Insight

SARS-CoV-2 infection as a cause of neurodegeneration

For the **dementia Commission** see **The Lancet Commissions** *Lancet* 2020; **396:** 413–46

For more on **Herpesviridae and neurotropic infection** see *J Alzheimers Dis* 2022; **88:** 1189–200

For more on **Herpesviridae and neurological disease** see *Science* 2022; **375:** 296–301

For more on **parkinsonian symptoms** see *Biochim Biophys Acta* 2009; **1792:** 714–21

For the **multicohort study** see **Articles** *Lancet Infect Dis* 2021; **21:** 1557–67

For the **study using data from the biobanks** see *Neuron* 2023; **111:** 1086–93

Neurodegenerative disease is attributed in roughly equal parts to genetic risks present at birth and modifiable risk factors, such as air pollution or brain injury, which differ between age groups and populations. Risk factors can interact, but the calculation of synergistic risk is complicated, so the standard approach is to present the marginal risk as partitioned between the individual causative factors. *The Lancet* Commission on dementia prevention, intervention, and care established 12 modifiable risk factors and described bidirectional interactions between delirium (which can arise from infectious disease) and dementia. It also outlined dementia as a risk factor for COVID-19 mortality, but could not investigate the risk of dementia after SARS-CoV-2 infection. Here, we discuss evidence of neurodegenerative disease risk from SARS-CoV-2 infection.

Infectious disease is now established as a cause of neurodegeneration, although neurological harm due to viral infection is difficult to quantify. Neurological symptoms from neurotropic infections are well documented, in particular for the Herpesviridae family, including Epstein–Barr virus and herpes simplex virus type 1. Neurological harm is not unique to Herpesviridae, and members of the Bornaviridae, Orthomyxoviridae (including influenza), Paramyxoviridae, Picornaviridae, Retroviridae, and Flaviviridae families have been linked to the development of parkinsonian symptoms. A multicohort study identified an increase in dementia risk after hospitalisation for an infectious disease. Relative risk (RR) following an infection was significant (1·22, 95% CI 1·09–1·36) in people with a follow up of a minimum of 10 years from hospital admission, and became higher (1·48, 95% CI 1·37–1·60) with follow-up until death, dementia diagnosis, or study completion (median of 15·4 years). The long lag time is concerning: hospitalisations due to infectious disease can therefore be expected to lead to dementia diagnoses with a substantial time delay.

A longitudinal study of SARS-CoV-2 sequelae over decades is obviously unavailable but, so far, the estimated lifetime cumulative risk of dementia due to hospitalisation for any viral infection is 1·48 (95% CI 1·15–1·91). By comparison, persistent herpes infection carried an RR of 2·1 (95% CI 1·40–3·14). After hospitalisation for infection, the RR was highest for vascular dementia 2·09 (95% CI 1·59–2·75), and lowest for Alzheimer's disease 1·20 (95% CI 1·08–1·33). The increased risk for vascular dementia points to inflammatory processes leading to endothelial damage. SARS-CoV-2 infects endothelial cells, producing coagulopathy and vascular congestion during the acute phase of infection. RR for ischaemic stroke, of which vascular dementia is a common sequela, is 2·8 (95%CI 2·2–3·4) in the 6 months following SARS-CoV-2 infection and 2·7 (95% CI 2·3–3·2) over 12 months. RRs following SARS-CoV-2 infection are shown in the figure. A study using data from the Finnish

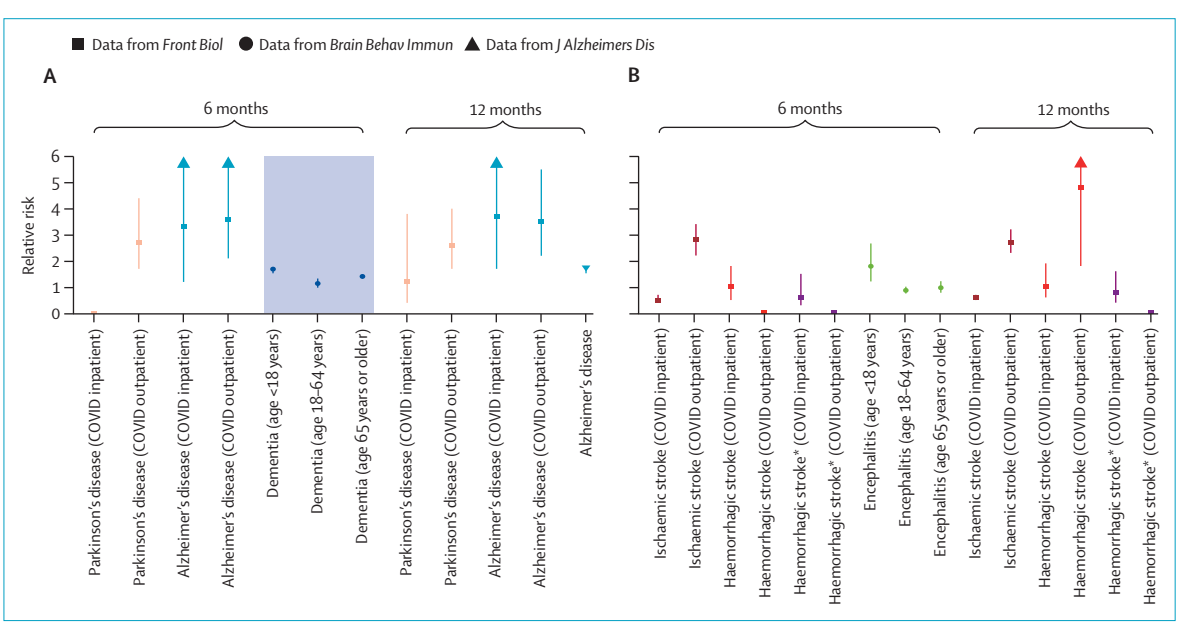

Figure: **Relative risks of (A) neurodegenerative disease and (B) cerebrovascular disease following SARS-CoV-2 infection**
Risks highlighted in the blue square are relative to other respiratory infections, while other risks are relative to baseline. Younger patients have a greater risk than older patients, and outpatients have higher relative risks than inpatients. Zero relative risk indicates insufficient data. Data for this figure were extracted from *Front Neurol* 2022; **13:** 904796; *Brain Behav Immun* 2022; **103:** 154–62; and *J Alzheimers Dis* 2022; **89:** 411–14. *Patients with subarachnoid haemorrhage.

and UK Biobanks, with the goal of discriminating the risk of dementia due to different viral infections, found a hazard ratio (HR) of 4·62 (95% CI 3·81–5·59) for vascular dementia following influenza and pneumonia with a substantial time-lag in the analysis of the Finnish databank, and 6·79 (95% CI 5·40–8·53) for the data from the UK biobank. The HR for influenza with pneumonia was considerably smaller than for severe CNS infections. For example, the HR from meningitis was 62·20 (95% CI 18·35–210·78). However, COVID-associated encephalitis is rare, while respiratory symptoms are common. A study including health records from 919 731 individuals in Denmark found a high RR of 3·5 (95% CI 2·2–5·5) for Alzheimer's disease following a positive SARS-CoV-2 test. Notably, the RR for outpatients was not significantly higher than that for hospital inpatients. The study showed a difference in the RR of ischaemic stroke following influenza infection (1·7, 95% CI 1·2–2·4) versus SARS-CoV-2 infection (2·7, 95% CI 2·3–3·2). These findings indicate that COVID-19 might confer a larger risk of dementia than influenza, and that (in the short term) the risk of severe neurological impairment as a sequela of SARS-CoV-2 is significant, driven by vascular and probably other complex (possibly amyloid-centric) processes.

A retrospective study of people infected by SARS-CoV-2 reported that neurological and psychiatric disorders were more common after COVID-19 than after other respiratory infections. Adults were at increased risk of cognitive decline even 2 years after infection, while children were only transiently at risk, within about 75 days after infection. Compared with adults, children were at higher risk of: epilepsy or seizures; encephalitis; and nerve, nerve root, and plexus disorders, during the 2 years after infection. These increased risks led the investigators to suggest that the potential causes of sequelae can persist well after apparent recovery.

The mechanisms underlying the delayed initiation of neurodegeneration are not established, although some evidence exists of senescent cells, viral particles, and amyloidogenic proteins lingering for long timescales after the production of infective virions has slowed or stopped. SARS-CoV-2 proteins have been detected at autopsy. The proteins can form linear structures radiating from neuronal cell bodies that might trigger amyloid deposition, but further neuropathological investigations are warranted.

The Bradford-Hill criteria provide a framework to prove causality (appendix). A direct correlation has been reported between prior SARS-CoV-2 infection and increased risk of Alzheimer's disease (figure). This direct association is robust, as the analyses included data from more than half of the population of Denmark and did a rigorous stratification and exclusion process for confounders, such as age, sex, and comorbidity. Direct evidence should show appropriate temporal sequence, which is contentious: it remains difficult to distinguish between the dementia cases hypothetically triggered by SARS-CoV-2 infection and those merely accelerated by it. Direct evidence of a causal link is therefore available but problematic, and will remain so until the full time course of the infection can be analysed epidemiologically. Reverse causation (ie, whether Alzheimer's disease increases vulnerability to SARS-CoV-2 infection) is difficult to disentangle. Mechanistic evidence reveals, although not in detail, inflammation in patients with COVID-19, and controlled experiments show prolonged neuroinflammation after mild SARS-CoV-2 infection in macaques. While a comprehensive aetiology is not elucidated yet, SARS-CoV-2 infection relates to other known aetiological routes that lead to Alzheimer's disease, which share the common feature of neuroinflammation (panel). In light of this evidence, SARS-CoV-2 infection should be considered as a risk factor for Alzheimer's disease, even though the distinction between causation versus disease acceleration is not clear. The relative severity of COVID might vary across viral strains; however, the incidence of neurological outcomes following infection do not appear to change across strains, given that neuroinflammatory harm is inherent to viral life cycle. Therefore, we should not assume that the effects of SARS-CoV-2 infection will be self-limiting.

Vaccination reduces mortality and serious cardiovascular symptoms for at least 1 year post-infection. Diet and lifestyle factors that are normally protective against dementia might be also of value here, including caloric restriction and other interventions to control chronic inflammation. In our opinion, antiviral therapy should be considered even for moderate SARS-CoV-2 infections to reduce the severity of symptoms and limit the likelihood of sequelae. Patients (especially children and those with post-acute sequelae) should be supported and followed up.

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***Panel*: SARS-CoV-2 and neuroinflammation**

- Oxidative stress is both a cause and a consequence of neuroinflammation. Inflammatory markers are elevated in patients with COVID-19 proportionally to disease severity.
- Inflammation signals in patients with COVID-19, such as TNF-α, IL-1β, NF-κB, IL-6, might be also biomarkers for Alzheimer's disease.
- In vitro, SARS-CoV-2 infection increases phosphorylation and aggregation of tau, which can be a causative factor for Alzheimer's disease.
- SARS-CoV-2 viral proteins contain amyloidogenic regions, which might drive amyloid formation.
- The pathophysiology of long COVID remains unclear but implicated pathways include sustained neuroinflammation, altered microcirculation, and hypometabolism, particularly in the autonomic nervous system. The gut–brain axis is strongly involved in these pathways.

For the **study including health records in Denmark** see *Front Neurol* 2022; **13:** 904796

For the **retrospective study of patients with SARS-CoV-2 infection** see **Articles** *Lancet Psychiatry* 2022; **9:** 815–27

For more on **amyloidogenic virus proteins in SARS-CoV-2** see *Nat Commun* 2022; **13:** 3387

For more on **SARS-CoV-2 infection in the brain at autopsy** see *Nature* 2022; **612:** 758–63

For more on **neuroinflammation in SARS-CoV-2 infected macaques** see *J Neuroinflammation* 2023; **20:** 179

See **Online** for appendix