-efficacy, stigma and existing structural discrimination. In a national general practice patient survey in England with a sample size of over 750,000 people aged 16 years and older, 4.8% of surveyed individuals reported

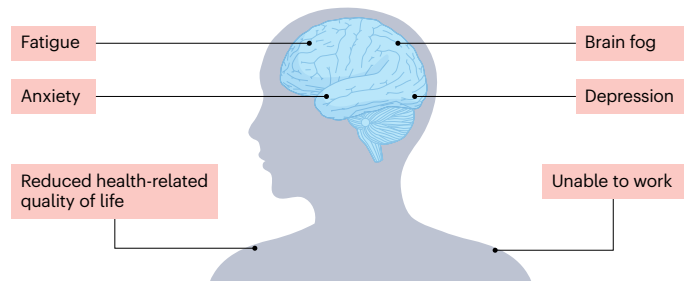


Fig. 3 | Change in functional, cognitive and emotional behaviour with long COVID. Patients with neurological and psychological symptoms of long COVID experience a variety of symptoms affecting their cognitive, psychological and functional abilities, which may lead to profound effects on quality of life.

having long COVID, whereas 9.1% said they were unsure if they had long COVID¹⁹⁹. Individuals aged ≤ 25 years, male individuals, and people from some minority ethnic groups, including Asian, Black or Arab backgrounds, were more likely to be unsure about having long COVID than the referent group for that demographic category.

Health-related quality of life

Health-related quality-of-life (HRQoL) is adversely affected by long COVID. Indeed, one analysis of over 7,000 individuals using the EuroQol EQ-5D questionnaire found higher odds of reporting a loss in quality-of-life in those with long COVID, with disability being the largest predictor of loss in HRQoL²⁰⁰. Other common tools used to assess the effects of COVID-19 and long COVID on HRQoL include SF-36, and generic and system-specific tools (such as pulmonary disease-specific tools)²⁰¹.

Stigma

The burden of long COVID and its effect on quality of life are compounded by multiple barriers that those with lived experience face to access recognition, care and support^{117,184,202}. High levels of multiple types of stigma are associated with long COVID, including enacted stigma (perceived experiences of discrimination), anticipated stigma (expectations of poor treatment) and internalized stigma (self-stereotyping, shaming or blaming)^{117,203}. Struggling with long COVID stigma is also apparent in children and adolescents, in whom they can have serious implications for social and educational interactions, care and support²⁰⁴. Experiencing stigma while struggling with and seeking help for long COVID can have adverse mental health outcomes that may compound the experiences of neuropsychiatric symptoms as part of the complex multisystem nature of long COVID²⁰⁵.

Experiences of long COVID-associated stigma are strong in people from minority ethnic groups in Western countries and are tied to limited public and professional awareness as well as intersectional stereotyping^{206,207}. Those experiencing neuropsychiatric symptoms may hesitate to seek help due to fear of mental health labelling without addressing the multisystem nature of long COVID. Better awareness and training is needed among healthcare and community support professionals, as well as employers, about the stigma associated with reporting symptoms and seeking help for long COVID¹¹⁸.

Outlook

The next steps in advancing clinical care and research innovation for the neurological and psychological manifestations of long COVID require improving several key domains: standardization of definitions and

assessments, greater understanding of the pathophysiology underlying the disorder, and a greater number of high-quality randomized controlled trials of potential therapeutics. To make significant advances in understanding long COVID, further work must be undertaken to standardize definitions and nomenclature used to define the disorder. Using consistent terminology will also improve the recognition of long COVID across clinical and research domains. Standardized objective assessments to evaluate long COVID symptomatology should be further refined and disseminated. In addition, to further progress our understanding of the putative neurobiological mechanisms underlying long COVID, future mechanistic studies must focus on replication of findings and refinement of conceptual models.

Effective therapies are desperately needed to improve mental health, neurological symptoms and overall quality of life in those with long COVID. Additional high-quality randomized controlled trials that evaluate therapeutics, especially those with a focus on repurposing and testing novel agents, may have promise. Future trials should focus on enrolling a diverse and representative patient population with consideration of the perspectives of people with long COVID and consideration of the role of social determinants of health in patient experiences and outcomes.

Published online: 24 December 2025

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Acknowledgements

J.E.W. and E.W.E. are supported by NIA 1R01AG085873 and by the Department of Veterans Affairs Geriatric Research, Education and Clinical Center. M.J.P. is supported on K23A1157875 and 1R01NS136197. E.W.E. is supported by the National Institute on Aging (NIA) R01AG058639, NIA 1R01AG085873 and VA Merit 1RX002992. A.I. is supported by the Else Kröner Fresenius Prize for Medical Research 2023, grants from National Institute of Allergy and Infectious Disease (NIAID) R01AI157488, the Howard Hughes Medical Institute Collaborative COVID-19 Initiative, the Howard Hughes Medical Institute Emerging Pathogens Initiative, and the Howard Hughes Medical Institute. C.L.Y. is supported by The Brazilian National Council for Scientific and Technological Development (CNPQ 403307/2021-0, 445340/2024-0, 315953/2021-7). D.D.F. is supported by the Canadian Institutes for Health Research (grant no. 185352, Long COVID Web) and the Schmidt Initiative for Long Covid (SILC-2023-006, LC-Optimize and SILC-2024-004, LC-Revitalize, NCT06928272).

Author contributions

All authors contributed to all sections of the manuscript.

Competing interests

J.E.W. received research support from the Department of Veterans Affairs Office of Rural Health, Ac-Immune, IONIS therapeutics, Bristol Meyers Squibb and Ono therapeutics outside the submitted work. M.J.P. received consulting fees from Gilead Sciences, AstraZeneca, BioVie, Apellis Pharmaceuticals and BioNTech, and research support from Aerium

Therapeutics and Shionogi, outside the submitted work. R.H. received grant funding from Fresenius Kabi Germany and Austrian Science Fund; and has received payments or honoraria from BD, Integra, Neuroptics and Zoll, not related to the submitted work. N.A.A. is a Long Covid Kids Charity Champion, is a scientific adviser to the Long Covid Support Charity, and has contributed in an advisory capacity to WHO and the EU Commission's Expert Panel on effective ways of investing in health meetings in relation to post-COVID-19 conditions. E.W.E. has NIH funding for an ongoing clinical trial of immunomodulation in long COVID for which the JAK-STAT medical intervention is donated by Eli Lilly; E.W.E. has no financial relationship with Eli Lilly and has no stocks or paid consultancies with Eli Lilly. C.L.Y. is supported by CNPQ. D.G., S.O., D.D.F., S.R.F., A.I., T.B., A.P. and D.A. declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41572-025-00674-7>.

Peer review information *Nature Reviews Disease Primers* thanks N. Babel; D. Marazziti; and B. Michael, who co-reviewed with R. Matthews, for their contribution to the peer review of this work.

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