COVID AND NEUROLOGICAL RISK

Professor Paul Harrison discusses his cutting-edge research into COVID and risk of dementia, brain fog and psychosis.

The long-term physical effects of a COVID infection have been investigated, analysed and discussed at length, but not quite so much has been said about the psychiatric and neurological repercussions of the viral infection. What lasting impact might the virus have had on people's levels of depression and anxiety, and on diagnoses of conditions such as dementia, epilepsy and psychosis?

This imbalance has been redressed, in part, by the publication in August's *The Lancet Psychiatry* of "Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of two-year retrospective cohort studies including 1,284,437 patients". Conducted by a team from the University of Oxford, the study found that some conditions were more common two years after the onset of a COVID infection, but others were not.

Roots of the research

Lead author Professor Paul Harrison, from the university's department of psychiatry, says the roots of the research were laid down in the early days of the pandemic, amid concerns, based on evidence from previous viral outbreaks, that this new virus would bring an increased risk of a range of mental problems.

"There was a theoretical reason to think that SARS-CoV-2 might produce similar problems. Then, fairly early in the pandemic, we began to hear anecdotal reports of people who had developed COVID and didn't seem to be recovering from it as quickly as one might have hoped. As an academic psychiatrist I'm interested in these sorts of questions, so we took the opportunity to do research in the area to try and put some robust numbers on the scale and the nature of the association between having had a COVID infection and then developing a range of psychiatric and neurological diagnoses."
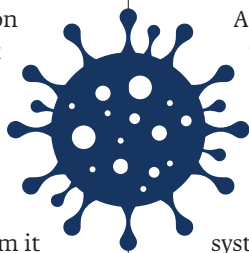
As with so much of the other research that has centred around COVID, this study took full advantage of the recent trend for healthcare systems to move over to electronic health records.

"There are a number of different systems in different parts of the world, and we happened to have access to TriNetX," says Harrison. This particular network consists of around 89 million de-identified records collected from hospitals and other healthcare providers mostly in the US but also in the UK, Spain, Bulgaria, India, Malaysia, Taiwan and Australia. "It is a big sample size, which gives us a lot of power to identify what the risks might be and the factors associated with different people."

Risk trajectory

Harrison's team have been delving into this gigantic block of data to identify everybody who had a confirmed diagnosis of COVID infection and then to compare them with otherwise matched patients who'd had been diagnosed with other infections – all with the goal of getting a sense of what, if anything, might be different, in terms of the psychiatric and neurological effects, between a COVID infection and those other infections. This latest paper from the team represents the biggest and the longest follow-up

risk of being given a new diagnosis."

The paper sets out the data in all their richness, but, in essence, the team found two categories of risk trajectory. "One was actually very transient," says Harrison. "The common mental health problems that we had been concerned about – those greater risks had disappeared within a few months, at the most, compared to other infections. It appeared that COVID was maybe having a short-lived effect as a stressor, precipitating diagnoses of depression and anxiety. But taking a two-year perspective, there was no greater risk of getting depression or anxiety after COVID than other infections."

However, the picture changed when looking at the more neurological-based conditions. "These are things such as dementia and brain fog, but also psychosis, which is a psychiatric problem. For these conditions, the risks didn't seem to go away. Even two years after COVID infection, people were still more likely to get a diagnosis than with other infections. This suggest there are two clusters of risk and that there might be different mechanisms at play."

Emerging theories

Since the start of the pandemic, a number of theories have emerged to explain the association between a COVID infection and mental health issues. A direct viral or persistent viral infection of the nervous system is one theory. A second is that it is collateral damage from the body's immune response. A third is the propensity of COVID to cause blood clots, or microthrombi. "This is the theory where the most evidence is beginning to accumulate. Other researchers are using brain scanning of different sorts,

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particularly MRI, to identify potential changes in brain structures or connectivity, which may be part of the underlying mechanisms causing these problems to develop."

The team is now involved in PHOSP-COVID, a large study looking at the long-term health of patients in the UK who had been hospitalised with COVID. "Some of those patients are approaching the two-year follow-up, and we are looking at their risks of these mental health issues and what, if anything, are the biomarkers that predict their persistence two years later."

For Harrison, one of the key lessons of the TriNetX-based research is just how quickly results can be extracted from electronic health records. "We can't underestimate the value of that. My normal research is lab-based, and all that stopped overnight during the first lockdown. But I was able to switch with some of my team immediately to doing this research from home perfectly happily. We have produced good data on the scale and nature of the association between this particular virus and subsequent mental and brain health, and there's a real sense that this is important public health research." **BMS**

of the outcomes for those patients.

"Previous studies have suggested that in the first few months after a COVID infection, people were at greater risk of a range of mental and neurological disorders. But we also wanted to see how long those risks last and whether the trajectory of risk is the same for all the different disorders. So we simply measured up to two years after COVID infection the

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