

Long COVID: confronting a growing public health crisis



In May, 2021, *The Lancet Respiratory Medicine* published a Series of papers about the pathophysiology of acute COVID-19. More than 1 year into the pandemic, high-quality evidence from randomised controlled trials (RCTs) was shaping the management and outcomes of acute COVID-19, but striking evidence of post-acute impairments—spanning physical, cognitive, and mental health domains and lasting for weeks or months after the initial infection—was also accumulating. Now, more than 3 years after the emergence of SARS-CoV-2, at least 65 million people worldwide are estimated to have post-acute sequelae of COVID-19—also known as the post-COVID-19 condition or long COVID—and there is an urgent need for preventive, rehabilitative, and therapeutic strategies to avert an overwhelming public health crisis.

In a new *Lancet Respiratory Medicine* Series about the post-acute sequelae of COVID-19, Sally J Singh and colleagues discuss the origins of respiratory sequelae and consider the promise of adapted pulmonary rehabilitation programmes and physiotherapy techniques for breathing management. Pratik Pandharipande and colleagues review the epidemiology and pathophysiology of neuropsychological sequelae of COVID-19-related critical illness, highlighting the combined threat of long COVID and post-intensive care syndrome (PICS), and outline potential mitigation strategies. Finally, Matteo Parotto and colleagues discuss pathophysiological mechanisms of diverse, multisystem sequelae in adult survivors of critical illness, including longitudinal effects of endothelial and immune system dysfunction, and consider the challenges of providing appropriate care and support for patients.

Vaccination against SARS-CoV-2 appears to reduce the risk of developing long COVID, and Pandharipande and colleagues emphasise that optimum management in the acute phase could mitigate sequelae of COVID-19-related critical illness. In a recent RCT, early outpatient treatment with metformin in the acute phase was associated with a lower incidence of long COVID, but its mechanism of action remains unclear.

Studies have identified functional impairments and symptoms involving multiple organ systems (eg, fatigue, breathlessness, joint pain, and cognitive impairment) after acute COVID-19, and provided insights into the causes and pathophysiology of post-acute sequelae. However, no consensus has been

reached on the definition of long COVID and no reliable diagnostic biomarkers or tests are available. A reliance on patient self-reporting and the difficulty of distinguishing specific effects of SARS-CoV-2 infection and COVID-19 from the progression of pre-existing comorbidities or from overlapping chronic conditions, such as PICS, are challenges for research. Nevertheless, promising rehabilitative approaches and treatment candidates (eg, antivirals, immunomodulators, anti-inflammatory agents, and anticoagulants) have been identified. Support for large-scale, coordinated, multidisciplinary research initiatives will be essential to explore causes, phenotypes, the course of individual symptoms and symptom clusters, and underlying mechanisms of long COVID, to identify diagnostic and prognostic biomarkers, and to develop targeted interventions to prevent or ameliorate persistent symptoms. A consensus-based core outcome set provides a framework for the standardised assessment of adults in future studies.

Potential predictors of long COVID include age, sex, genetics, the severity and management of acute disease, pre-existing comorbidities, and socioeconomic status, which demand further study to inform clinical care and research. In addressing the global burden of long COVID, the needs of vulnerable populations must be considered, including the urgent needs of patients in low-income and middle-income countries, where resources for research and clinical care might be scarce. Research participants should reflect the global population of patients with long COVID, and diverse patient groups should be consulted in the setting of research priorities, the design and conduct of studies, and the development of models of care and support. Access to a well-resourced long COVID or PICS clinic with a well-trained, interprofessional team is a priority for patients and their families.

Post-acute sequelae of COVID-19 can have a devastating impact on individuals' health, wellbeing, daily activities, and livelihoods. Effects on health systems, economies, and society are also substantial and growing. On May 5, 2023, WHO announced that COVID-19 no longer constitutes a public health emergency of international concern. However, the post-acute sequelae of COVID-19 are a growing public health crisis on a global scale that demands a focused, well-resourced, and patient-centred response. ■ *The Lancet Respiratory Medicine*



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Published Online
July 19, 2023
[https://doi.org/10.1016/S2213-2600\(23\)00268-0](https://doi.org/10.1016/S2213-2600(23)00268-0)

For more on the **physical, cognitive, and mental health impacts of COVID-19** see **Articles** *Lancet Respir Med* 2021; 9: 1275–87

For more on **long COVID** see *Nat Rev Microbiol* 2023; 21: 133–46

For the paper by Singh and colleagues see **Series** page 709

For the paper by Pratik Pandharipande and colleagues see **Series** page 726

For the paper by Matteo Parotto and colleagues see **Series** page 739

For more on the **trial of metformin** see **Articles** *Lancet Infect Dis* 2023; published online June 8. [https://doi.org/10.1016/S1473-3099\(23\)00299-2](https://doi.org/10.1016/S1473-3099(23)00299-2)

For more on the **pathophysiology of long COVID** see **Comment** *Lancet Infect Dis* 2023; 23: 393–95

For more on the **core outcome set for post-COVID-19 condition** see **Position Paper** *Lancet Respir Med* 2022; 10: 715–24