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Current status and future perspectives on the mechanistic and pathophysiological understanding of long COVID

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Abstract

Background Viral and infectious illnesses can exert profound and enduring effects on population health and well-being. In the aftermath of SARS-CoV-2 infection, post-acute sequelae, collectively referred to as Long COVID, have emerged as a major global health challenge, affecting more than 400 million people and contributing to estimated annual economic costs exceeding $1 trillion.

Scope of the review Long COVID encompasses a wide and heterogeneous spectrum of debilitating symptoms, including cognitive dysfunction, sleep disturbances, severe fatigue, and post-exertional malaise. Despite its substantial burden, fundamental uncertainties remain regarding its underlying pathophysiology, the development of robust diagnostic criteria, and the identification of effective therapeutic options.

Key insights This review synthesises current evidence on the biological mechanisms thought to contribute to Long COVID, spanning immune dysregulation, viral persistence, autonomic dysfunction, microvascular pathology, and other emerging hypotheses. We examine advances and limitations in contemporary diagnostic approaches and critically appraise existing treatment strategies, highlighting inconsistencies and gaps that hinder clinical consensus.

Implications By integrating interdisciplinary insights, this review underscores the urgent need for mechanistic clarity, validated diagnostic frameworks, and rigorously evaluated treatment pathways. Addressing these gaps will be essential to developing effective, evidence-based management strategies and mitigating the long-term impact of Long COVID on global health.

Plain language summary

COVID-19 has caused millions of deaths worldwide, but its impact goes beyond the initial infection. Some people develop Long COVID, a condition where symptoms persist or appear months after infection, even in mild or asymptomatic cases. Long COVID affects multiple body systems and can involve over 200 symptoms, often resembling chronic fatigue syndrome. Its causes remain unclear, and there are no proven treatments or reliable diagnostic tests. Research into blood biomarkers and symptom patterns holds promise, but progress is slow due to the complexity of the condition. This review explores current knowledge, gaps, and future directions for research, diagnosis, and treatment.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for acute COVID-19, has caused over seven million deaths worldwide[1]. However, the burden of COVID-19 extends beyond the acute phase, with an estimated excess of 15 million deaths globally linked to SARS-CoV-2-related complications[2]. Following infection, a subset of individuals do not fully recover but instead develop new, persistent, or episodic symptoms that significantly impair their quality of life and disrupt daily functioning[3,4]. The risk of developing Long COVID increases with the severity of the initial illness. A population-based cohort study found that individuals with mild to moderately severe COVID-19 were three times more likely to develop Long COVID than asymptomatic individuals. In contrast, those with severe or critical illness had nearly a tenfold increased risk[5]. Importantly, even asymptomatic infection can result in long-term sequelae[6]. These persistent symptoms are referred to by various terms, including ongoing symptomatic COVID-19, post-COVID-19 condition or syndrome, and post-acute sequelae of COVID-19 (PASC). However, the

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most widely recognised term, originating from the patient community, is Long COVID[7–9].

Definitions of Long COVID have been revised multiple times, reflecting both limited understanding of its underlying mechanisms and the growing recognition that it encompasses several subtypes[10]. Current definition is persistence or emergence of new symptoms three months after initial SARS-CoV-2 infection, lasting for at least two months and not explained by an alternative diagnosis[11]. Long COVID is a complex, multisystem condition associated with over 200 reported symptoms, ranging in severity from mild to debilitating presentations[12]. In some cases, the illness follows an episodic pattern, but its overall clinical course and trajectory remain poorly understood. Notably, there is substantial symptomatic and clinical overlap with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), another condition often triggered by viral infection[13].

Currently, no curative treatments for Long COVID have been established, mainly due to its poorly understood and likely heterogeneous pathophysiological basis. Progress has also been hampered by the absence of clear diagnostic criteria and validated biomarkers. Although research has advanced our understanding of potential mechanisms underlying Long COVID, significant gaps remain in the knowledge required to develop practical diagnostic tools, treatments, and management strategies. Anecdotal evidence from several pharmacological trials suggests potential therapeutic benefit; however, these findings have yet to be rigorously tested in large-scale, randomised controlled trials. Furthermore, the limited availability of tools to stratify patients, such as predictive biomarkers or detailed clinical and physiological assessments, continues to impede the design and implementation of effective clinical trial programmes.

Identifying blood-based biomarkers for the diagnosis and treatment of Long COVID has been a key research priority; however, progress has been limited by the condition's heterogeneous nature. Inconsistencies across studies, such as variation in which cyto-/chemokines are examined, differences in assay sensitivity, and a lack of standardisation in sample collection, have further hindered biomarker discovery. Important variables, including illness duration, time of day or season of sample collection[14], and the presence of pre-analytical stressors (especially in individuals prone to post-exertional malaise [PEM] or post-exertional symptom exacerbation [PESE]), are rarely accounted for. A systematic review by Thomas et al.[15] identified several candidate blood biomarkers associated with Long COVID, reflecting immunological and inflammatory dysfunction, endothelial/vascular impairment, metabolic disruption, and clotting abnormalities. However, no disease-specific biomarker or set of biomarkers has yet been validated, and distinct subtypes of Long COVID may likely require different diagnostic signatures. Proteomic analyses measuring over 6500 proteins at various post-infection time points have revealed transient complement system alterations in individuals with Long COVID, which tend to normalise in those who recover naturally. Given the complexity of the condition, future research may need to focus on subtype-specific biomarker profiles to enable patient stratification and guide targeted treatment strategies. Emerging machine learning approaches, such as those described by Liew et al.[16], have begun to link symptom clusters with specific biomarker patterns, offering promising avenues to refine diagnostics and therapeutic approaches.

In this review, we synthesise clinical literature on Long COVID to explore current understanding of its prevalence, pathophysiology, and potential treatment options. Where relevant, we also incorporate comparative insights from studies on ME/CFS and Lyme disease, conditions that share overlapping features of post-infection-associated symptoms. Priority was given to studies employing stringent diagnostic and inclusion criteria to minimise confounding from factors such as hospitalisation during acute infection, pre-existing comorbidities, and unrelated etiologies. This review aims to identify key knowledge gaps and highlight new directions for therapeutic development that may guide future collaborative research efforts.

Prevalence and economic burden of long COVID

The global prevalence of Long COVID remains uncertain, largely due to the absence of standardised diagnostic criteria, inconsistent public health surveillance, and regional differences in pandemic dynamics. Recent studies estimate that between 65 and 400 million people worldwide have experienced persistent symptoms following confirmed SARS-CoV-2 infection[7,17]. Despite this wide range, these figures are likely conservative, and the true global health burden is almost certainly higher. The lack of diagnostic clarity often results in patients consulting multiple healthcare providers, many of whom may lack the expertise to manage the condition effectively. Collectively, this leads to increased medical costs and delayed access to care. Additionally, the inability of many individuals with Long COVID to work contributes significantly to both economic losses and broader societal impacts. While precise estimates of the global economic burden are still emerging, preliminary analyses suggest it could exceed $1 trillion annually[17]. As research advances, the full scope of Long COVID's impact on global economies, healthcare systems, and population health will become increasingly clear[18].

Theories of long COVID pathophysiology

Long COVID is a sequela of SARS-CoV-2 infection and a unique condition driven by complex, interacting mechanisms (Fig. 1), resulting in a wide range of symptoms that significantly impact quality of life[19]. Here, we provide a comprehensive overview of the leading hypotheses regarding the underlying pathophysiology of Long COVID. Emerging empirical evidence implicates several interconnected mechanisms, including immune dysregulation (such as autoimmunity), gut microbiome dysbiosis, coagulopathies, and viral persistence. Additional contributing factors include vascular abnormalities, endothelial dysfunction, autonomic nervous system dysregulation, and neuronal impairments. Together, these findings suggest that Long COVID is a multifactorial condition involving complex, systemic disruptions across immune, vascular, and neurological domains.

Immunological dysfunction

Circulating cytokines

The immune system plays a crucial role in combating acute infections and has been a major focus of research aimed at understanding the pathological mechanisms underlying Long COVID. First, we describe alterations in circulating cytokines observed in patients with Long COVID, before discussing recent evidence suggesting altered immune cell function and autoimmunity.

Inflammatory cytokines and chemokines are dysregulated over a period of 7–14 months in individuals with Long COVID[20,21], although significant variability exists between patients. Among these, interleukin-6 (IL-6) has received considerable attention in soluble immune analyses. IL-6 is produced by various cell types, including macrophages, lymphocytes, skeletal muscle, and endothelial cells, and resident cells of the brain[22], which plays a major role in the proinflammatory response during the acute phase of infection[22]. It also serves as a prognostic marker for adverse disease outcomes following acute infection. It can be influenced by comorbidities such as cardiovascular disease and type 2 diabetes mellitus, as well as psychological stress and acute exercise[23,24].

Giannitrapani et al.[25] demonstrated that abnormally high IL-6 levels during acute infection were associated with an increased risk of developing Long COVID and a decline in mobility after 12 months. Similarly, Son et al.[26] reported strong associations between IL-6, tumour necrosis factor-α (TNF-α), and vascular cell adhesion molecule 1 (VCAM-1) at 6 months post-infection with overall Long COVID symptoms. However, IL-6 levels did not correlate with specific symptoms such as fatigue, cough, or dyspnoea up to 12 months after infection. Attempts to identify biochemical risk factors for Long COVID have proposed a cytokine triad consisting of IL-6, interleukin-1 beta (IL-1β), and TNF-α[27]. Patel et al.[28] identified angiopoietin 1 (Ang1) and platelet P-selectin as key vascular biomarkers in Long COVID using machine learning approaches[29]. Whether these markers, alone or in

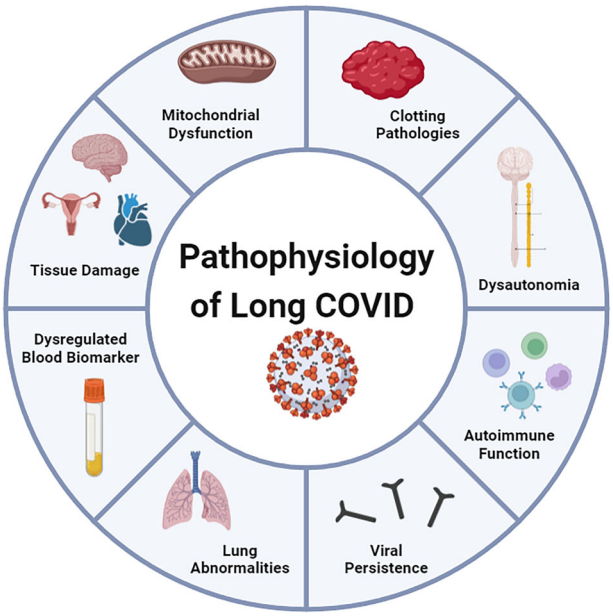

Fig. 1 | Summary of the pathophysiology of Long COVID. A graphic representation of the known pathophysiology of Long COVID by M.Faghy created in BioRender (https://biorender.com/shortURL) is licensed under CC BY 4.0.

combination with others, can serve as specific diagnostic tools for Long COVID requires further study.

Altered T-cell recognition of SARS-CoV-2 antigens or broader T-cell dysfunction in Long COVID remains an area of considerable debate[30]. Antiviral immune responsiveness, including the expression of immune exhaustion markers, is likely linked to the presence of a long-term viral antigen reservoir[31,33]. One study reported generalised functional exhaustion of CD8 + T cells in Long COVID patients, demonstrated by extremely low levels of CD8+ interferon-gamma (IFN-γ) and TNF-α production in response to nonspecific stimulants, with similar findings observed in ME/CFS[34]. Significant uncertainties remain regarding whether viral persistence results from insufficient adaptive immunity or if it paradoxically drives excessive adaptive immune responses, as well as the extent to which persistence reflects active viral replication versus latency. Given this complexity, common inflammatory cytokine markers lack specificity for Long COVID. A more detailed understanding of the roles these cytokines play in the pathophysiology of Long COVID is essential to advancing diagnostic and therapeutic strategies.

Immune cell alterations

Recent literature on Long COVID has increasingly focused on alterations in immune cell function and responses to pathogens[30,33]. However, it remains unclear whether these immune changes are a primary driver of disease pathogenesis, such as through autoimmunity, or a secondary response to other underlying factors like viral persistence, chronic/latent viral reactivation, or microthrombosis, or perhaps a combination of both. Patterson et al.[35] report that T-cell activation, marked by elevated IFN-γ and interleukin-2 (IL-2), alongside impaired T-cell recruitment, suggests a dysfunctional antiviral response. Dysregulation of CD4+ and CD8 + T cells in this context may indicate T-cell exhaustion. Su et al.[36] observed an expansion of cytotoxic T cells in individuals exhibiting the gastrointestinal Long COVID phenotype 2–3 months after infection. Additionally, stimulation with PMA and ionomycin has been shown to increase intracellular production of IL-2, IL-4, IL-6, IFN-γ, and TNF-α in both CD4+ and CD8 + T cells in people with Long COVID[37]. However, this pattern was not observed in CD8 + T cells from patients with ME/CFS, where IFN-γ and TNF-α responses were absent[34]. Evidence also implicates monocytes in Long COVID pathogenesis[35,38]. For instance, Scott et al.[39] identified distinct monocyte signatures, such as expression of prostaglandin-generating enzyme cyclooxygenase-2 (COX-2), interleukin-8 receptor beta (IL-8Rβ, also known as CXCR2), C-X-C chemokine receptor type 6 (CXCR6), and the adhesion molecule P-selectin glycoprotein ligand-1 (PSGL-1), which appear to be associated with fatigue and dyspnoea in Long COVID patients.

Autoimmunity

Epidemiological and immunological studies have linked viral and bacterial infections, including SARS-CoV-2, to an increased risk of autoimmune diseases such as vasculitis, type 1 diabetes, and inflammatory bowel disease[30,40–42]. This risk was most pronounced early in the pandemic (2020–2021), particularly following severe infections with pre-Delta variants and among unvaccinated populations[43–45]. More recent data suggest a reduced risk with Omicron variants and vaccination[46]. Long COVID may involve autoimmune dysregulation triggered by prolonged immune activation involving B and T cells[30,47,48], with latent virus reactivation, especially Epstein-Barr virus (EBV), known to be implicated in multiple sclerosis, potentially contributing[49]. Although autoimmune diseases arise from genetic and environmental factors[50], the role of COVID-19–induced autoimmunity in Long COVID pathophysiology remains unclear.

Autoantibodies (AABs) have been investigated as biomarkers for acute and post-acute COVID-19. Neutralising AABs against type I interferons (IFNs), prevalent in men, older adults, and fatal COVID-19 cases, correlate with disease severity and may persist post-infection[51–53]. However, longitudinal studies indicate limited persistence of these AABs beyond 6–8 months and inconsistent associations with Long COVID symptoms[36,54]. Some reports link baseline IFN-α2 AABs with respiratory symptoms[54], and implicate AABs targeting type III IFN (IFN-λ)[55].

Antinuclear antibodies (ANA) and extractable nuclear antigen (ENA) AABs are frequently detected in Long COVID patients up to 12 months post-infection, particularly against SS-B/La and U1-snRNP[26]. These autoantibodies show variable associations with fatigue, dyspnoea, and neurocognitive symptoms[56]. Dysregulated AABs targeting G-protein-coupled receptors (GPCRs), involved in autonomic nervous system function, are strongly linked to symptom severity and patterns[57–59]. In Long COVID patients with biopsy-confirmed small fibre neuropathy, 25% exhibited autoantibodies against gangliosides regulating GPCR activity[60], although other studies report no persistent AABs in similar cohorts[61].

Variability in study design, including cohort selection, timing of sampling, assay methods, and range of AAB targets, likely contributes to

inconsistent findings. Supporting this, a conformationally sensitive protein array screening ~20,000 human proteins identified elevated AABs against PITX2 and FBXO2 in Long COVID patients ~14 months post-infection, correlating with palpitations and cognitive disturbances[62]. Other AABs associated with Long COVID include those targeting thyroid peroxidase, thyroglobulin, IL-2, and CD8B[55,63]. Notably, some AABs may be protective; for example, anti-chemokine AABs were inversely correlated with Long COVID development at 1 year[64]. To clarify the predictive role of autoantibodies, longitudinal studies with serial sampling, detailed phenotyping, larger cohorts, and optimised assays are essential. Improved methodologies and replication will aid in identifying patient subgroups likely to benefit from AAB-targeted or immunomodulatory treatments. The detection of autoantibodies linked to autonomic, neurocognitive, immune, mitochondrial, and vascular dysfunction has spurred early trials employing plasmapheresis, intravenous immunoglobulin (IVIg), and other immunomodulators.

Therapeutic apheresis techniques such as INUSpheresis and immunoadsorption, which remove circulating autoantibodies, are under investigation for Long COVID[65,66] and have shown promise in ME/CFS[67]. Biomarker analyses suggest that reductions in neurotransmitter AABs, lipids, inflammatory markers, and fibrinogen correlate with clinical improvement and may help identify likely responders[68]. These findings emphasise the need for a precision medicine approach that tailors therapies based on predictive clinical and biomarker profiles, especially given a recent randomised trial of plasma exchange showed safety but no efficacy for Long COVID symptoms, quality of life, or function[69].

Anti-GPCR antibody therapies are a promising avenue, although their efficacy and safety require further validation. Preliminary reports suggest that intravenous immunoglobulin (IVIg), commonly used to treat autoimmune disorders and thought to act partly through anti-idiotypic antibodies that neutralise autoantigens, autoantibodies, and cytokines, may alleviate symptoms of Long COVID[70]. Small case series and retrospective studies report symptomatic improvements, including fatigue and cognitive deficits, following IVIg treatment, with ongoing clinical trials currently evaluating its efficacy[70–72].

Emerging immunomodulators such as BC007, an aptamer neutralising functional GPCR autoantibodies, have shown potential in early trials for improving fatigue and microcirculatory dysfunction in Long COVID subsets[73,74]. Similarly, low-dose naltrexone (LDN), which modulates immune responses by attenuating microglial activation and proinflammatory cytokine production, possibly via non-opioid pathways including TRPM3 channel regulation, has shown preliminary promise. Retrospective reviews and observational studies report improvements in fatigue, PEM, sleep disturbances, and quality of life among Long COVID patients treated with LDN, warranting further controlled trials incorporating predictive clinical and biomarker criteria[75–79]. A retrospective review of 59 Long COVID patients treated off-label with LDN reported improvements in fatigue, PEM, unrefreshing and disrupted sleep, and overall functional status[80]. Additional observational studies have similarly reported symptom improvement, enhanced well-being, and better quality of life in subsets of Long COVID patients[77–79]. Further research is needed to identify clinical and biomarker predictors of treatment response and to incorporate these into the design of randomised controlled trials.

Despite growing evidence, the mechanisms linking SARS-CoV-2 infection to autoimmunity remain incompletely understood. Proposed pathways include immune dysregulation involving inflammation, immune exhaustion, and expansion of naïve B cells producing autoantibodies[81]; persistent viral antigen exposure; direct activation of autoreactive plasmablasts; molecular mimicry potentially via amyloidogenic cross-seeding[82]; gut microbiome dysbiosis[83]; and reactivation of latent herpesviruses, particularly EBV, possibly mediated by epitope homology[84]. The contribution of Long COVID-associated autoantibodies to cellular and tissue injury across organ systems, including their functional effects, requires further elucidation. Future research should identify specific autoantigen targets and assess homology with microbial and viral proteins, with trials focusing on patient subsets defined by autoantibody profiles and clinical phenotypes to optimise therapeutic outcomes.

Viral persistence/chronic viral reactivation

The persistence of live (chronic productive infection or defective viral persistence) or reactivated viruses (latent infection) is an area of great importance in increasing the pathological understanding of Long COVID. Despite symptomatic resolution, some people are not able to fully clear a virus (Fig. 2), and the continued presence of a virus or parts of a virus is linked to increased antigen detection[85]. Similarities have been observed with single-stranded DNA viruses, such as Ebola virus, Zika virus, enterovirus, and measles[31,86]. Research has identified persistent SARS-CoV-2 proteins and microthromboses in tissue, including skeletal muscle, and autopsy studies[30,31,87]. The gastrointestinal tract, however, has undoubtedly been the most studied site for SARS-CoV-2 reservoirs, and viral antigen profiles have also been found in stool samples post-SARS-CoV-2 infection[88], irrespective of a persistent symptom profile[89–92]. In other words, individuals vary considerably in their ability to resist both initial and post-infection virions and their products.

The evidence and role of viral persistence in the pathophysiology of chronic disease were established long before SARS-CoV-2 and Long COVID[93,94]. Viral persistence and viral reservoirs can play an important role in Long COVID and, more broadly, chronic disease presentation. Several trials of antiviral medications are ongoing and show promise in reducing the symptom burden of Long COVID. However, combined therapeutic approaches are likely needed to address the broader pathologies of Long COVID.

Proal et al.[32], concluded that SARS-CoV-2 ribonucleic acid (RNA) and protein are present in a range of tissue types collected weeks or months after acute COVID-19, including in brain regions, lymph nodes, the thorax, sciatic nerve, ocular tissue, the cervical spinal cord, the brainstem, and the olfactory nerve[95]. The brain and the brainstem are particularly vulnerable to acute and chronic damage from various sources, particularly viral invasion, inflammation, and vascular activation[96]. Data from single molecular arrays enable high-sensitivity detection of low-abundance proteins, including SARS-CoV-2 antigens in serum. One year post-infection, ~60% of people with Long COVID demonstrated the presence of SARS-CoV-2 spike proteins and a greater number of organ systems involved in symptoms that were not evident in controls[97–99]. Whole-body positron emission tomography on twenty-four people with Long COVID[100] demonstrated increased T-cell activation in several anatomical regions compared to pre-pandemic controls. There was increased uptake in the brainstem, spinal cord, bone marrow, nasopharyngeal and hilar lymphoid tissue, cardiopulmonary tissues, and gut wall. Following in situ hybridisation, SARS-CoV-2 RNA and immunohistochemical studies were completed in a subset of participants with Long COVID symptoms. Elevated cellular SARS-CoV-2 RNA in rectosigmoid lamina propria tissue was observed in all participants, confirming that viral persistence could be associated with long-term immunological perturbations in Long COVID.

Greater consideration of chronic viral reactivation is also warranted, given the growing evidence that supports a potential contributing role in the pathophysiology of Long COVID. Several studies have highlighted the reactivation of latent viruses, including EBV, human herpesviruses (e.g., HHV-6), and cytomegalovirus (CMV), in individuals with post-acute sequelae of SARS-CoV-2 infection. Peluso et al.[101] and Maguire et al.[102] identified serological and transcriptional signatures consistent with viral reactivation in Long COVID cohorts. Similarly, Vojdani et al.[103] and Bernal et al.[104] provide immunological and molecular evidence suggesting that reactivation of latent viral reservoirs may contribute to ongoing inflammation, immune dysregulation, and multisystem symptoms observed in Long COVID These findings support the hypothesis that chronic viral reactivation, alongside viral persistence, may be a key driver of sustained pathology in a subset of patients.

While the pathophysiologic evidence of viral persistence/chronic viral reactivation is mounting, further studies are needed into the exact

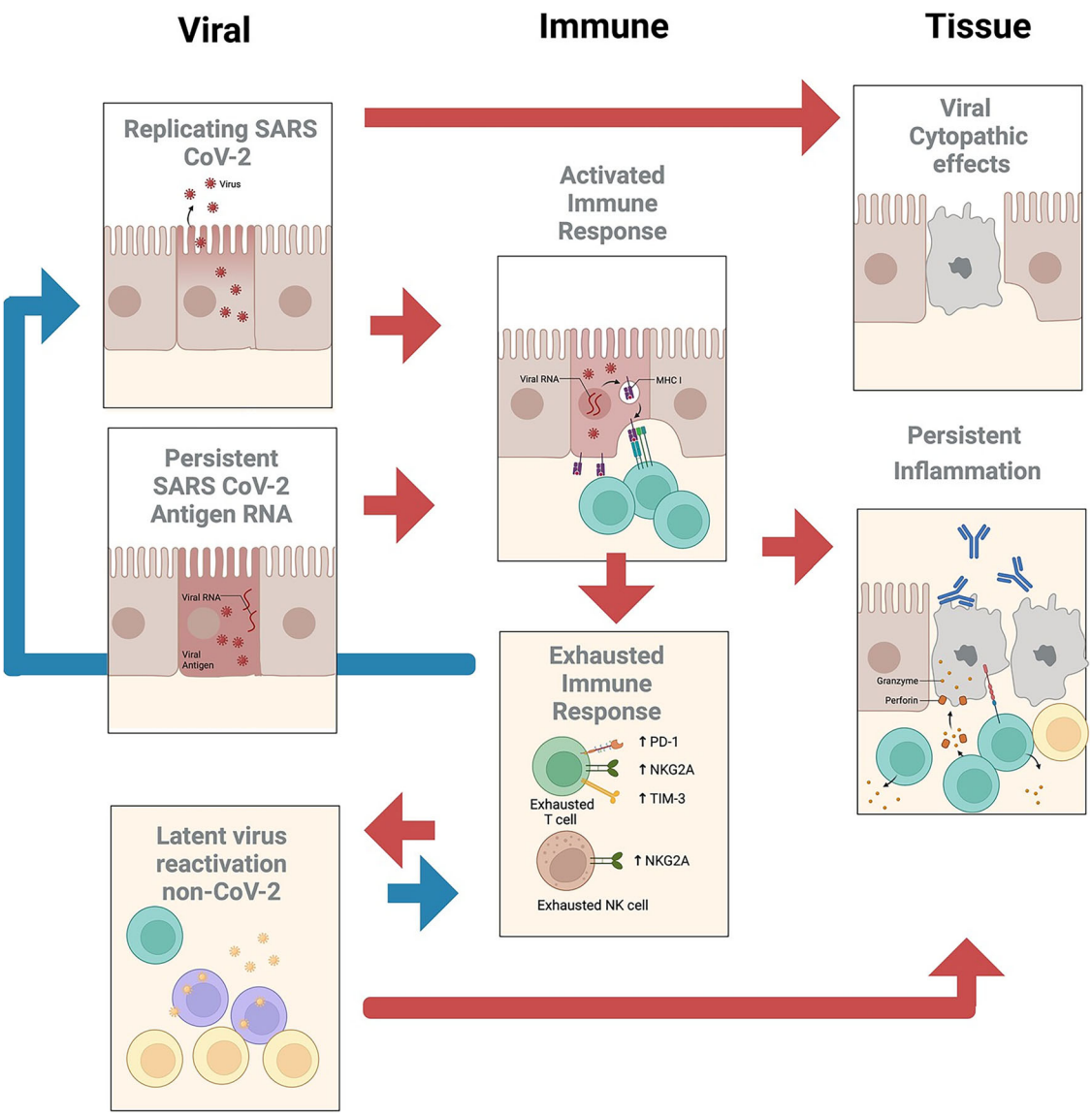

Fig. 2 | The role of viral persistence in Long COVID. Mechanistic insight into the role of viral persistence across different systems and tissues in the context of Long COVID, image published by Chen et al.[108].

mechanisms in the pathology of Long COVID. Particularly, the observation that previously infected individuals without Long COVID symptoms also have remnants of viral proteins in tissue[87] and plasma[105] suggests possible additional contributing factors. However, it must be verified utilising more advanced methodologies to better understand the impact that persistent pathogens may be having on host tissue. For instance, spatial transcriptomics is a relatively novel technique that enables the mapping of gene expression within the spatial context of biopsied tissues whilst preserving the intricate architecture and cellular interactions of the sample. In acute SARS-CoV-2 research, this approach has already proven to be invaluable in uncovering the spatial landscape of lung pathology during COVID-19 progression[106]. In Long COVID, techniques such as spatial transcriptomics can be applied to better quantify and understand which tissues are most likely to host viral reservoirs. These localised immune responses are triggered by persistent pathogens and viral remnants in vulnerable individuals, and how these processes may also reactivate latent pathogens[32,107,108]. The implementation of advanced techniques such as spatial transcriptomics allows researchers to go beyond the simple identification of persistent pathogens or viral remnants in study participants and utilise preserved spatial context to explore the complex interplay between viral persistence, immune responses, and latent viral reactivation in Long COVID.

Endothelial pathology, platelet hyperactivation, and clotting pathologies

Persistent endothelial cell damage, clotting abnormalities, and increased platelet activation are central pathological processes often linked to viral or spike protein persistence, latent virus reactivation, and immune-related factors in people with Long COVID[7,30,33,109–112]. The glycocalyx matrix in the capillary endothelium, which serves as a fluid barrier, can be shed due to heightened inflammatory mediators, resulting in significant alterations in microvascular resistance and capillary blood flow[113]. SDC-1 has emerged as a reliable marker for assessing glycocalyx injury disease[114]. This study highlights endothelial damage in convalescent COVID-19 patients with mild disease progression, suggesting that glycocalyx injury can persist even in the absence of severe disease[114].

Capillary rarefaction, which refers to the reduction in the number or density of capillaries within a given tissue or organ, leads to impaired microcirculation and reduced oxygen and nutrient delivery. It is commonly observed in conditions associated with chronic inflammation, endothelial

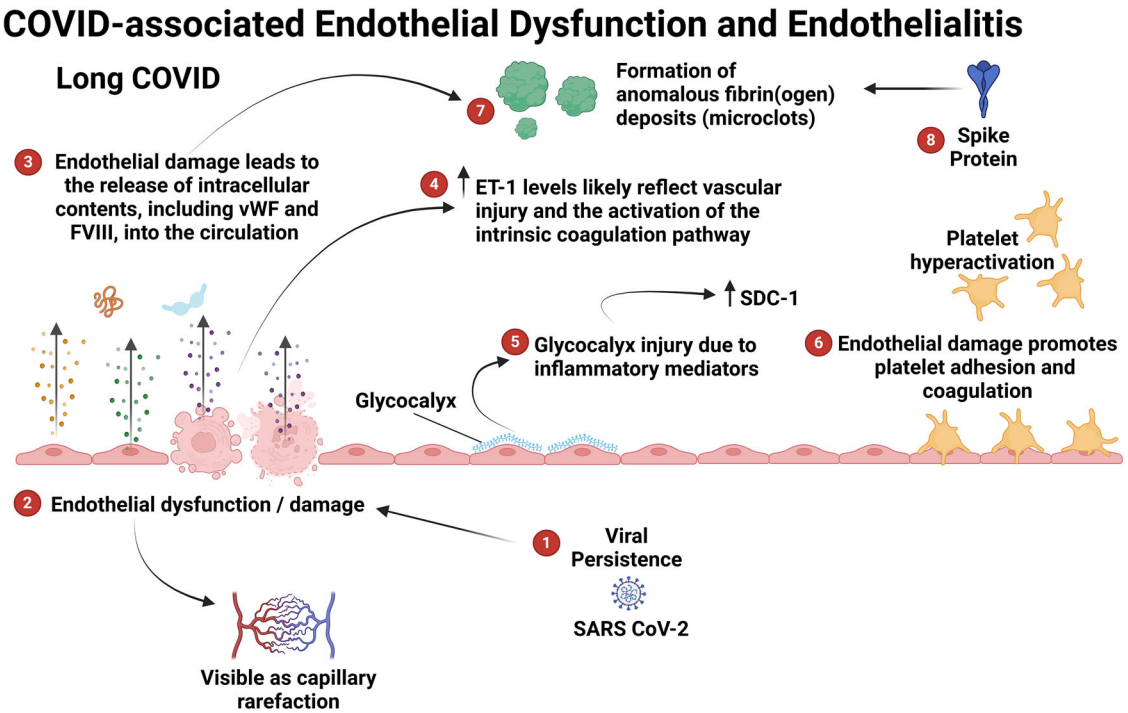

Fig. 3 | COVID-associated endothelial dysfunction and endothelialitis. Multiple factors contribute to endothelial dysfunction and damage in Long COVID, with (1) viral persistence being a key driver of endothelial injury. (2) Endothelial damage leads to (3) the release of intracellular components, such as vWF and FVIII, into circulation, which in turn contributes to the formation of anomalous microclot deposits (7). Elevated levels of ET-1 (4) and SDC-1 (5) serve as markers of vascular and glycocalyx injury, respectively. Platelet hyperactivation is a well-established feature of Long COVID, with endothelial damage further promoting platelet adhesion (6) and coagulation. Additionally, the finding of capillary rarefaction in Long COVID may also indicate vascular damage. (8) Research has shown that the spike protein of SARS-CoV-2 directly induces the formation of anomalous fibrin(ogen) deposits in purified soluble fibrinogen (fibrinaloids)[204]. Spike protein can also induce anomalous deposits in plasma from healthy individuals. The extent of amyloidogenicity might be related to virulence[205]. It is therefore evident that the formation of these deposits is on the disease pathway. By A. Kruger created in BioRender (https://biorender.com/shortURL) is licensed under CC BY 4.0.

dysfunction, and vascular abnormalities, such as hypertension and diabetes. Capillary rarefaction can result from capillary degeneration, impaired angiogenesis, or structural remodelling of the microvasculature. It has also been observed in Long COVID patients via sublingual video microscopy[115], further indicating endothelial dysfunction or damage. Endothelial cells may also exhibit apoptotic behaviour long after infection, disrupting communication between endothelial cells and vascular smooth muscle cells[113], further contributing to disease pathology. Moreover, elevated levels of endothelin 1 (ET-1) have been detected in Long COVID patients five months after acute infection, in contrast to those who had recovered from COVID-19 and healthy individuals[110]. These increased ET-1 levels likely reflect vascular injury and the activation of the intrinsic coagulation pathway[116].

Various pathologies leading to endothelial damage promote platelet adhesion and coagulation, impairing organ function and perpetuating platelet hyperactivation through upregulated expression of inflammatory and adhesion molecules[117]. Endothelial damage leads to the release of intracellular contents, including von Willebrand factor (vWF) and Factor VIII (FVIII), into the circulation[118], contributing to the formation of anomalous fibrin(ogen) amyloid deposits or microclots (Fig. 3), which in turn contribute to tissue hypoxia and further injury[119], as well as multiple other observables[82,119,120]. Microthrombi have been identified in post-mortem studies of COVID-19 patients[121] and individuals with Long COVID have anomalous microclots in circulation[112,122]. The persistent endothelial inflammation, the presence of anomalous (insoluble) microclot deposits, platelet hyperactivation, and their association with chronic Long COVID symptoms are well-documented[7,30,123]. These studies underscore the role of microthrombogenesis in Long COVID. Anomalous deposits, like other amyloid proteins, exhibit greater resistance to fibrinolysis and have also been detected in skeletal tissue[87], suggesting they could contribute to Long COVID pathophysiology[82,119,122,123]. Recent evidence during repeated submaximal exercise demonstrates fragmentation of microclots, which is linked to increased inflammation and impaired oxygen transport in people with Long COVID[124]. These factors can provide a plausible explanation for diverse tissue-specific dysfunctions observed in Long COVID.

Mechanistic insights into the most common symptoms of long COVID

Next, we discuss the primary symptoms of Long COVID and deepen the discussion of the pathophysiology of each symptom, linking it to the proposed underlying causes of Long COVID described above. Since most research has focused on postural orthostatic tachycardia syndrome (POTS), PEM/PESE, respiratory abnormalities, cognitive dysfunction and sleep disturbances, we decided to focus on these primary symptoms but acknowledge that this list is not exclusive and that there is a broad range of symptoms that vastly impact the lives of people with Long COVID.

Neurological manifestations of long COVID

Dysautonomia and POTS

Orthostatic intolerance, including POTS and orthostatic hypotension, is reported in around half of people with Long COVID[125]. There is a plausible link between damage to the autonomic nervous system and Long COVID symptoms, but the exact pathophysiology remains unknown. Orthostatic intolerance is a hallmark feature of Long COVID dysautonomia. Upon standing, there is an instantaneous shift of ~0.5–1 L of blood to the capacitance vessels in the lower extremities and splanchnic circulation[126,127]. An additional 10-25% of the plasma volume is driven out of the vasculature into the interstitial space[127,128]. A well-functioning autonomic nervous system detects these hemodynamic changes. It invokes immediate autocompensatory mechanisms, resulting in peripheral vasoconstriction and an increase in systemic vascular resistance to maintain venous return to the

heart[127,129]. However, in Long COVID, it is thought that the autonomic nervous system may not detect and respond to gravitational changes correctly, resulting in the pooling of venous blood in the lower limbs when standing up, which may lead to an exaggerated increase in heart rate to maintain cardiac output. The ability of anomalous microclots to induce hypoxia provides a plausible mechanistic explanation for POTS. What the heart may be doing is detecting the hypoxia and having a compensatory increase in the heart rate[120].

POTS is likely underpinned by multiple aetiologies that converge to produce a similar clinical phenotype, often overlapping with other well-defined syndromes such as ME/CFS and post-treatment Lyme disease[130]. A primary reduction in circulating plasma volume (hypovolemic POTS) will lead to reflex sympathetic vasoconstriction to maintain blood pressure at the cost of an increased heart rate, which has been reported in ~70% of people with Long COVID[131]. Therapeutic strategies that aim to increase the circulating plasma volume, such as increased salt and water intake and the use of desmopressin, can improve symptoms. A patchy denervation of the small nerve fibres to the blood vessels in the extremities has been observed in up to 20%-40% of people with Long COVID (neuropathic POTS)[125]. This small fibre neuropathy may result from damage through a viral or autoimmune insult[132,133]. Consequently, an abnormal sympathetic tone reduces the ability to vasoconstrict, causing compensatory tachycardia.

Abnormal sweating, bladder control problems, gastric issues, skin discolouration, increased venous pooling in the legs, as well as syncope and palpitations are commonly observed. Many people with POTS describe "adrenaline surges" and are found to have elevated levels of circulating plasma norepinephrine (Hyperadrenergic POTS). Norepinephrine levels measured during orthostasis may be up to four times higher in POTS patients compared to healthy controls[133]. Some people have also been identified as having a genetic loss-of-function mutation of the norepinephrine transporter, which is responsible for norepinephrine clearance, increasing circulating levels of norepinephrine at rest and during standing up. It might explain why many people feel tremulous and anxious in response to innocuous stimuli. The underlying factors that contribute to POTS in Long COVID are currently poorly understood.

A dysfunctional autonomous nervous system (dysautonomia), disordered tissue perfusion, endothelial inflammation and dysfunction and/or chronic inflammation might all contribute. The endothelial glycocalyx may be damaged, increasing the endothelial permeability[113], and causing plasma to leak into the interstitial fluid[134,135]; however, more research is required to test this hypothesis. Additionally, the autonomic nervous system dysfunction likely contributes to the development of POTS. Indeed, the autonomic nervous system dysfunction has been implicated in the pathophysiology of Long COVID more generally. People with Long COVID showed significant diaphragmatic dysfunction and reductions in maximum inspiratory pressure, implicating the phrenic nerve in respiratory muscle weakness[136,137]. Damage to endothelial cells surrounding the vagus nerve, which carries sympathetic and parasympathetic fibres of the autonomic nervous system, and/or inflammatory immune cell infiltration into the vagus nerve, might affect vagal nerve activity and contribute to dysautonomia[138–140]. A recent post-mortem study detected SARS-CoV-2 remnants in the vagus nerve, suggesting that viral infiltration has the potential to affect nerve function[139]. Direct evidence of such a hypothesis is lacking and requires more detailed studies.

A link between inflammation and dysautonomia in Long COVID has been hypothesised. The inflammatory vagus nerve reflex is integral in regulating inflammation homeostasis via a cholinergic neural reflex mechanism. This inflammatory reflex controls innate immune responses and inflammation during pathogen invasion and tissue injury[141]. Efferent vagal fibres from the dorsal motor nucleus inhibit cytokine storms via cholinergic pathways[142]. Therapeutic agents targeting the efferent vagal nerve fibres, therefore, may not only help relieve disabling symptoms of dysautonomia but also be potentially disease-modifying by modulating chronic inflammation in people with Long COVID. Whether treatments targeting the vagus nerve will help with reducing dysautonomia, POTS, and other Long COVID-related symptoms represents an important area of future study.

Cognitive dysfunction and brain fog

Many of the neurological and neuropsychiatric symptoms seen in individuals with Long COVID appear to involve neuroinflammatory cascades triggered by systemic inflammation. This inflammation may contribute to the disruption of the blood-brain barrier (BBB) or enable direct viral neuroinvasion, particularly via infection of the olfactory bulb (Fig. 4). Immune system dysregulation, in conjunction with systemic vascular impairment, has been observed in individuals experiencing COVID-related cognitive dysfunction. These findings suggest that BBB leakage and post-COVID cognitive dysfunction may be interrelated[143]. In addition, the accumulation of viral antigens and microglial dysfunction has been identified alongside significant vascular inflammation in the brains of deceased COVID-19 patients[144].

Whilst aged individuals are particularly vulnerable to COVID-19 complications, it is widely acknowledged that younger patients can also be adversely affected, including through long-term neurological symptoms. Early in the pandemic, some studies detected neuroinflammatory responses without evidence of active viral presence in the brain[145]. However, later research identified persistent SARS-CoV-2 RNA and confirmed viral neuroinvasion in human, monkey, and mouse brains[95,146–148]. The neuroinvasive potential of coronaviruses had already been established in previous strains following airway exposure, with common entry routes including the olfactory nerve, retrograde transport via cranial nerves, or infiltration through the bloodstream or infected immune cells[149–152]. SARS-CoV-2 spike and nucleocapsid proteins, as well as viral RNA, have been found in brain tissue and across the skull–meninges–brain axis from days to even years after acute infection[95,146,153]. Persistent viral presence in brain tissue may contribute to prolonged neurological symptoms in Long COVID, potentially through mechanisms such as impaired serotonin transmission[154]. Notably, both cerebral organoids and post-mortem brain tissue from individuals with COVID-19 have shown that SARS-CoV-2 can disrupt synaptic homeostasis and increase the expression of synaptic proteins[155,156].

In summary, current evidence suggests that neurological complications following COVID-19 may arise from systemic inflammation leading to neuroinflammation, and in some cases, from direct viral infection and its inflammatory consequences. Clarifying the pathways of viral entry and the mechanisms of cellular damage will be crucial for understanding and treating Long COVID's neurological outcomes.

Respiratory symptoms

Pulmonary abnormalities are frequently reported in patients with Long COVID[157] and may arise from chronic airway inflammation, pulmonary endothelialitis, fibrosis[158], restrictive parenchymal physiology[159], dysfunctional breathing (e.g., due to dysautonomia), chest tightness, or dyspnoea[158]. Whether these changes reflect a core feature of Long COVID or result from broader systemic pathophysiology remains uncertain. Impaired lung function may also be driven by hemodynamic disturbances in pulmonary circulation, leading to reduced alveolar gas exchange[160,161]. Dhawan et al.[162] identified signs of pulmonary small-vessel disease and parenchymal involvement. Furthermore, paired expiratory axial CT scans often reveal widespread lobular and regional low-attenuation areas indicative of air trapping, a contributor to ventilation/perfusion ($\dot{V}/Q$) mismatch and reduced exercise tolerance. Patients presenting with persistent respiratory symptoms may benefit from advanced imaging modalities, such as CT pulmonary angiography with dual-energy sequencing, which can support both diagnosis and mechanistic understanding[163]. These techniques could help characterise small-vessel perfusion abnormalities and clarify the long-term pulmonary vascular sequelae of COVID-19 and Long COVID[162].

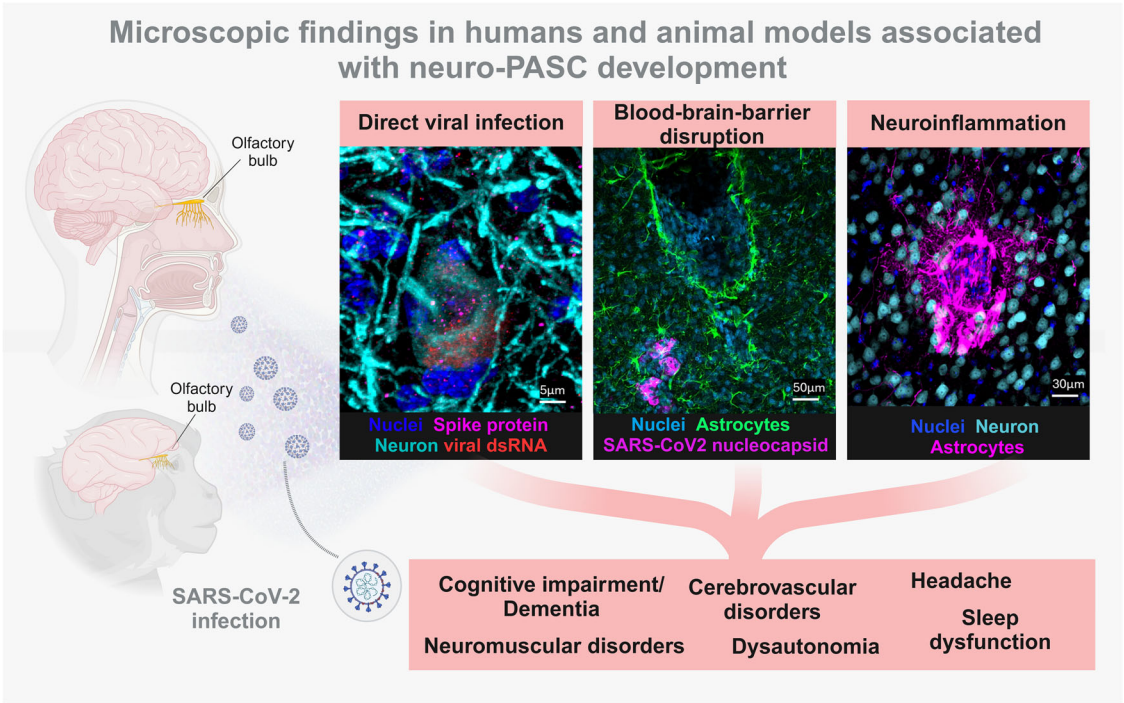

Fig. 4 | Microscopic findings associated with neuro-PASC in primates. Humans and macaques develop similar viral diseases and share common histopathological markers, such as (1) infection of neurons and glial cells, detected by colocalization with different viral markers (SARS-CoV-2 spike and nucleocapsid proteins, double-stranded RNA). (2) Disruption of the blood-brain barrier (BBB), with viral presence associated with vascular abnormalities. (3) astrocyte-associated neuroinflammatory response. By D. Beckman, created in BioRender (https://biorender.com/shortURL) is licensed under CC BY 4.0.

Fatigue and PEM

Chronic fatigue is one of the most prevalent and debilitating symptoms reported by individuals with Long COVID, characterised by an inability to perform physical or cognitive tasks that would typically fall within their normal energy capacity. Approximately 50%-80% of patients also experience PEM, a hallmark feature involving the worsening or emergence of new symptoms following physical, mental, or cognitive exertion that exceeds a highly individual and variable threshold[164] (Fig. 5). The onset of PEM typically occurs within 48 hours of exertion and may persist for days, weeks, or even months[165]. There is substantial overlap between the clinical presentation and proposed pathophysiological mechanisms of Long COVID and ME/CFS, in which PEM is a core diagnostic criteria[166]. Given the strong association between exertion and symptom exacerbation, many patients identify PEM as a primary contributor to their reduced functional capacity and diminished quality of life. As such, patients often remain physically inactive to avoid PEM. Interventions such as graded exercise therapy, designed to increase activity levels over time, have been linked to adverse outcomes in this population and are considered high-risk for inducing PEM[167]. Despite these data on risks of PEM/PESE, the role and appropriateness of physical activity and exercise training remain widely debated for people with Long COVID and ME/CFS[164,168].

The exact pathophysiological mechanisms underlying PEM remain unclear. However, current evidence suggests that the mechanisms responsible for reduced exercise capacity and excessive fatigue in Long COVID differ from those driving PEM specifically[87]. Individuals with Long COVID consistently exhibit lower maximal oxygen uptake and peak power output during cycle ergometer testing compared to age- and sex-matched controls[87,169]. These deficits are likely attributable to peripheral impairments rather than significant pulmonary or cardiac dysfunction. Structural and morphological changes in skeletal muscle appear to play a significant role in this reduced exercise tolerance and persistent fatigue[87,170]. Recent literature has identified five key mechanisms contributing to skeletal muscle dysfunction in Long COVID: local hypoxia (including impaired oxygen delivery and potential reactive oxygen species production), physical deconditioning, electrophysiological abnormalities, autoimmune processes, and central fatigue (see ref. 123 for more details).

Skeletal muscle changes have also been associated with the earlier onset of fatigue, with some alterations potentially resulting from repeated episodes of PEM[87]. Additionally, capillary abnormalities, endothelial dysfunction, and microclot formation/fragmentation may impair oxygen delivery, although the exact mechanisms behind endothelial dysfunction in Long COVID remain unknown. Muscle fibres in individuals with Long COVID tend to be more glycolytic and exhibit reduced mitochondrial respiration[171]. Biomarkers indicate decreased mitochondrial content, biogenesis, and function, including diminished cytochrome c oxidase activity, subsarcolemmal mitochondrial accumulation, and disrupted cristae architecture[171,172]. These mitochondrial impairments contribute to the accelerated development of fatigue. Moreover, abnormalities in fatty acid oxidation during exercise have been reported[173,174], along with exaggerated blood lactate accumulation. While the cause of this lactate buildup remains unclear, it may reflect a very low ventilatory threshold in some patients and is consistent with a pattern of chronic ischaemia-reperfusion injury[119].

Mitochondrial dysfunction may play a central role in the pathophysiology of Long COVID, given its widespread impact on cellular and systemic function[175]. SARS-CoV-2 has been shown to bind to mitochondria and utilise ATP to support viral replication[176]. Nasopharyngeal samples from individuals with acute SARS-CoV-2 infection reveal impaired transcription of both nuclear and mitochondrial genes, which may trigger an antiviral immune response while simultaneously disrupting mitochondrial function[177]. The Wiskott-Aldrich Syndrome Protein Family Member 3 (WASF3) has been implicated in the disrupted formation of mitochondrial respiratory supercomplexes and impaired respiration in ME/CFS. It is also associated with endoplasmic reticulum stress in skeletal muscle[178]. However, the precise role of WASF3 or other mitochondrial abnormalities in contributing to fatigue and exercise intolerance in Long COVID remains unclear. Developing pharmacological treatments aimed at restoring mitochondrial function may hold promise for alleviating fatigue and preventing PEM. However, such therapies must target the specific

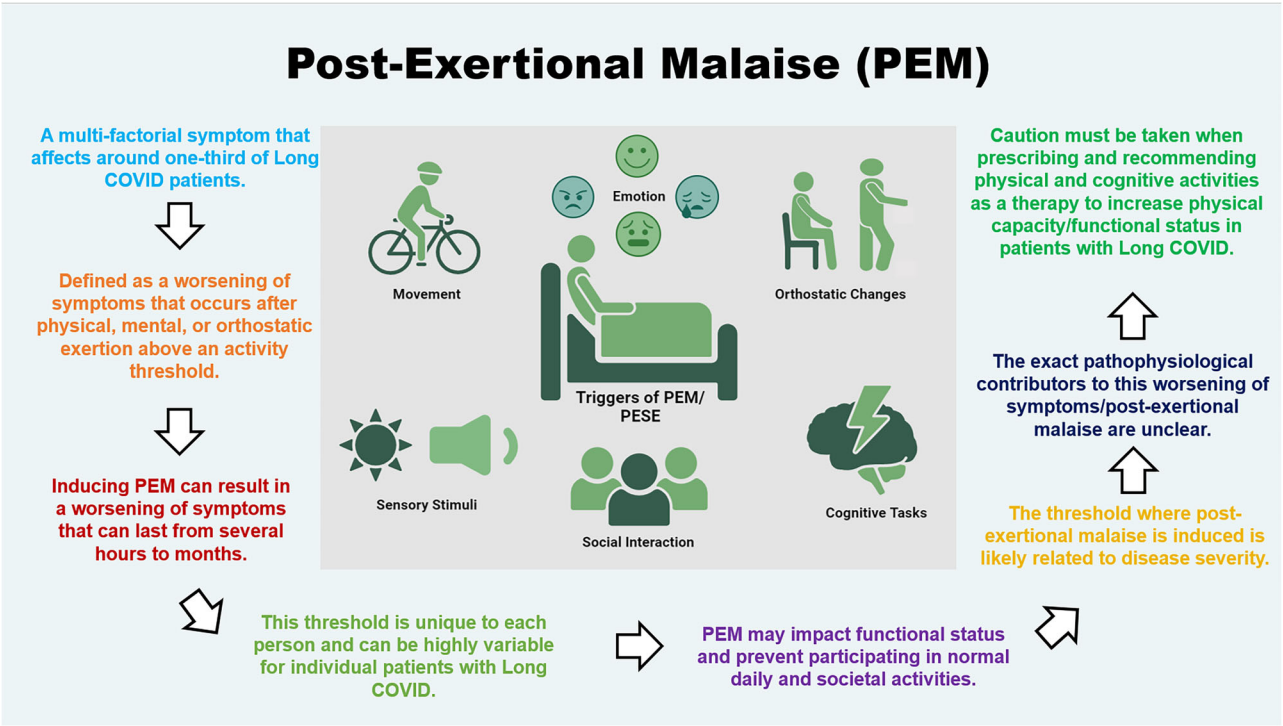

Fig. 5 | Visual representation of Post-Exertional Malaise/Post-Exertional Symptom Exacerbation. A graphic summary of the known causes and contributors to PEM/PESE in people with Long COVID.

mitochondrial pathologies involved, and further research is needed to guide these interventions. Notably, acute exertion beyond the threshold that triggers PEM initiates a cascade of symptoms, the origins of which remain unknown. This cascade is not restricted to skeletal muscle involvement, as mental or cognitive exertion and even emotional stress can also precipitate PEM or PESE. It suggests that a blood-borne or neurologically mediated factor may initiate PEM, although more research is required to identify the underlying mechanisms.

PEM may be partly explained by cellular damage caused by reactive oxygen species (ROS) in the context of ischaemia-reperfusion injury[119]. Local skeletal muscle changes following the onset of PEM include further deterioration in mitochondrial respiration, compounding the mitochondrial abnormalities already observed in individuals with Long COVID[87]. Evidence of exercise-induced muscle damage has been reported in muscle biopsies both before[172] and following maximal exercise in people with Long COVID[87]. Additionally, immune-mediated structural changes in the skeletal muscle microvasculature may contribute to exercise-induced fatigue and muscle pain[179]. As skeletal muscle pain is often triggered by local inflammation and the release of cytokines by infiltrating immune cells, these mechanisms may help explain the pain experienced after exertion that exceeds the PEM threshold[175–178].

Currently, there are no established cures or pharmacological treatments for PEM. Therefore, effective symptom management strategies, such as pacing, are essential. While there is emerging evidence supporting the role of physical therapy in managing PEM (REF), there remains no compelling evidence across post-acute infectious syndromes that graded exercise therapy (GET) is effective in restoring pre-infection levels of function[180]. Prior studies supporting GET have been subject to extensive critique[181–184], due to issues such as vague inclusion criteria, high drop-out rates, unclear exercise prescriptions, and failure to measure PEM-related outcomes. Until further research is available that can outline the biomechanistic causes of PEM, the World Health Organisation[185], Centres for Disease Control[186], National Institute for Health and Care Excellence[187,188], and World Physiotherapy[189] Guidelines explicitly do not recommend graded exercise therapy as a treatment for people with Long COVID.

In the absence of effective medications to raise the PEM threshold or shorten its duration, the most widely used strategy for managing PEM is pacing. Pacing involves encouraging individuals to remain as active as possible without exceeding their PEM threshold[190], by organising daily activities within their established functional limits[191]. This strategy aims to prevent and reduce the frequency and severity of PEM episodes. To be effective, pacing strategies must be highly individualised, accounting for the fluctuating and episodic nature of Long COVID. Incorporating objective biophysical monitoring tools, such as blood lactate levels[192], heart rate, and heart rate variability, can support the development of personalised pacing plans[193]. These physiological markers can be integrated into daily routines and offer near real-time feedback[194], helping individuals remain within their energy envelope and avoid triggering PEM. While pacing does not provide a cure, it offers a practical approach to improving functional status, quality of life, and fatigue management in the absence of pharmacological treatments. However, despite its widespread use, the efficacy of pacing as a management strategy for PEM has not yet been rigorously studied, highlighting an urgent need for further research.

Sleep disturbances in long COVID

People with acute COVID-19, particularly those who experienced more severe symptoms during the initial infection, and those with Long COVID, frequently report excessive daytime sleepiness, low mood, and a diminished quality of life[195]. Hospitalisation for COVID-19 is associated with a significantly increased risk of breathlessness and sleep disorders compared to non-hospitalised individuals. In a study involving 2,320 participants, those who were not hospitalised showed a higher risk of circadian rhythm sleep disorders[196]. Mediation analysis indicated that anxiety accounted for 18–39% of the observed effects, while muscle weakness contributed 27–41%. One of the most comprehensive multinational studies on sleep quality in COVID-19 survivors identified at least six separate domains of sleep disturbance and confirmed that the severity of the initial infection was an independent predictor of poor sleep outcomes[197]. Despite these findings, there remains a critical need to better understand the underlying pathology of self-reported sleep disturbances and insomnia in Long COVID.

Table 1 | A table summarising some important research/knowledge gaps that could improve the pathophysiological understanding of Long COVID

1 Pathophysiological mechanisms •Investigate the underlying biological mechanisms driving Long COVID symptoms, including immune dysregulation, viral persistence, endothelial dysfunction, mitochondrial impairment, and autonomic nervous system involvement. •Explore biomarkers that can objectively characterise disease subtypes and severity.
2 Standardised case definitions and diagnostic criteria •Develop and validate standardised, globally accepted diagnostic criteria and case definitions to improve comparability across studies and enable accurate diagnosis. •Incorporate objective measurements (e.g., biomarkers, imaging, physiological monitoring) alongside clinical symptoms.
3 Epidemiology and natural history •Conduct large-scale, longitudinal cohort studies across diverse populations to map the incidence, prevalence, risk factors, and natural progression of Long COVID. •Assess disparities in Long COVID outcomes related to demographics, socioeconomic status, geography, and access to care.
4 Diagnostic tools and biomarkers •Validate accessible, cost-effective diagnostic tools and biomarkers to guide diagnosis, prognosis, and treatment decisions globally. •Leverage wearable technologies and digital health platforms for continuous symptom and physiological monitoring.
5 Therapeutics and management strategies •Test repurposed and novel pharmacological interventions in randomised controlled trials, focusing on symptom clusters and pathophysiological targets. •Evaluate non-pharmacological interventions such as pacing, physical therapy, cognitive rehabilitation, and mental health support. •Develop personalised treatment algorithms informed by biomarkers and patient characteristics.
6 Impact on mental health and quality of life •Investigate the psychological and social impacts of Long COVID, including anxiety, depression, sleep disturbances, and cognitive impairment. •Develop integrated care models addressing both physical and mental health sequelae.
7 Health systems and policy research •Assess the burden of Long COVID on healthcare systems and develop scalable care models suitable for different resource settings. •Explore strategies for equitable access to diagnosis, treatment, and rehabilitation services worldwide.
8 Global collaboration and data sharing •Foster international research collaborations to share data, harmonise protocols, and accelerate discovery. •Prioritise inclusion of low- and middle-income countries to ensure findings are globally representative.
9 Patient and public involvement •Engage patients and communities in the design, conduct, and dissemination of research to ensure relevance and acceptability. •Incorporate patient-reported outcomes and lived experience into research frameworks.
10 Long-term outcomes and post-pandemic preparedness •Monitor long-term outcomes to identify potential chronic sequelae and inform guidelines for post-pandemic rehabilitation. •Integrate Long COVID research into broader pandemic preparedness and response strategies.

Objective assessments, such as polysomnography, should be more widely utilised. These have shown a marked reduction in slow-wave sleep and the presence of both sleep-onset and sleep-maintenance insomnia, often characterised by prolonged periods of wakefulness after sleep onset[198]. Of particular concern is the presence of REM sleep behaviour disorder (RBD), a parasomnia involving dream-enactment behaviours due to the loss of REM sleep atonia[199]. RBD and REM sleep without atonia are both associated with alpha-synucleinopathies and are known risk factors for developing neurodegenerative diseases such as Parkinson's disease[200]. A prospective cohort study of individuals with Long COVID reported excessive daytime sleepiness, including central hypersomnolence and new-onset narcolepsy, in 3.2% of participants. This study also noted a signal suggesting an increased risk of central hypersomnolence syndromes and narcolepsy in this population[201]. The importance of sleep is well documented, but research on Long COVID is currently still in its infancy. Still, the impact of sleepiness in people with Long COVID on physical and mental well-being, functional status, and quality of life should be better studied. Whilst the importance of sleep for health is well-established, research into sleep disturbances in Long COVID remains in its early stages. Further investigation is urgently needed to better understand how sleep dysfunction affects physical and mental well-being, functional capacity, and overall quality of life in people with Long COVID.

Guidance for clinical practice

Long COVID continues to represent a significant unmet clinical need and is contributing to rising healthcare costs on a global scale. While advancing our understanding of the underlying pathophysiology remains central to addressing this condition, the development of precision or personalised medicine approaches is unlikely to progress meaningfully without increased research efforts aimed at uncovering the biological mechanisms of this novel disease. In parallel with deeper pathological insight, there is an urgent need to expand access to diagnostic testing that can support clinical decision-making in Long COVID. Where symptom profiles and underlying pathologies overlap with other conditions, there is potential to repurpose existing licensed medications, an approach that should be evaluated at scale.

Effective symptom management strategies must increasingly leverage wearable technologies capable of tracking biomarkers such as heart rate variability (HRV). These tools, when combined with artificial intelligence and machine learning, can deliver real-time, objective feedback to both patients and clinicians. Where feasible, integrating this physiological data with biological insights will allow for the refinement of treatment strategies and ultimately improve patient outcomes.

Moving long COVID research forward

While international and collaborative research efforts have advanced the pathophysiological understanding of Long COVID, many areas still require further investigation before effective management and curative treatments can be integrated into standard clinical care. Although numerous multicentre trials have enhanced our pathological insights. Notably, in the United States, NIH RECOVER-TLC (Researching COVID to Enhance Recovery-Treating Long COVID), an ongoing programme sponsored by the National Institute of Allergy and Infectious Diseases, which aims to identify and pilot the most promising treatment avenues for specific Long COVID subsets by fostering integration of data from pathobiological studies with clinical data from observational cohorts cohorts[202]. However, there remains a significant gap in mechanistic understanding, which has hindered the development of clear diagnostic criteria applicable to clinical practice and service delivery pathways[203].

Until the key mechanisms of Long COVID are elucidated and curative therapies developed, individuals living with this episodic disability must

have access to high-quality, evidence-based, condition-specific interventions aimed at alleviating and managing their symptoms. To support these global efforts, sustained commitment and investment from governments, policymakers, and research funding bodies are essential to prevent the emergence of substantial public health and socioeconomic burdens. Accordingly, in Table 1, we propose key research priorities necessary for advancing mechanistic knowledge, which can inform the development of condition-specific diagnostic approaches and care pathways that incorporate effective treatment and management strategies.

Conclusion

Long COVID represents a significant and complex global health challenge, characterised by a wide spectrum of persistent symptoms driven by multifactorial pathophysiological mechanisms. Although research has advanced considerably, critical gaps remain in identifying definitive diagnostic biomarkers, fully understanding disease mechanisms, and developing effective treatments. The intricate interplay between immune dysregulation, endothelial dysfunction, viral persistence, and coagulation abnormalities underscores the necessity for interdisciplinary research to unravel the underlying pathways of Long COVID. Future research must prioritise large-scale, rigorously controlled studies to establish pathology-specific biomarker profiles, refine diagnostic criteria, and develop targeted therapeutic interventions. Addressing the heterogeneity of Long COVID through precision medicine approaches will be crucial for improving patient stratification and optimising treatment strategies. Moreover, sustained investment and international collaboration are essential to alleviate the long-term health and socioeconomic impacts of this condition. Until curative therapies emerge, emphasis on evidence-based symptom management, early diagnosis, and patient-centred care remains vital to enhancing quality of life and reducing disease burden. As Long COVID research stands at a critical crossroads, bridging these knowledge gaps will not only revolutionise care for those affected but also provide valuable insights into other post-viral syndromes and chronic inflammatory diseases.

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Competing interests

The authors declare no competing interests.

Additional information

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