National Task Group on Intellectual Disabilities and Dementia Practices

Long COVID and MCI / Dementia Bibliography

(October 6, 2022)

This is a bibliography of selective articles related to Long COVID in general where indications are noted of potential basis for or progression or association with dementia. It is updated periodically and open to use. Abstracts and excerpts were taken from readily available source on the Internet. We are not responsible for any omissions or inaccuracies and recommend seeking access to the original articles for the detailed information provided in each article.

Citation	Abstract
Amen Clinics. (2019) **When Does Brain Fog Become a Concern?** https://www.amenclinics.com/blog/when-does-brain-fog-become-a-concern/	Mild Cognitive Impairment or Dementia **Losing your train of thought, feeling overwhelmed by the decision-making process, having trouble navigating familiar areas**—these brain fog symptoms could be related to mild cognitive impairment (MCI) or a form of dementia such as Alzheimer's disease. Having brain fog or feeling like your memory is slipping when you're in your 40s, 50s, 60s, 70s, or even in your 80s is common, but it's not normal. It can be a sign of impending doom. If you live to the age of 85, you have a nearly 50% chance of being diagnosed with Alzheimer's or another form of dementia. Taking action early to reduce the risk factors that contribute to dementia can help you reduce symptoms of cognitive dysfunction. No matter your age, persistent symptoms of brain fog should be taken seriously. If you're struggling with your thinking or memory, now is the time to seek an evaluation. Finding the root cause of your cognitive problems can help you find the right treatment plan. The earlier you start with targeted solutions, the more effective they will be at helping you clear brain fog.
Baschi, Roberta; Luca,Antonina ; Nicoletti,Alessandra ; Caccamo,Maria ; Cicero,Calogero Edoardo ; D'Agate,Concetta ; Di Giorgi,Lucia ; La Bianca,Giuseppe ; Lo Castro,Tiziana ; Zappia,Mario ; Monastero,Roberto **Changes in Motor, Cognitive, and Behavioral Symptoms in Parkinson's Disease and Mild Cognitive**	The effects of the COVID-19 lockdown on subjects with prodromal phases of dementia are unknown. The aim of this study was to evaluate the motor, cognitive, and behavioral changes during the COVID-19 lockdown in Italy in patients with Parkinson's disease (PD) with and without mild cognitive impairment (PD-MCI and PD-NC) and in patients with MCI not associated with PD (MCInoPD).Methods: A total of 34 patients with PD-NC, 31 PD-MCI, and 31 MCInoPD and their caregivers were interviewed 10 weeks after the COVID-19 lockdown in Italy, and changes in cognitive, behavioral, and motor symptoms were examined. Modified standardized scales, including the

Impairment During the COVID-19 Lockdown Frontiers in Psychiatry, 2020, 11(?), 1664-0640 https://www.frontiersin.org/articles/10.3389/fpsyt.2020.590134	Neuropsychiatric Inventory (NPI) and the Movement Disorder Society, Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I and II, were administered. Multivariate logistic regression was used to evaluate associated covariates by comparing PD-NC vs. PD-MCI and MCInoPD vs. PD-MCI.Results: All groups showed a worsening of cognitive (39.6%), pre-existing (37.5%), and new (26%) behavioral symptoms, and motor symptoms (35.4%) during the COVID-19 lockdown, resulting in an increased caregiver burden in 26% of cases. After multivariate analysis, PD-MCI was significantly and positively associated with the IADL lost during quarantine (OR 3.9, CI 1.61â€“9.58), when compared to PD-NC. In the analysis of MCInoPD vs. PD-MCI, the latter showed a statistically significant worsening of motor symptoms than MCInoPD (OR 7.4, CI 1.09â€“45.44). Regarding NPI items, nighttime behaviors statistically differed in MCInoPD vs. PD-MCI (16.1% vs. 48.4%, p = 0.007). MDS-UPDRS parts I and II revealed that PD-MCI **showed a significantly higher frequency of cognitive impairment** (p = 0.034), fatigue (p = 0.036), and speech (p = 0.013) than PD-NC. On the contrary, PD-MCI showed significantly higher frequencies in several MDS-UPDRS items compared to MCInoPD, particularly regarding pain (p = 0.001), turning in bed (p = 0.006), getting out of bed (p = 0.001), and walking and balance (p = 0.003). Conclusion: The COVID-19 quarantine is associated with the worsening of cognitive, behavioral, and motor symptoms in subjects with PD and MCI, particularly in PD-MCI. There is a need to implement specific strategies to contain the effects of quarantine in patients with PD and cognitive impairment and their caregivers.
Blomberg B, Cox RJ, Langeland N. **Long COVID: A growing problem in need of intervention**. Cell Rep Med. 2022 Feb 14;3(3):100552. doi: 10.1016/j.xcrm.2022.100552. PMID: 35474749; PMCID: PMC8841141.	The number of people who have survived COVID-19 is overwhelming—official figures approach half a billion. Thus, any long-term consequences in COVID-19 survivors could have a huge impact on public health and on healthcare services in the coming months and years, with potentially 100 million individuals affected. Long COVID is still an emerging clinical concept that is not fully characterized. Studies have identified numerous symptoms potentially related to long COVID. A consensus process led by the World Health Organization has gathered support for a case definition consisting of a clinical picture dominated by a combination of dyspnea, fatigue, and cognitive symptoms, such as impaired memory and concentration, that impacts daily functioning and lasts beyond three months after the onset of acute COVID-19. Other common accompanying symptoms include disturbed taste and/or smell, gastrointestinal discomfort, chest pain, paresthesia, headache, and depression. Management of long COVID lacks proven medical therapies. However, physical rehabilitation is considered helpful. Cognitive therapy has been promising in the management of other post-infectious syndromes, but any benefit in long COVID remains to be determined.
Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, Rodrigues NB, Subramaniapillai M, Di Vincenzo JD,	COVID-19 is associated with clinically significant symptoms despite resolution of the acute infection (i.e., post-COVID-19 syndrome).

Cao B, Lin K, Mansur RB, Ho RC, Rosenblat JD, Miskowiak KW, Vinberg M, Maletic V, McIntyre RS. **Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis**. Brain Behav Immun. 2022 Mar;101:93-135. doi: 10.1016/j.bbi.2021.12.020. Epub 2021 Dec 29. PMID: 34973396; PMCID: PMC8715665.	Fatigue and cognitive impairment are amongst the most common and debilitating symptoms of post-COVID-19 syndrome. To quantify the proportion of individuals experiencing **fatigue and cognitive impairment 12 or more weeks following COVID-19 diagnosis**, and to characterize the inflammatory correlates and functional consequences of post-COVID-19 syndrome. Systematic searches were conducted without language restrictions from database inception to June 8, 2021 on PubMed/MEDLINE, The Cochrane Library, PsycInfo, Embase, Web of Science, Google/Google Scholar, and select reference lists. Primary research articles which evaluated individuals at least 12 weeks after confirmed COVID-19 diagnosis and specifically reported on fatigue, cognitive impairment, inflammatory parameters, and/or functional outcomes were selected. Two reviewers independently extracted published summary data and assessed methodological quality and risk of bias. A meta-analysis of proportions was conducted to pool Freeman-Tukey double arcsine transformed proportions using the random-effects restricted maximum-likelihood model. The co-primary outcomes were the proportions of individuals reporting fatigue and cognitive impairment, respectively, 12 or more weeks following COVID-19 infection. The secondary outcomes were inflammatory correlates and functional consequences associated with post-COVID-19 syndrome. The literature search yielded 10,979 studies, and 81 studies were selected for inclusion. The fatigue meta-analysis comprised 68 studies, the cognitive impairment meta-analysis comprised 43 studies, and 48 studies were included in the narrative synthesis. Meta-analysis revealed that the proportion of individuals experiencing fatigue 12 or more weeks following COVID-19 diagnosis was 0.32 (95% CI, 0.27, 0.37; $p < 0.001$; n = 25,268; $I2 = 99.1\%$). The proportion of individuals exhibiting cognitive impairment was 0.22 (95% CI, 0.17, 0.28; $p < 0.001$; n = 13,232; $I2 = 98.0$). Moreover, narrative synthesis revealed elevations in proinflammatory markers and considerable functional impairment in a subset of individuals. A significant proportion of individuals experience persistent fatigue and/or cognitive impairment following resolution of acute COVID-19. The frequency and debilitating nature of the foregoing symptoms provides the impetus to characterize the underlying neurobiological substrates and how to best treat these phenomena. Cognitive impairment ascertained via any validated tool for performance-based cognitive function (e.g., MoCA, TICS, SCIP), or clinical diagnosis of cognitive impairment. **Self-report or non-validated measure of cognitive impairment/'brain fog', mental slowness, deficits in attention, executive, processing, memory, learning, articulation, and/or psychomotor coordination.**
DiSogra, R.M.	When a COVID-19 survivor reports that they have been diagnosed with brain fog or mild cognitive impairment (BF/MCI), or these terms

Are COVID-19 "Brain Fog" Symptoms and an Auditory Processing Disorder Related? (March 10, 2022). *Hearing Review.* https://hearingreview.com/hearing-loss/hearing-disorders/apd/covid-19-brain-fog-symptoms-auditory-processing-disorder-related	appear in a medical report, hearing care professionals should be aware that many of **the BF/MCI symptoms are very similar to those seen in patients with (central) auditory processing disorder.** This article reviews the research on this subject and provides recommendations. Many people have struggled with the aftereffects of COVID-19 for more than 3 weeks or longer after diagnosis.1-3 These side effects include (but are not limited to) fatigue, mild cognitive issues, and low tolerance to mental activity. They also can reoccur at any time with no warning. Individuals with these persistent symptoms have been labeled "long-haulers" in the press and social media, most often exhibiting symptoms of mild cognitive impairment (MCI).2,5 However, another term started to appear in professional literature and on social media that described the symptoms of MCI as "brain fog" (BF). Because this pandemic was like no other that we have seen in over a century, the after-effects of the virus were initially thought to be short term (2-6 weeks), like most other viruses. However, as time went on, this sub-group of survivors (long-haulers) continued to have serious medical issues related to the virus well beyond two months. The Indiana University School of Medicine (IUSM) published a survey of over 1,500 COVID-19 survivors,6 and the authors identified 50 symptoms that included: #1 fatigue (n = 1,567), #4 difficulty concentrating or focusing (n = 924), and #9 memory problems (n = 714). Hearing loss was not listed. Interestingly, persons with hearing loss usually have the same auditory behaviors and communication complaints that are listed in Table 1a (see also Definitions). It is only when an audiologist conducts a comprehensive evaluation of the peripheral auditory system that a more specific diagnosis can be reached.
Duong, Diana **Even mild COVID-19 may have long-term brain impacts** CMAJ August 30, 2021 193 (34) E1360-E1361; DOI: https://doi.org/10.1503/cmaj.1095958 https://www.cmaj.ca/content/193/34/E1360	Research presented at the Alzheimer's Association International Conference suggests even mild cases of COVID-19 may be associated with cognitive deficits months after recovery. One Argentinian study of 234 seniors who previously had COVID-19 found that more than half showed some degree of cognitive impairment months later. One in three had severe "dementia-like" impairments in memory, attention, and executive function — a much higher proportion than the 5%–8% of seniors in the general population who have dementia at a given time. "This could be the start of a dementia-related epidemic fueled by this latest coronavirus," stated presenting author Dr. Gabriel de Erausquin of the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases at UT Health San Antonio. Researchers will follow the study participants over the next three to five years to see if these problems resolve or worsen. The study didn't look at participants' cognitive performance prior to infection. However, those who lost their sense of smell while sick with COVID-19 tended to have more severe cognitive impairments months

	later, even if their other symptoms had been mild. According to de Erausquin, “once the virus has affected the olfactory bulb and caused effects there — changes that we can see with imaging — then other places in the brain that are connected to it also become abnormal, either in function or structure or both.” Other research presented linked SARS-CoV-2 infection with an uptick in biomarkers of brain injury, neuroinflammation and Alzheimer disease. One American study of 310 patients with COVID-19 found that those with new neurological symptoms had higher levels of t-tau, NfL, GFAP, pTau-181, and UCH-L1 in their blood, as well as indicators of inflammation such as C-reactive protein, compared to patients without neurological symptoms. “These findings suggest patients who had COVID-19 may have an acceleration of Alzheimer-related symptoms and pathology,” according to presenting author Dr. Thomas Wisniewski of the New York University Grossman School of Medicine. Earlier this year, de Erausquin and others reported that brain inflammation, stroke and other common complications of viral infections have longstanding links with neurodegenerative disorders. “Therefore, it seems likely to expect that COVID-19-related cardiovascular and cerebrovascular disease will also contribute to a higher longterm risk of cognitive decline and dementia in recovered individuals.” Several recent studies have documented cognitive deficits post-COVID but like the research presented at the Alzheimer’s Association conference, data on patients’ performance before infection are lacking. One British study of 81 337 people in EClinicalMedicine found that those who previously had COVID-19 tended to score lower on measures of intelligence, reasoning, problem-solving and planning than people who were never infected. “These results accord with reports of long-COVID, where ‘brain fog,’ trouble concentrating and difficulty finding the correct words are common,” according to the authors. People who had been hospitalized and put on ventilators had the greatest impairments, but even those who had relatively mild symptoms showed some deficit. In another study of 57 Americans receiving inpatient rehabilitation after hospitalization for COVID-19, four in five had mild to severe cognitive impairments. More than half had deficits in working memory, while two in five had impaired processing speed, divided attention, and trouble switching between mental tasks. Similar deficits have also been noted in patients after recovery from other coronaviruses. A 2020 systematic review and meta-analysis found that delirium was common in the acute stage of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. Following up with patients six weeks to 39 months later, more than 15% reported sleep disorders, mood swings, trouble concentrating, impaired memory and other mental challenges. Based on this growing body of evidence, British researchers warned in March that health systems will likely see an “influx of patients with psychiatric and cognitive problems who were otherwise healthy prior

	to COVID-19." They urged doctors to consider detailed cognitive evaluations for anyone reporting new neurological symptoms after infection with SARS-CoV-2. In the meantime, the Alzheimer's Association has formed an international consortium to study the long-term effects of COVID-19 on the brain. "These new data point to disturbing trends showing COVID-19 infections leading to lasting cognitive impairment and even Alzheimer's symptoms," stated Heather Snyder of the Alzheimer's Association. "It is imperative that we continue to study what this virus is doing to our bodies and brains."
Fong, T. (March 17, 2022) **Brain fog: Memory and attention after COVID-19.** Harvard Health Publishing. https://www.health.harvard.edu/blog/brain-fog-memory-and-attention-after-covid-19-202203172707	What is brain fog? Brain fog, a term used to **describe slow or sluggish thinking,** can occur under many different circumstances — for example, when someone is sleep-deprived or feeling unwell, or due to side effects from medicines that cause drowsiness. Brain fog can also occur following chemotherapy or a concussion. In many cases, brain fog is temporary and gets better on its own. However, we don't really understand why brain fog happens after COVID-19, or how long these symptoms are likely to last. But we do know that this form of brain fog can affect different aspects of cognition.
Frontera JA, Boutajangout A, Masurkar AV, Betensky RA, Ge Y, Vedvyas A, Debure L, Moreira A, Lewis A, Huang J, Thawani S, Balcer L, Galetta S, Wisniewski T. **Comparison Of Serum Neurodegenerative Biomarkers Among Hospitalized COVID-19 Patients Versus Non-COVID Subjects with Normal Cognition, Mild Cognitive Impairment, Or Alzheimer's Dementia**. Alzheimers Dement. 2022 May;18(5):899-910. doi: 10.1002/alz.12556. Epub 2022 Jan 13. PMID: 35023610; PMCID: PMC9011610.	Neurological complications among hospitalized COVID-19 patients may be associated with elevated neurodegenerative biomarkers. Among hospitalized COVID-19 patients without a history of dementia (N = 251), we compared serum total tau (t-tau), phosphorylated tau-181 (p-tau181), glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), ubiquitin carboxy-terminal hydrolase L1 (UCHL1), and amyloid beta (Aβ40,42) between patients with or without encephalopathy, in-hospital death versus survival, and discharge home versus other dispositions. COVID-19 patient biomarker levels were also compared to non-COVID cognitively normal, mild cognitive impairment (MCI), and Alzheimer's disease (AD) dementia controls (N = 161). Admission t-tau, p-tau181, GFAP, and NfL were significantly elevated in patients with encephalopathy and in those who died in-hospital, while t-tau, GFAP, and NfL were significantly lower in those discharged home. These markers correlated with severity of COVID illness. NfL, GFAP, and UCHL1 were higher in COVID patients than in non-COVID controls with MCI or AD. Neurodegenerative biomarkers were elevated to levels observed in AD dementia and associated with encephalopathy and worse outcomes among hospitalized COVID-19 patients.
George, July **COVID Brain Changes Show Parallels with Alzheimer's Disease** February 4, 2022 Medical News – Medpage Today https://www.medpagetoday.com/neurology/generalneurology/97034	Persistent brain fog and cardiac symptoms in people with COVID-19 led Marks and co-authors to investigate how ryanodine receptors were affected in COVID-19. "What we found is really, I think, quite unexpected," Marks said. "Not only did we find defective ryanodine receptors in the hearts and lungs of deceased COVID patients, we also found them in their brains."

	The researchers analyzed signaling molecules in brain lysates of COVID-19 patients and controls and found evidence linking SARS-CoV-2 infection to activation of TGF-β signaling and oxidative overload. They also found high levels of phosphorylated tau in COVID-19 patients' brains, both in areas where tau is typically located in Alzheimer's and in other sites. No changes in pathways leading to amyloid beta formation were seen. The findings may mean that a COVID-19 immune response causes brain inflammation which leads to dysfunctional ryanodine receptors and altered cellular calcium dynamics, then to increases in phosphorylated tau, Marks and colleagues noted. "We propose a potential mechanism that may contribute to the neurological complications caused by SARS-CoV-2: defective intracellular Ca2+ regulation and activation of Alzheimer's disease-like neuropathology," they wrote. Leaky RyR2 channels may be a therapeutic target to ameliorate some of the cognitive defects associated with SARS-CoV-2 infection and long COVID, the researchers suggested. Lab studies that treated COVID-19 patient brain samples with a drug targeting RyR2 channels prevented the calcium leak. The treatment, known as ARM210, currently is undergoing clinical testing at NIH for RyR1-related myopathy. "Future experiments will explore calcium channels as a potential therapeutic target for the neurological complications associated with COVID-19," Marks and co-authors wrote.
Grace Kenny, Kathleen McCann, Conor O'Brien, Stefano Savinelli, Willard Tinago, Obada Yousif, John S Lambert, Cathal O'Broin, Eoin R Feeney, Eoghan De Barra, Peter Doran, Patrick W G Mallon, All-Ireland Infectious Diseases (AIID) Cohort Study Group. **Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms, Open Forum Infectious Diseases** Volume 9, Issue 4, April 2022, ofac060, https://doi.org/10.1093/ofid/ofac060	We aimed to describe the clinical presentation of individuals presenting with prolonged recovery from coronavirus disease 2019 (COVID-19), known as long COVID. This was an analysis within a multicenter, prospective cohort study of individuals with a confirmed diagnosis of COVID-19 and persistent symptoms >4 weeks from onset of acute symptoms. We performed a multiple correspondence analysis (MCA) on the most common self-reported symptoms and hierarchical clustering on the results of the MCA to identify symptom clusters. Two hundred thirty-three individuals were included in the analysis; the median age of the cohort was 43 (interquartile range [IQR], 36–54) years, 74% were women, and 77.3% reported a mild initial illness. MCA and hierarchical clustering revealed 3 clusters. Cluster 1 had predominantly pain symptoms with a higher proportion of joint pain, myalgia, and headache; cluster 2 had a preponderance of cardiovascular symptoms with prominent chest pain, shortness of breath, and palpitations; and cluster 3 had significantly fewer symptoms than the other clusters (2 [IQR, 2–3] symptoms per individual in cluster 3 vs 6 [IQR, 5–7] and 4 [IQR, 3–5] in clusters 1 and 2, respectively; $P < .001$). Clusters 1 and 2 had greater functional impairment, demonstrated by significantly longer work absence, higher dyspnea scores, and lower scores in SF-36 domains of general

	health, physical functioning, and role limitation due to physical functioning and social functioning. Conclusions Clusters of symptoms are evident in long COVID patients that are associated with functional impairments and may point to distinct underlying pathophysiologic mechanisms of disease.
Greenhalgh, T., Sivan, M. , Delaney, B., Evans, R., & Milne, R. **Long Covid – An Update For Primary Care** BMJ 2022;378:e072117. 1-8. doi: 10.1136/bmj-2022-072117	This article updates and extends a previous BMJ Practice Pointer published in August 2020 when almost no peer reviewed research or evidence-based guidance on the condition was available. In this update we outline how clinicians might respond to the questions that patients ask. The term "long covid" refers to prolonged symptoms following infection with SARS-CoV-2 that are not explained by an alternative diagnosis. It embraces the National Institute for Health and Care Excellence (NICE)'s terms "ongoing symptomatic covid-19" (symptoms lasting 4-12 weeks) and "post covid-19 syndrome" (symptoms beyond 12 weeks), the US Centers for Disease Control and Prevention's group of "post-covid conditions," and the World Health Organization's "post covid-19 condition." Long covid may be diagnosed late or not at all, so both generalists and specialists should be alert to it as a differential, while also being aware that patients can develop other persistent symptoms following acute covid-19 that are not necessarily caused by covid-19. Long covid is characterized by a constellation of general and organ specific symptoms, the commonest of which are summarized in the infographic contained in the article. These multiple manifestations lead to difficulties with daily activities such as washing and dressing, low exercise tolerance, and impaired ability to work (either at all or partially), and result in reduced quality of life. Symptoms typically occur across multiple systems concurrently but sometimes one organ system (e.g., cardiovascular) dominates. Phenotyping studies have identified several symptom clusters, with severe cases characterized by greater number and intensity of symptoms and greater functional impairment.33 -35 Some patients' long covid follows a fairly constant course, while others experience relapsing and remitting symptoms, sometimes with particular triggers.
Hampshire, A., Chatfield, D.A., Manktelow, A., Jolly, A., Trender, W., P.J., Martina Del Giovane, H., Newcombe, V.F.J., Outtrim, J.G., Warne, B., Bhatti, J., Pointon, L., Elmer, A., Sithole, N., Bradley, J., Kingston, N., Sawcer, S.J., Bullmore, E.T., Rowe, J.B., & Menon, D.K. **Multivariate Profile and Acute-Phase Correlates Of Cognitive Deficits In A COVID-19 Hospitalised Cohort.** *eClinicalMedicine,* 2022; 47: 101417 DOI: 10.1016/j.eclinm.2022.101417	Preliminary evidence has highlighted a possible association between severe COVID-19 and persistent cognitive deficits. Further research is required to confirm this association, determine whether cognitive deficits relate to clinical features from the acute phase or to mental health status at the point of assessment, and quantify rate of recovery. 46 individuals who received critical care for COVID-19 at Addenbrooke's hospital between 10th March 2020 and 31st July 2020 (16 mechanically ventilated) underwent detailed computerised cognitive assessment alongside scales measuring anxiety, depression and post-traumatic stress disorder under supervised conditions at a mean follow up of 6.0 (± 2.1) months following acute illness. Patient and matched control (N = 460) performances were transformed into standard deviation from expected scores, accounting for age and

	demographic factors using N = 66,008 normative datasets. Global accuracy and response time composites were calculated (G_SScore & G_RT). Linear modelling predicted composite score deficits from acute severity, mental-health status at assessment, and time from hospital admission. The pattern of deficits across tasks was qualitatively compared with normal age-related decline, and early-stage dementia. COVID-19 survivors were less accurate (G_SScore=-0.53SDs) and slower (G_RT=+0.89SDs) in their responses than expected compared to their matched controls. Acute illness, but not chronic mental health, significantly predicted cognitive deviation from expected scores (G_SScore (p=0.0037) and G_RT (p = 0.0366)). The most prominent task associations with COVID-19 were for higher cognition and processing speed, which was qualitatively distinct from the profiles of normal ageing and dementia and similar in magnitude to the effects of ageing between 50 and 70 years of age. A trend towards reduced deficits with time from illness (r∼=0.15) did not reach statistical significance. Interpretation Cognitive deficits after severe COVID-19 relate most strongly to acute illness severity, persist long into the chronic phase, and recover slowly if at all, with a characteristic profile highlighting higher cognitive functions and processing speed.
Hampshire, Adam; William Trender, Samuel R Chamberlain, Amy E. Jolly, Jon E. Grant, Fiona Patrick, Ndaba Mazibuko, Steve CR Williams, Joseph M Barnby, Peter Hellyer, Mitul A Mehta **Cognitive deficits in people who have recovered from COVID-19.** eClinical Medicine. VOLUME 39, 101044, SEPTEMBER 01, 2021. DOI:https://doi.org/10.1016/j.eclinm.2021.101044	There is growing concern about possible cognitive consequences of COVID-19, with reports of 'Long COVID' symptoms persisting into the chronic phase and case studies revealing neurological problems in severely affected patients. However, there is little information regarding the nature and broader prevalence of cognitive problems post-infection or across the full spread of disease severity. In this study, we sought to confirm whether there was an association between cross-sectional cognitive performance data from 81,337 participants who between January and December 2020 undertook a clinically validated web-optimized assessment as part of the Great British Intelligence Test, and questionnaire items capturing self-report of suspected and confirmed COVID-19 infection and respiratory symptoms. People who had recovered from COVID-19, including those no longer reporting symptoms, exhibited significant cognitive deficits versus controls when controlling for age, gender, education level, income, racial-ethnic group, pre-existing medical disorders, tiredness, depression, and anxiety. The deficits were of substantial effect size for people who had been hospitalized (N = 192), but also for non-hospitalized cases who had biological confirmation of COVID-19 infection (N = 326). Analyzing markers of premorbid intelligence did not support these differences being present prior to infection**. Finer grained analysis of performance across sub-tests supported the hypothesis that COVID-19 has a multi-domain impact on human cognition**.

	These results accord with reports of 'Long Covid' cognitive symptoms that persist into the early-chronic phase. They should act as a clarion call for further research with longitudinal and neuroimaging cohorts to plot recovery trajectories and identify the biological basis of cognitive deficits in SARS-COV-2 survivors.
Henneghan, Ashley M. ; Kimberly A. Lewis, Eliana Gill, and Shelli R. Kesler **Cognitive Impairment in Non-critical, Mild-to-Moderate COVID-19 Survivors** Front. Psychol., 17 February 2022 https://doi.org/10.3389/fpsyg.2022.770459	Importance: Previous studies of post-acute COVID-19 syndrome have focused on critical cases with severe disease. However, most cases are mild to moderate in disease severity. Objective: We aimed to examine cognitive outcomes in cases of non-critical, mild-to-moderate COVID-19. Design, Setting, and Participants: In this cross-sectional study, we enrolled 72 adults aged 22 to 65 years in Central Texas who had non-critical, mild-to-moderate COVID-19 infection between 13 January 2021 and 20 April 2021. Main Outcomes and Measures: We remotely administered cognitive-behavioral testing to determine the frequency of cognitive impairment and examine demographic, clinical, and psychosocial contributors to impairment. Results: The frequency of objective cognitive impairment was 40%. The largest number of participants (24%) showed impairment on a measure of executive functioning. Attention and processing speed was more impaired in males (OR = 1.5, 95%CI = 0.23–2.9). Males endorsed lower adherence to social distancing guidelines (U = 590, p = 0.01), which was in turn associated with cognitive impairment across participants (r = −0.30, p = 0.01). Younger age was correlated with impairment (r = −0.26, p = 0.03) but was also associated with racial/ethnic minority status (r = −0.31, p = 0.01) and increased psychological symptoms (p < 0.04). Greater number of COVID-19 symptoms was correlated with lower subjective cognitive function (r = −0.38, p = 0.001) as well as psychosocial function (r > 0.24, p < 0.05). Moderate COVID-19 severity was associated with attention/processing speed impairment (r = 0.27, p = 0.03), increased pain (r = 0.31, p = 0.01), and higher number of COVID-19 symptoms (r = 0.32, p = 0.01). Conclusion and Relevance: **Mild or moderate COVID-19 infection may be associated with cognitive impairments**, especially in the domain of executive functioning. A subgroup of younger individuals may be more vulnerable to cognitive and psychosocial effects of COVID-19
KW Miskowiak, K.W., Fugledalen L., Jespersen, A.E., Sattler, S.M., Podlekarev, D. Rungbye, J., Porsberg, C.M. & Johnsen, S. **Trajectory Of Cognitive Impairments Over 1 Year After COVID-19 Hospitalization: Pattern, Severity, And Functional Implications** European Neuropsychopharmacology, June 2022, 59, 82-92.	The ongoing Coronavirus Disease (COVID-19) pandemic has so far affected more than 500 million people. Lingering fatigue and cognitive difficulties are key concerns because they impede productivity and quality of life. However, the prevalence and duration of neurocognitive sequelae and association with functional outcomes after COVID-19 are unclear. This longitudinal study explored the frequency, severity, and pattern of cognitive impairment and functional implications 1 year after hospitalization with COVID-19 and its trajectory from 3 months after hospitalization. Patients who had been hospitalized with COVID-19 from our previously published 3-months study at the Copenhagen University Hospital were re-invited for a 1-year follow-up assessment

https://doi.org/10.1016/j.euroneuro.2022.04.004	of cognitive function, functioning and depression symptoms. Twenty-five of the 29 previously assessed patients (86%) were re-assessed after 1 year (11±2 months). Clinically significant cognitive impairments were identified in 48-56 % of patients depending on the cut-off, with verbal learning and executive function being most severely affected. This was comparable to the frequency of impairments observed after 3 months. Objectively measured cognitive impairments scaled with subjective cognitive difficulties, reduced work capacity and poorer quality of life. Further, cognitive impairments after 3 months were associated with the severity of subsequent depressive symptoms after 1 year. In conclusion, the stable cognitive impairments in approximately half of patients hospitalized with COVID-19 and negative implications for work functioning, quality of life and mood symptoms underline the importance of screening for and addressing cognitive sequelae after severe COVID-19.
Ledford, H. **Long-COVID treatments: why the world is still waiting: After a slow start, researchers are beginning to test ways to combat the lasting symptoms of the disease.** 9 August 2022, Nature, News Feature https://www.nature.com/articles/d41586-022-02140-w	A key barrier to developing long-COVID treatments has been uncertainty about the condition's root cause. Over the past two years, a number of hypotheses have emerged as frontrunners, and researchers hope that insight into which ones are correct could help them to develop therapies. Evidence is mounting that lingering SARS-CoV-2 — or fragments of it — continues to cause trouble by stimulating the immune system. There are also signs that the infection generates antibodies that mistakenly attack the body's own proteins, causing damage long after the initial illness. Researchers have found hints that COVID-19 could cause microscopic blood clots that block oxygen flow to tissues. It is also possible that a SARS-CoV-2 infection can wreak long-term havoc on gut microorganisms. These hypotheses are not mutually exclusive: many researchers think that long COVID can have multiple causes. Each idea suggests a route to relief. Antiviral drugs might vanquish persistent reservoirs of SARS-CoV-2. Drugs that suppress the immune system could quench a misguided immune response. Powerful anti-coagulants could dissolve micro-clots. Although evidence is gradually accumulating in support of each of these possibilities, their links to long COVID are still tenuous enough to give some investigators pause before launching clinical trials. "The hypotheses are getting a bit stronger," says Altmann. "But they're not cast iron." Plus, there is no shortlist of key symptoms to help to enrol participants or sort them into subgroups. More than 200 symptoms have been associated with the syndrome1, and many — such as fatigue and brain fog, two of the most common and debilitating — are hard to measure objectively, and can wax and wane. "I've had a whole list of symptoms; half of them I've forgotten," says Mewar, who keeps a library of photographs of the medicines she has tried, to keep track of her treatments amid the brain fog that permeates her memory. "They would come and go, here a week, and then gone."

	Some of the most logical candidate drugs for long COVID are still not being tested in trials. Several antivirals are used against acute COVID-19. Some researchers think these drugs could ease the symptoms of long COVID, too — particularly as evidence grows that a lingering SARS-CoV-2 reservoir could trigger the condition. Two antivirals were approved by the US Food and Drug Administration at the end of last year — molnupiravir (Lagevrio), made by Merck in Rahway, New Jersey, and Ridgeback Biotherapeutics in Miami, Florida; and a combination consisting of nirmatrelvir and ritonavir (Paxlovid), made by Pfizer in New York City. Another drug, remdesivir (Veklury), made by Gilead Sciences in Foster City, California, has been used to treat COVID-19 since the early days of the pandemic. But there are still no registered studies directly looking at whether these antivirals — which are expensive and in relatively short supply compared with generic drugs — could ease long-COVID symptoms.
Liu, Yu-Hui; Chen, Yang; Wang, Qing-Hua et al. **One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China - A Longitudinal Cohort Study** JAMA Neurol. 2022;79(5):509-517. doi:10.1001/jamaneurol.2022.0461	Importance Determining the long-term impact of COVID-19 on cognition is important to inform immediate steps in COVID-19 research and health policy. Objective To investigate the 1-year trajectory of cognitive changes in older COVID-19 survivors. Design, Setting, and Participants This cohort study recruited 3233 COVID-19 survivors 60 years and older who were discharged from 3 COVID-19–designated hospitals in Wuhan, China, from February 10 to April 10, 2020. Their uninfected spouses (N = 466) were recruited as a control population. Participants with pre-infection cognitive impairment, a concomitant neurological disorder, or a family history of dementia were excluded, as well as those with severe cardiac, hepatic, or kidney disease or any kind of tumor. Follow-up monitoring cognitive functioning and decline took place at 6 and 12 months. A total of 1438 COVID-19 survivors and 438 control individuals were included in the final follow-up. COVID-19 was categorized as severe or non-severe following the American Thoracic Society guidelines. Main Outcomes and Measures The main outcome was **change in cognition 1 year after patient discharge**. Cognitive changes during the first and second 6-month follow-up periods were assessed using the Informant Questionnaire on Cognitive Decline in the Elderly and the Telephone Interview of Cognitive Status-40, respectively. Based on the cognitive changes observed during the 2 periods, cognitive trajectories were classified into 4 categories: stable cognition, early-onset cognitive decline, late-onset cognitive decline, and progressive cognitive decline. Multinomial and conditional logistical regression models were used to identify factors associated with risk of cognitive decline. Among the 3233 COVID-19 survivors and 1317 uninfected spouses screened, 1438 participants who were treated for COVID-19 (691 male [48.05%] and 747 female [51.95%]; median [IQR] age, 69 [66-74] years) and 438 uninfected control individuals (222 male [50.68%] and 216

	female [49.32%]; median [IQR] age, 67 [66-74] years) completed the 12-month follow-up. The incidence of cognitive impairment in survivors 12 months after discharge was 12.45%. Individuals with severe cases had lower Telephone Interview of Cognitive Status-40 scores than those with non-severe cases and control individuals at 12 months (median [IQR]: severe, 22.50 [16.00-28.00]; non-severe, 30.00 [26.00-33.00]; control, 31.00 [26.00-33.00]). Severe COVID-19 was associated with a higher risk of early-onset cognitive decline (odds ratio [OR], 4.87; 95% CI, 3.30-7.20), late-onset cognitive decline (OR, 7.58; 95% CI, 3.58-16.03), and progressive cognitive decline (OR, 19.00; 95% CI, 9.14-39.51), while non-severe COVID-19 was associated with a higher risk of early-onset cognitive decline (OR, 1.71; 95% CI, 1.30-2.27) when adjusting for age, sex, education level, body mass index, and comorbidities. In this cohort study, COVID-19 survival was associated with an increase in risk of longitudinal cognitive decline, highlighting the importance of immediate measures to deal with this challenge.
Majithia, M., & Ribeiro, S.P. **COVID-19 and Down syndrome: the spark in the fuel.** *Nat Rev Immunol*. 2022 Jul;22(7):404-405. doi: 10.1038/s41577-022-00745-w. PMID: 35672483; PMCID: PMC9171732.	{Abstract}"In individuals with Down syndrome, immune dysregulation is partially caused by chromosome 21 trisomy. Here, we discuss how these immune differences may result in poorer COVID-19 outcomes, including diminished responses to vaccination and possibly elevated risk for long COVID." {text} "Long COVID? Although the mechanisms of long COVID-19 development are incompletely understood, many of the factors that are reported to increase the risk of long COVID (such as an increased hospitalization time, a higher number of comorbidities, increased symptoms during the first week of illness and the presence of autoantibodies) are commonly seen in those with DS. As such, the development of long COVID is being evaluated in individuals with DS. However, accurately diagnosing long COVID in individuals with DS can be challenging for several reasons. For instance, there are difficulties in objectively evaluating long COVID symptoms (for example, brain 'fog' and fatigue) in individuals with DS, there may be a lack of complaints or even the lack of perception of those complaints by the caregivers. As such, there are still no reports in the literature on long COVID and DS, but the fact that individuals with DS present most of the factors that predispose to long COVID development suggests this is an important area for future study."
Ocon AJ. **Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome.** Front Physiol. 2013 Apr 5;4:63. doi: 10.3389/fphys.2013.00063. PMID: 23576989; PMCID: PMC3617392.	Chronic Fatigue Syndrome (CFS) is defined as greater than 6 months of persistent fatigue that is experienced physically and cognitively. **The cognitive symptoms are generally thought to be a mild cognitive impairment**, but individuals with CFS subjectively describe them as "brain fog." The impairment is not fully understood and often is **described as slow thinking, difficulty focusing, confusion, lack of concentration, forgetfulness, or a haziness in thought processes.** Causes of "brain fog" and mild cognitive impairment have been investigated. Possible physiological correlates may be because of

	chronic orthostatic intolerance (OI) in the form of the Postural Tachycardia Syndrome (POTS) and decreases in cerebral blood flow (CBF). In addition, fMRI studies suggest that individuals with CFS may require increased cortical and subcortical brain activation to complete difficult mental tasks. Furthermore, neurocognitive testing in CFS has demonstrated deficits in speed and efficiency of information processing, attention, concentration, and working memory. The cognitive impairments are then perceived as an exaggerated mental fatigue. This is experienced by those with CFS as "brain fog" and may be viewed as the interaction of physiological, cognitive, and perceptual factors. Thus, the cognitive symptoms of CFS may be due to altered CBF activation and regulation that are exacerbated by a stressor, such as orthostasis or a difficult mental task, resulting in the decreased ability to readily process information, which is then perceived as fatiguing and experienced as "brain fog." Future research looks to further explore these interactions, how they produce cognitive impairments, and explain the perception of "brain fog" from a mechanistic standpoint.
Rawlings, G.H., & Beail, N. **Long-COVID in people with intellectual disabilities: A call for research of a neglected area** British Journal of Learning Disabilities, 29 August 2022. 1-8. https://doi.org/10.1111/bld.12499	Long-COVID (also known as post-coronavirus-19 syndrome) is a term used to describe symptoms that people experience following their recovery from the COVID-19 virus. The severity of long-COVID is well recognized, with healthcare providers commissioning services to diagnose and treat those affected, as well as funded research into the condition. The authors performed a systematic search for relevant articles but were unable to find any research on long-COVID in people with intellectual disabilities. Due to the lack of data, we have only been able to make extrapolations from what is known about the condition within the general population. We provide an overview of long-COVID and its potential relevance to people with an intellectual disability. We have focused specifically on symptoms or signs, prevalence, risk factors and treatments of the condition in this group, highlighting areas for clinical practice and future research from a psychosocial perspective. We raise serious questions about our current understanding and the availability of the evidence-based to inform treatments tailored towards this population. This is the first report that we are aware of on the topic of long-COVID in people with an intellectual disability. The lack of research is preventing us from gaining a greater understanding of how the condition impacts people with an intellectual disability.
Sachs, J.D., Karim SSA, Aknin L, Allen J, Brosbøl K, Colombo F, Barron GC, Espinosa MF, Gaspar V, Gaviria A, Haines A, Hotez PJ, Koundouri P, Bascuñán FL, Lee JK, Pate MA, Ramos G, Reddy KS, Serageldin I, Thwaites J, Vike-Freiberga V, Wang C, Were MK, Xue L, Bahadur C, Bottazzi ME, Bullen C, Laryea-Adjei G, Amor YB, Karadag O,	The multiple failures of international cooperation include (1) the lack of timely notification of the initial outbreak of COVID-19; (2) costly delays in acknowledging the crucial airborne exposure pathway of SARS-CoV-2, the virus that causes COVID-19, and in implementing appropriate measures at national and global levels to slow the spread of the virus; (3) the lack of coordination among countries regarding suppression strategies; (4) the failure of governments to examine evidence and adopt best practices for controlling the pandemic and managing economic and social spillovers from other countries; (5) the

Lafortune G, Torres E, Barredo L, Bartels JGE, Joshi N, Hellard M, Huynh UK, Khandelwal S, Lazarus JV, Michie S. **The Lancet Commission on lessons for the future from the COVID-19 pandemic.** *Lancet.* 2022 Sep 14:S0140-6736(22)01585-9. doi: 10.1016/S0140-6736(22)01585-9. Epub ahead of print. PMID: 36115368.	shortfall of global funding for low-income and middle-income countries (LMICs), as classified by the World Bank; (6) the failure to ensure adequate global supplies and equitable distribution of key commodities—including protective gear, diagnostics, medicines, medical devices, and vaccines—especially for LMICs; (7) the lack of timely, accurate, and systematic data on infections, deaths, viral variants, health system responses, and indirect health consequences; (8) the poor enforcement of appropriate levels of biosafety regulations in the lead-up to the pandemic, raising the possibility of a laboratory-related outbreak; (9) the failure to combat systematic disinformation; and (10) the lack of global and national safety nets to protect populations experiencing vulnerability. The Commission's aim is to propose guideposts for strengthening the multilateral system to address global emergencies and to achieve sustainable development. In issuing this report, we commend the excellent work of many important international studies that have preceded our own, most notably those from the Independent Panel for Pandemic Preparedness and Response and the G20 High-Level Independent Panel on Financing the Global Commons on Pandemic Preparedness and Response. Section 1 of this Commission report provides a conceptual framework for understanding pandemics. Section 2 provides an annotated chronology of the COVID-19 pandemic and thematic findings regarding several issues. Section 3 presents our policy recommendations, particularly around multilateral cooperation centered at WHO to address global health crises, and around investments in preparedness for future health crises through strong national health systems and international financing and technology cooperation with the world's lower-income regions
Stellers, Frances Stead **New study suggests COVID increases risks of brain disorders** Washington Post, September 11, 2022 https://www.bendbulletin.com/coronavirus/new-study-suggests-covid-increases-risks-of-brain-disorders/article_af7d7301-a145-551a-bae5-046ad8e4bb7e.html	A study published in August in the Lancet Psychiatry **showed increased risks of some brain disorders two years after infection with the coronavirus**, shedding new light on the long-term neurological and psychiatric aspects of the virus. The analysis, conducted by researchers at the University of Oxford and drawing on health records data from more than 1 million people around the world, found that while the risks of many common psychiatric disorders returned to normal within a couple of months, **people remained at increased risk for dementia**, epilepsy, psychosis, and cognitive deficit (or brain fog) two years after contracting COVID. Adults appeared to be at particular risk of lasting brain fog, a common complaint among coronavirus survivors. The study was a mix of good and bad news findings, said Paul Harrison, a professor of psychiatry at the University of Oxford and the senior author of the study. Among the reassuring aspects was the quick resolution of symptoms such as depression and anxiety. David Putrino, director of rehabilitation innovation at Mount Sinai Health System in New York, who has been studying the lasting impacts of the coronavirus since early in the pandemic, said the study revealed some very troubling outcomes. "It allows us to see without a doubt the

	emergence of significant neuropsychiatric (conditions) in individuals that had COVID and far more frequently than those who did not," he said. Because it focused only on the neurological and psychiatric effects of the coronavirus, the study authors and others emphasized that it is not strictly long-COVID research. The researchers matched almost 1.3 million patients with a diagnosis of COVID-19 between Jan. 20, 2020, and April 13, 2022, with an equal number of patients who had other respiratory diseases during the pandemic. The data, provided by electronic health records network TriNetX, came largely from the United States but also included data from Australia, Britain, Spain, Bulgaria, India, Malaysia and Taiwan. The study group, which included 185,000 children and 242,000 older adults, **revealed that risks differed according to age groups, with people aged 65 and older at greatest risk of lasting neuropsychiatric affects.** Between 7 million and 23 million people in the United States have long COVID, according to recent government estimates — a catchall term for a wide range of symptoms including fatigue, breathlessness and anxiety that persist weeks and months after the acute infection has subsided. Those numbers are expected to rise as the coronavirus settles in as an endemic disease. or people between the ages of 18 and 64, a particularly significant increased risk was of persistent brain fog, affecting 6.4% of people who had had COVID compared with 5.5% in the control group. Six months after infection, children were not found to be at increased risk of mood disorders, although they remained at increased risk of brain fog, insomnia, stroke, and epilepsy. None of those affects was permanent for children. With epilepsy, which is extremely rare, the increased risk was larger. The study **found that 4.5% of older people developed dementia in the two years after infection, compared with 3.3% of the control group**. That 1.2-point increase in a diagnosis as damaging as dementia is particularly worrisome, the researchers said. The study's reliance on a trove of de-identified electronic health data raised some cautions, particularly during the tumultuous time of the pandemic. Tracking long-term outcomes may be hard when patients may have sought care through many different health systems, including some outside the TriNetX network. The study follows earlier research from the same group, which reported last year that a third of COVID patients experienced mood disorders, strokes, or dementia six months after infection with the coronavirus. While cautioning that it is impossible to make full comparisons among the effects of recent variants, including omicron and its subvariants, which are currently driving infections, and those that were prevalent a year or more ago, the researchers outlined some initial findings: Even though omicron caused less severe immediate symptoms, the longer-term neurological and psychiatric outcomes appeared similar to the

	delta waves, indicating that the burden on the world's health-care systems might continue even with less-severe variants.
Taquet, Maxime ; Rebecca Sillett, Lena Zhu, Jacob Mendel, Isabella Camplisson, Quentin Dercon, Paul J Harrison **Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients** Lancet Psychiatry 2022; 9: 815–27 https://www.thelancet.com/action/showPdf?pii=S2215-0366%2822%2900260-7	COVID-19 is associated with increased risks of neurological and psychiatric sequelae in the weeks and months thereafter. How long these risks remain, whether they affect children and adults similarly, and whether SARS-CoV-2 variants differ in their risk profiles remains unclear. Methods In this analysis of 2-year retrospective cohort studies, we extracted data from the TriNetX electronic health records network, an international network of de-identified data from health-care records of approximately 89 million patients collected from hospital, primary care, and specialist providers (mostly from the USA, but also from Australia, the UK, Spain, Bulgaria, India, Malaysia, and Taiwan). A cohort of patients of any age with COVID-19 diagnosed between Jan 20, 2020, and April 13, 2022, was identified and propensity-score matched (1:1) to a contemporaneous cohort of patients with any other respiratory infection. Matching was done on the basis of demographic factors, risk factors for COVID-19 and severe COVID-19 illness, and vaccination status. Analyses were stratified by age group (age <18 years [children], 18–64 years [adults], and ≥65 years [older adults]) and date of diagnosis. We assessed the risks of 14 neurological and psychiatric diagnoses after SARS-CoV-2 infection and compared these risks with the matched comparator cohort. The 2-year risk trajectories were represented by time-varying hazard ratios (HRs) and summarized using the 6-month constant HRs (representing the risks in the earlier phase of follow-up, which have not yet been well characterized in children), the risk horizon for each outcome (ie, the time at which the HR returns to 1), and the time to equal incidence in the two cohorts. We also estimated how many people died after a neurological or psychiatric diagnosis during follow-up in each age group. Finally, we compared matched cohorts of patients diagnosed with COVID-19 directly before and after the emergence of the alpha (B.1.1.7), delta (B.1.617.2), and omicron (B.1.1.529) variants. Findings We identified 1 487 712 patients with a recorded diagnosis of COVID-19 during the study period, of whom 1 284 437 (185 748 children, 856 588 adults, and 242 101 older adults; overall mean age 42·5 years [SD 21·9]; 741 806 [57·8%] were female and 542 192 [42·2%] were male) were adequately matched with an equal number of patients with another respiratory infection. The risk trajectories of outcomes after SARS-CoV-2 infection in the whole cohort differed substantially. While most outcomes had HRs significantly greater than 1 after 6 months (with the exception of encephalitis; Guillain-Barré syndrome; nerve, nerve root, and plexus disorder; and parkinsonism), their risk horizons and time to equal incidence varied greatly. Risks of the common psychiatric disorders returned to baseline after 1–2 months (mood disorders at 43 days, anxiety disorders at 58 days) and subsequently reached an equal

	overall incidence to the matched comparison group (mood disorders at 457 days, anxiety disorders at 417 days). By contrast, risks of cognitive deficit (known as brain fog), dementia, psychotic disorders, and epilepsy or seizures were still increased at the end of the 2-year follow-up period. Post-COVID-19 risk trajectories differed in children compared with adults: in the 6 months after SARS-CoV-2 infection, children were not at an increased risk of mood (HR 1·02 [95% CI 0·94–1·10) or anxiety (1·00 [0·94–1·06]) disorders, but did have an increased risk of cognitive deficit, insomnia, intracranial hemorrhage, ischemic stroke, nerve, nerve root, and plexus disorders, psychotic disorders, and epilepsy or seizures (HRs ranging from 1·20 [1·09–1·33] to 2·16 [1·46–3·19]). Unlike adults, cognitive deficit in children had a finite risk horizon (75 days) and a finite time to equal incidence (491 days). A sizeable proportion of older adults who received a neurological or psychiatric diagnosis, in either cohort, subsequently died, especially those diagnosed with dementia or epilepsy or seizures. Risk profiles were similar just before versus just after the emergence of the alpha variant (n=47 675 in each cohort). Just after (vs just before) the emergence of the delta variant (n=44 835 in each cohort), increased risks of ischemic stroke, epilepsy or seizures, cognitive deficit, insomnia, and anxiety disorders were observed, compounded by an increased death rate. With omicron (n=39 845 in each cohort), there was a lower death rate than just before emergence of the variant, but the risks of neurological and psychiatric outcomes remained similar. Interpretation This analysis of 2-year retrospective cohort studies of individuals diagnosed with COVID-19 showed that the increased incidence of mood and anxiety disorders was transient, with no overall excess of these diagnoses compared with other respiratory infections. In contrast, the increased risk of psychotic disorder, cognitive deficit, dementia, and epilepsy or seizures persisted throughout. The differing trajectories suggest a different pathogenesis for these outcomes. Children have a more benign overall profile of psychiatric risk than do adults and older adults, but their sustained higher risk of some diagnoses is of concern. The fact that neurological and psychiatric outcomes were similar during the delta and omicron waves indicates that the burden on the health-care system might continue even with variants that are less severe in other respects. Our findings are relevant to understanding individual-level and population-level risks of neurological and psychiatric disorders after SARS-CoV-2 infection and can help inform our responses to them.
Tavares-Júnior JWL, de Souza ACC, Borges JWP, Oliveira DN, Siqueira-Neto JI, Sobreira-Neto MA, Braga-Neto P. **COVID-19 associated cognitive impairment: A systematic review**. Cortex. 2022 Jul;152:77-97. doi: 10.1016/j.cortex.2022.04.006. Epub	COVID-19 has a wide range of clinical manifestations. Neurological manifestations in COVID-19 patients were demonstrated during the pandemic, including cognitive impairment. **This study aimed to determine any relationship between COVID-19 and cognitive complaints, such as dementia, mild cognitive impairment (MCI), or subjective cognitive decline (SCD).**

2022 Apr 18. PMID: 35537236; PMCID: PMC9014565.	We performed a systematic review of MEDLINE via Ebsco, Cochrane EMBASE, SCOPUS, and LILACS electronic databases of observational studies with COVID-19 patients confirmed by serology or PCR who developed new cognitive impairment or deteriorated from previous cognitive impairment after infection. A total of 3.520 articles were retrieved and read. Twenty-two studies were selected for our review. A wide range of cognitive assessment tools (n = 25) was used. The most described affected domains in these studies were executive functions, attention, and episodic memory. Thirteen studies showed a pattern of cognitive impairment in processing speed, inattention, or executive dysfunction assessed through working memory. This review highlights **the high frequency of cognitive impairment after COVID-19 infection.** However, we were unable to differentiate whether the cognitive impairment found corresponded to mild cognitive impairment or dementia through data from selected studies, and this issue serves as one objective of future studies to be addressed on this topic.
University of Cambridge. **Cognitive impairment from severe COVID-19 equivalent to 20 years of aging, study finds.** ScienceDaily. ScienceDaily, 3 May 2022. <www.sciencedaily.com/releases/2022/05/220503083108.htm>.	Cognitive impairment as a result of severe COVID-19 is similar to that sustained between 50 and 70 years of age and is the equivalent to losing 10 IQ points, say a team of scientists from the University of Cambridge and Imperial College London. The findings, published in the journal eClinicalMedicine, emerge from the NIHR COVID-19 BioResource. The results of the study suggest the effects are still detectable more than six months after the acute illness, and that any recovery is at best gradual. There is growing evidence that COVID-19 can cause lasting cognitive and mental health problems, with recovered patients reporting symptoms including fatigue, 'brain fog', problems recalling words, sleep disturbances, anxiety and even post-traumatic stress disorder (PTSD) months after infection. In the UK, a study found that around one in seven individuals surveyed reported having symptoms that included cognitive difficulties 12 weeks after a positive COVID-19 test. While even mild cases can lead to persistent cognitive symptoms, between a third and three-quarters of hospitalized patients report still suffering cognitive symptoms three to six months later. To explore this link in greater detail, researchers analyzed data from 46 individuals who received in-hospital care, on the ward or intensive care unit, for COVID-19 at Addenbrooke's Hospital, part of Cambridge University Hospitals NHS Foundation Trust. 16 patients were put on mechanical ventilation during their stay in hospital. All the patients were admitted between March and July 2020 and were recruited to the NIHR COVID-19 BioResource. The individuals underwent detailed computerized cognitive tests an average of six months after their acute illness using the Cognitron platform, which measures different aspects of mental faculties such as memory, attention, and reasoning. Scales measuring anxiety, depression and post-traumatic stress disorder were also assessed. Their data were compared against matched controls.

	This is the first time that such rigorous assessment and comparison has been carried out in relation to the aftereffects of severe COVID-19. COVID-19 survivors were less accurate and with slower response times than the matched control population -- and these deficits were still detectable when the patients were following up six months later. The effects were strongest for those who required mechanical ventilation. By comparing the patients to 66,008 members of the public, the researchers estimate that the magnitude of cognitive loss is similar on average to that sustained with 20 years ageing, between 50 and 70 years of age, and that this is equivalent to losing 10 IQ points. Survivors scored particularly poorly on tasks such as verbal analogical reasoning, a finding that supports the commonly-reported problem of difficulty finding words. They also showed slower processing speeds, which aligns with previous observations post COVID-19 of decreased brain glucose consumption within the frontoparietal network of the brain, responsible for attention, complex problem-solving and working memory, among other functions. Professor David Menon from the Division of Anaesthesia at the University of Cambridge, the study's senior author, said: "Cognitive impairment is common to a wide range of neurological disorders, including dementia, and even routine ageing, but the patterns we saw -- the cognitive 'fingerprint' of COVID-19 -- was distinct from all of these." While it is now well established that people who have recovered from severe COVID-19 illness can have a broad spectrum of symptoms of poor mental health -- depression, anxiety, post-traumatic stress, low motivation, fatigue, low mood, and disturbed sleep -- the team found that acute illness severity was better at predicting the cognitive deficits. The patients' scores and reaction times began to improve over time, but the researchers say that any recovery in cognitive faculties was at best gradual and likely to be influenced by a number of factors including illness severity and its neurological or psychological impacts. Professor Menon added: "We followed some patients up as late as ten months after their acute infection, so were able to see a very slow improvement. While this was not statistically significant, it is at least heading in the right direction, but it is very possible that some of these individuals will never fully recover." There are several factors that could cause the cognitive deficits, say the researchers. Direct viral infection is possible, but unlikely to be a major cause; instead, it is more likely that a combination of factors contribute, including inadequate oxygen or blood supply to the brain, blockage of large or small blood vessels due to clotting, and

	microscopic bleeds. However, emerging evidence suggests that the most important mechanism may be damage caused by the body's own inflammatory response and immune system. While this study looked at hospitalized cases, the team say that even those patients not sick enough to be admitted may also have tell-tale signs of mild impairment. Professor Adam Hampshire from the Department of Brain Sciences at Imperial College London, the study's first author, said: "Around 40,000 people have been through intensive care with COVID-19 in England alone and many more will have been very sick, but not admitted to hospital. This means there is a large number of people out there still experiencing problems with cognition many months later. We urgently need to look at what can be done to help these people."
Vyas, Arvind; Vasim Raja Panwar, Vaibhav Mathur, Parth Patel, Surabhi Mathur, Arvind Sharma, Raja Babu Panwar & Rajeev Gupta (2022) **Mild cognitive impairment in COVID-19 survivors: Measuring the brain fog**. International Journal of Mental Health, 51:2, 142-151, DOI: 10.1080/00207411.2021.1988402	The coronavirus disease 2019 (COVID-19) pandemic has been impacting individuals throughout the world. Millions have been affected, and while many have recovered, a growing number of recovered COVID-19 patients are reportedly **facing neurological symptoms, described as "slow thinking," "difficulty** in focusing," "confusion," "lack of concentration," "forgetfulness," or "haziness in thought process." These experiences of mental fatigue, associated with and related to mild cognitive impairments, may be conceptually defined as "brain fog." To study the prevalence and severity of these brain fog symptoms in COVID-19 recovered patients, and examining their association with age, gender, and COVID-19 symptom severity. A total of 300 patients who tested positive for Real-Time Reverse Transcriptase–Polymerase Chain Reaction (RT-PCR) for SARSCoV-2 during April–August 2020 were included in our study after complete recovery from their acute illness. They were assessed for brain fog symptoms using the 9-item validated Wood's mental fatigue inventory. The **overall cumulative prevalence of any components of brain fog was 34%,** with a mean score of 6.11 ± 1.7 in those who experienced it. Males were more affected than females (42.3% vs. 29.1%) with males scoring higher than females. The mean score was higher in severe ill and Intensive Care Unit (ICU) patients and those who required oxygen or were on a ventilator.
Wisniewski, T. et al COVID-19 Infection Associated with **Uptick in Alzheimer's Biomarkers in the Blood** AAIC 2021 abstracts, Denver, Colorado https://aaic.alz.org/downloads2021/COVID-19_and_Long-Term_Cognitive_Dysfunction.pdf	Certain biological markers in blood — including total tau (t-tau), neurofilament light (NfL), glial fibrillary acid protein (GFAP), ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), and species of amyloid beta (Aβ40, Aβ42) and phosphorylated tau (pTau-181) — are indicators of injury in the brain, neuroinflammation and Alzheimer's disease. To study the presence of these blood biomarkers, neurodegeneration and neuroinflammation in older patients who were hospitalized with COVID-19, Thomas Wisniewski, M.D., a professor of neurology, pathology and psychiatry at New York

	University Grossman School of Medicine, and colleagues took plasma samples from 310 patients who were admitted to New York University Langone Health with COVID-19. Of the patients, 158 were positive for SARS-CoV-2 with neurological symptoms and 152 were positive for SARS-CoV-2 without neurologic symptoms. The most common neurological symptom was confusion due to toxic-metabolic encephalopathy (TME). In patients who were initially cognitively normal with and without TME related to COVID-19 infection, the researchers found higher levels of t-tau, NfL, GFAP, pTau-181, and UCH-L1 in COVID-19 patients with TME compared to COVID-19 patients without TME. There were no significant differences with Aβ1-40, but the pTau/Aβ42 ratio showed significant differences in patients with TME. Additionally, t-tau, NfL, UCH-L1 and GFAP significantly correlated with markers of inflammation such as C-reactive peptide, which may suggest inflammation-related blood-brain barrier disruption accompanying neuronal/glial injury. "These findings suggest that **patients who had COVID-19 may have an acceleration of Alzheimer's related symptoms and pathology**," Wisniewski said. "However, more longitudinal research is needed to study how these biomarkers impact cognition in individuals who had COVID-19 in the long term."
Xu, E., Xie, Y., & Ziyad, A-A. **Long-term neurologic outcomes of COVID-19** *Nature Medicine,* 2022, Sept 22, https://doi.org/10.1038/s41591-022-02001-z	The neurologic manifestations of acute COVID-19 are well characterized, but a comprehensive evaluation of postacute neurologic sequelae at 1 year has not been undertaken. Here we use the national healthcare databases of the US Department of Veterans Affairs to build a cohort of 154,068 individuals with COVID-19, 5,638,795 contemporary controls and 5,859,621 historical controls. We use inverse probability weighting to balance the cohorts, and estimate risks and burdens of incident neurologic disorders at 12 months following acute SARS-CoV-2 infection. Our results show that in the postacute phase of COVID-19, there was increased risk of an array of incident neurologic sequelae including ischemic and hemorrhagic stroke, cognition and memory disorders, peripheral nervous system disorders, episodic disorders (for example, migraine and seizures), extrapyramidal and movement disorders, mental health disorders, musculoskeletal disorders, sensory disorders, Guillain–Barré syndrome, and encephalitis or encephalopathy. We estimated that the hazard ratio of any neurologic sequela was 1.42 (95% confidence intervals 1.38, 1.47) and burden 70.69 (95% confidence intervals 63.54, 78.01) per 1,000 persons at 12 months. The risks and burdens were elevated even in people who did not require hospitalization during acute COVID-19. Limitations include a cohort comprising mostly White males. Taken together, our results provide evidence of increased risk of long-term neurologic disorders in people who had COVID-19.