Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A longer look at COVID-19 and neuropsychiatric outcomes

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Early in the pandemic, concerns were raised about the potential for serious and widespread neurological and psychiatric adverse outcomes following COVID-19, on the basis of a systematic review of observational studies done in patients infected during previous coronavirus epidemics.[1] Interpretation was hampered by the absence of a comparison group of individuals who had similar infections. The first large-scale attempt to redress this issue was published by Maxime Taquet and colleagues[2] who found, using real-world data, that a first psychiatric diagnosis was more common in patients with COVID-19 in the 14–90 days after SARS-CoV-2 infection than in those with several other acute illnesses. In *The Lancet Psychiatry*, Taquet and colleagues expand on this finding by estimating incidence rates and relative risks of 14 neurological and psychiatric diagnoses in patients in the 6 months after a COVID-19 diagnosis.[3] Using data from a large electronic health records network (> 81 million patients), the authors defined a primary cohort of 236 379 patients who had a COVID-19 diagnosis, one matched control cohort of 105 579 patients diagnosed with influenza, and another matched control cohort of 236 038 patients diagnosed with any respiratory tract infection including influenza in the same period. All included patients were older than 10 years, had an index event on or after Jan 20, 2020, and were still alive on Dec 13, 2020.

Taquet and colleagues showed that, in the 6 months after SARS-CoV-2 infection, about a third of individuals had a neurological or psychiatric disorder (incidence 33·62%, 95% CI 33·17–34·07, for any diagnosis; 12·84%, 12·36–13·33, for any first diagnosis), substantially more than comparative figures for influenza.[3] Most of the neurological or psychiatric disorders assessed were more common in patients who had COVID-19 than in those who had influenza (hazard ratio [HR] 1·44, 95% CI 1·40–1·47 for any diagnosis; 1·78, 1·68–1·89, for any first diagnosis) and those who had other respiratory tract infections (1·16, 1·14–1·17, for any diagnosis; 1·32, 1·27–1·36, for any first diagnosis).

Big-data studies of this kind have intrinsic limitations, even when drawing on 81 million people, 236 379 of whom had COVID-19. In this pandemic context, not all individuals who are infected with SARS-CoV-2 (particularly those with mild or asymptomatic illness) will be diagnosed, which could result in some contamination of the comparison groups. Additionally, as with many non-public administrative health-care records, data are scarce on family history of neurological or psychiatric disorders and previous illness, especially if different providers were involved in managing records. As an additional limitation, 2020 was an atypically low-incidence year for influenza because of social distancing measures,[4] although Taquet and colleagues did sensitivity analyses comparing their results with the rates of sequelae of patients with influenza in 2019 and 2018, which supported their main findings.

This study has several important implications. A relationship between COVID-19 and ischaemic stroke has been well described,[5] though COVID-19 seems to be a stronger risk factor for intracranial haemorrhage, albeit a rarer event, than for ischaemic stroke. Data on a relationship with dementia have been sparse, and the high HR (1·88, 95% CI 1·27–2·77) for dementia in patients with COVID-19 compared with influenza is concerning, although this could indicate better case

ascertainment. Fortunately, initial alarming reports of Guillain-Barré syndrome in relation to COVID-19 do not seem to have been borne out by this or other large-scale epidemiological studies.[6] Similarly, concerns about a wave of encephalitis lethargica, analogous to that sometimes linked to the 1918 influenza pandemic,[7] were not supported by the rather equivocal relationship between COVID-19 infection and parkinsonism. From the outbreak start in Wuhan, China, we can say with growing confidence that delayed neuropsychiatric sequelae such as post-encephalitic parkinsonism do not occur after COVID-19—unless the delay exceeds 1 year.

The pattern of neurological and psychiatric outcomes observed in Taquet and colleagues' study across the spectrum of COVID-19 severity is also instructive. While the HRs for COVID-19 with hospitalisation versus without were generally higher than 2 for neurological disorders including stroke, parkinsonism, Guillain-Barré syndrome, neuromuscular or muscle disease, encephalitis, and dementia, more modest ratios were observed for common mental disorders such as incident mood disorder (HR 1·53, 95% CI 1·33–1·75), anxiety disorder (1·49, 1·34–1·65), substance use disorder (1·68, 1·40–2·01), and insomnia (1·49, 1·28–1·74). This suggests that, although almost all neurological and psychiatric outcomes were more frequent in patients with more severe COVID-19 than in those with mild disease, these psychiatric disorders might be more driven by general effects, including psychosocial aspects of infection, rather than a direct effect of COVID-19 on the brain.

The latest study by Taquet and colleagues permits the question: will severe, enduring, and less common conditions such as psychoses behave more like neurological disorders or common mental disorders? Among the COVID-19 cohort, a first diagnosis of a psychotic disorder was substantially more common in patients hospitalised with COVID-19 (HR 2·77, 95% CI 1·99–3·85), and most especially in those with encephalopathy (5·62, 2·93–10·77), than in those who were not hospitalised. This link with encephalopathy seems important, even if the underlying mechanism turns out to be indirect.[8] However, caution is required in interpreting this apparent association. First, it might be a consequence of difficulties in distinguishing primary psychotic disorders from delirium.[9] Second, all affected patients were, on average, 53 years old (population mean age 46 years, SD 19·7), so patients with first-onset psychosis were likely to have been much older than cases of schizophrenia and related disorders with a peak age of onset in early adulthood. The findings by Taquet and colleagues could be consistent with the psychoses being triggered by external causes but, more likely, they could be exacerbations of pre-existing conditions unknown to the health-care provider. Additionally, an association between psychosis (and dementia) and encephalopathy could be due to reverse causality.

Finally, Taquet and colleagues' study points us towards the future, both in its methods and implications. Researchers need to be able to observe and anticipate the neurological and psychiatric outcomes of future emerging health threats by use of massive, international, real-world clinical data. Selection biases will remain an issue, not necessarily mitigated by sample size,[10] and thus the onus should be on countries with public health-care systems to enable truly comprehensive national data to be available for research. Sadly, many of the disorders identified in this study tend to be chronic or recurrent, so we can anticipate that the impact of COVID-19 could be with us for many years.

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