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Neuropsychiatric sequelae of COVID-19: long-lasting, but not uniform

Lancet Psychiatry 2022
Published Online
August 17, 2022
https://doi.org/10.1016/S2215-0366(22)00302-9
See Online/Articles
https://doi.org/10.1016/10.1016/S2215-0366(22)00260-7

Early in the COVID-19 pandemic, in our research group we reviewed the psychiatric outcomes of individuals who had been infected by one of two previous coronavirus epidemics: severe acute respiratory syndrome (known as SARS) and Middle East respiratory syndrome (known as MERS).[1] The main weakness of the previous literature was the absence of any valid comparison group. Symptoms such as insomnia, anxiety, mood changes, impaired concentration, irritability, fatigue, and traumatic memories were common, and still reported months and years after initial diagnosis. However, without a control group, knowing whether risk of these psychiatric outcomes was actually increased after contracting disease was difficult and it was impossible to estimate the size of any association.

In several previous studies, Maxime Taquet and colleagues have innovatively used the largely US-based TriNetX database to analyse the electronic health-care records of hundreds of thousands of patients with COVID-19.[2–4] Their particular contribution has been to leverage an appropriate control group of individuals who have had another respiratory tract infection.

In their new Article in *The Lancet Psychiatry*, Taquet and colleagues[5] aim to address various outstanding issues regarding the variation of neurological and psychiatric sequelae of COVID-19 in terms of longitudinal course, age, and the effect of SARS-CoV-2 variants. In their longitudinal cohort study based on electronic patient records, they matched individuals who had a recorded case of COVID-19 using propensity scores to individuals with another respiratory infection and without COVID-19 in the database.

Determining the longitudinal trajectory of neurological and psychiatric sequelae is particularly poignant. As we emerge from the acute phase of the COVID-19 pandemic, understanding whether or not the ensuing risks for neuropsychiatric sequalae as a result of SARS-CoV-2 infection are transient or persistent is crucial. Taquet and colleagues' research—at least over a follow-up period of 2 years—indicates that this risk depends on which neurological or psychiatric outcome is being considered.

Numerous studies have shown an increased risk of mood and anxiety disorders after SARS-CoV-2 infection. The current study found that the risk of both mood and anxiety disorders peaks during acute SARS-CoV-2 infection and then returns to the baseline risk in the control group within a couple of months. Interestingly, thereafter, the hazard ratio continues to decrease, such that an individual's risk of developing such disorders is actually lower than in the control group after just a few weeks. This results in an equal incidence of mood or anxiety disorders by approximately 15 months after infection (417 days for anxiety disorders and 457 for mood disorders) between the two groups. However, psychological or socioeconomic factors associated with being tested for COVID-19 might have acted as confounders for this analysis, and so the results should be interpreted with caution.

Concerningly, several neurological and psychiatric outcomes never reached an equal incidence or even a risk horizon, meaning that even 2 years after COVID-19, some neuropsychiatric sequelae were continuing to occur at a higher frequency than among the control group. Two of these outcomes merit particular consideration: psychotic disorders and dementia.

When studies first began to report cases of psychotic disorders during or shortly after COVID-19, there was criticism based on the supposition that delirium, which commonly features delusions and hallucinations as part of a transient altered mental status, was the most probable explanation.[6] The current study found that, in fact, the risk of psychotic disorder remained increased throughout the 2-year follow-up period, so delirium is unlikely to be the main explanation. However, how valid such diagnoses are in routinely collected data remains uncertain.

In the general population, individuals who have had COVID-19 have been found to have substantial deficits on computerised cognitive batteries.[7] Taquet and colleagues found that this deficit does indeed seem to translate into an increased risk of a diagnosis of dementia. However, dementia has an insidious onset and the cohort is likely to have had some participants with undiagnosed or subclinical cases at baseline. Although concerning, the findings regarding psychosis and dementia need replication in a cohort in which there is more thorough ascertainment of case status.

As well as finding differences between outcomes, Taquet and colleagues also found that there were differences between age groups, with children generally having a more benign course. The authors' attempt to ascertain differences in outcomes between SARS-CoV-2 variants is laudable, but should be interpreted with caution. Pressure on health-care services, awareness of long-term sequelae of COVID-19, and different thresholds for seeking SARS-CoV-2 testing are all likely confounders that have had a role in altering the supposed risks across time periods, which were used by the authors as a proxy for variants. However, overcoming such limitations in time-series analyses is very difficult and Taquet and colleagues' study provides preliminary evidence.

This study is the first to attempt to examine some of the heterogeneity of persistent neurological and psychiatric aspects of COVID-19 in a large dataset. It highlights some clinical features that merit further investigation, but it must be complemented by prospective studies that provide more validation of outcomes.

GL has received grants from Wellcome Trust and University College London Hospital Biomedical Research Centre. JPR declares no competing interests.

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