Looking for lights in the fog of long-term neurological COVID

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A new study provides evidence for an association between COVID-19 and long-term neurological syndromes. The findings highlight the need for further research into the long-term neurological consequences of SARS-CoV-2 infection and the development of strategies that lessen the effects of these consequences on patient quality of life and on healthcare systems.

A large body of literature has reported a higher rate of neurological syndromes during acute COVID-19 than in healthy individuals. However, whether SARS-CoV-2 infection leads to a higher risk of long-term neurological consequences is still unclear. A wide spectrum of symptoms, including impaired concentration, headache, hyposmia, fatigue and myalgias, can persist for months after infection as part of a constellation now referred to as long COVID. The neurological syndromes that make up long COVID vary widely among individuals, and the relationship between these symptoms and SARS-CoV-2 infection is a matter of debate — it can be coincidental, consequential or interacting. The existing data on long COVID are rather heterogeneous, probably as a result of differences among the study populations and diagnostic criteria used, a lack of standardized assessment and the high risk of recall bias, which applies to all studies of SARS-CoV-2. Furthermore, one study reported that long-term neurological symptoms might be more associated with the belief of having been infected with SARS-CoV-2 than with having laboratory-confirmed SARS-CoV-2 infection, thus limiting the interpretation of available data. Nevertheless, neurological long COVID represents a substantial health and economic burden, which demonstrates an urgent need to disentangle the involvement of different neurological disorders by various mechanisms and to develop effective strategies for prevention and care.

The study by Xu and colleagues expands on evidence concerning the long-term complications of COVID-19 and provides new insights into this complex and evolving situation. The researchers analysed approximately 14 million medical records in a dataset from the US Department of Veterans Affairs, which is the nation’s largest integrated healthcare system. These records included data from approximately 150,000 people who had tested positive for COVID-19 and survived the first 30 days after infection. The cohort included individuals affected by the entire spectrum of COVID-19 severity, including a large proportion of individuals who had not been admitted to hospital, 16,764 individuals who had been admitted to hospital and 5,389 individuals who were admitted to intensive care units (ICU). Statistical modelling was used to compare neurological outcomes in the COVID-19 group with neurological outcomes in two control groups: a group of more than 5.6 million individuals without COVID-19 evaluated during the same time frame (contemporary control group) and a group of more than 5.8 million individuals evaluated before the global COVID-19 pandemic (historical control group). Key limitations of the study included a large predominance of white males in the cohort and the absence of matched patient groups that were hospitalized or treated at home with infectious diseases other than COVID-19, as well as a group of asymptomatic COVID-19 individuals.

Compared with the control participants, participants who had COVID-19-related symptoms had an increased risk of several central and peripheral nervous system outcomes 1 year after infection. These neurological syndromes included cerebrovascular diseases, encephalitis, fatigue, cognitive problems, mental health disorders, neuropathies and muscular disorders. The authors estimated that the hazard ratio of any neurological sequelae 1 year after infection was ~1.4, with a burden of ~70 per 1,000 people.

Importantly, previous findings have reported that only 5–20% of individuals infected with SARS-CoV-2 have symptoms and only 5–20% of individuals with symptoms will require hospitalization. Age, premorbid health status and frailty have an important role in modulating the short and long-term outcomes of COVID-19. Several studies have shown that COVID-19-related symptoms and clinical course are more severe in individuals who are older and have multimorbidities than in younger, healthy adults. This issue is crucial, as most data on long COVID are derived from hospitalized or symptomatic individuals, who are at higher risk of deterioration and long-term disease burden, but also present with worse premorbid health conditions than individuals with asymptomatic infection. A large body of literature has shown that up to a third of individuals hospitalized with acute COVID-19 either experience worsening of premorbid neurological disturbances or present with new neurological complications during hospitalization. Furthermore, there is evidence that most individuals with long COVID either already had a premorbid neurological disease or are affected by the consequences of a COVID-19-related neurological disorder, such as stroke or encephalitis.

"the incidence […] was significantly increased with greater severity of the acute COVID-19 infection"

The study by Xu and colleagues builds on previous literature by providing separate adjusted ratios for hospitalized and non-hospitalized individuals, as well as those admitted to ICU. Compared
with the contemporary control group, the incidence of long-term neurological outcomes was significantly increased with greater severity of the acute COVID-19 infection, with the lowest incidence observed in non-hospitalized individuals and the highest in individuals admitted to ICU. In addition, the risk of most neurological sequelae of COVID-19—especially mental health disorders—increased with increasing age, which supports the claim that the long-term burden of COVID-19 frequently represents non-specific effects of hospitalization on frail patients and might not be a unique feature of COVID-19. These results are of great relevance for the neurology community, as older patients are at higher risk of hospitalization for COVID-19, but also of cerebrovascular events and neurodegenerative diseases, which might underlie several symptoms thought to be part of the long COVID spectrum. We therefore speculate that the nervous system is a highly vulnerable system in individuals with multisystemic COVID-19, and that age, frailty and premorbid health status are the key susceptibility factors behind most of the long-term neurological disorders that follow SARS-CoV-2 infection.

Interestingly, younger adults exhibited a higher COVID-19-related risk of memory and cognitive disorders, sensory disorders and other neurological disorders (including Guillain–Barré syndrome and encephalitis or encephalopathy), probably owing to a combination of immunological and psychological factors. Indeed, neuroimaging studies have reported that COVID-19 can affect brain health by triggering an abnormal inflammatory response, which has been claimed to be the main pathogenetic mechanism of both short-term and long-term symptoms of COVID-19\(^{1,2}\). Several biological, psychological and social factors might also weaken resilience to COVID-19 and contribute to the long-term burden of the disease (Fig. 1). Overcoming the challenge of the long-term consequences of COVID-19 therefore requires us to take into account the complexity of premorbid health status and severity of disease, to unravel the contributions of different conditions in order to identify possible avenues for the most appropriate care.

**Fig. 1 | Model of potential risk factors associated with brain vulnerability and long-term neurological sequelae of COVID-19.** Older age, premorbid health status, somatic multimorbidity and psychological factors have a major role in modulating the severity of COVID-19 and its consequences. The severity of COVID-19 affects brain vulnerability and might trigger either the acute onset of neurological disease or the worsening of existing neurological conditions. Medical and mental health status, as well as socioeconomic conditions, influence the final global burden of long-term neurological syndromes.

Data on vaccinated individuals and from long-term (2-year) follow-up of individuals who had COVID-19 now suggest a global reduction in the long-term burden of COVID-19\(^{3,4,10}\). The study by Xu and colleagues\(^3\) thus elicits further consideration and provides a unique opportunity for health systems to reconsider prevention strategies to tackle the burden of long COVID. The new data, together with previous findings, demonstrate a strong need to develop a common strategy to shelter brain health from COVID-19 and thereby to preserve mental health and wellbeing in the post-pandemic era.

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**Competing interests**

The authors declare no competing interests.