



## PRACTICE POINTER

## Cognitive dysfunction after covid-19

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## What you need to know

- Cognitive problems are common after acute SARS-CoV-2 infection and can be disabling and frightening
- Symptoms tend to improve, but this may take up to a year. Those with chronically persistent symptoms lasting more than 12 months have a lower chance of improving
- Symptoms usually fluctuate
- Assessment should be directed to documenting the nature and trajectory of the impairment and excluding alternative diagnoses
- Self-management techniques may help patients manage their condition

As of March 2023, when the Office for National Statistics stopped collecting data on this condition, 1.879 million individuals had self-assessed as having long covid—symptoms lasting more than 12 weeks following acute covid-19 infection. Of these, the proportion of individuals with symptoms lasting two years or more is around 42%, suggesting a decline in new cases of long covid but a persistence of those with ongoing symptoms.<sup>1</sup> Some systematic reviews and meta-analyses have reported that up to a third of such individuals have persistent symptoms of cognitive impairment,<sup>2,3</sup> but estimates vary widely and are complicated by methodological heterogeneity—eg, study size, assessment approach, follow-up duration, and different sampling frames (from self-reported surveys<sup>4</sup> to large retrospective matched cohort studies of health records<sup>5</sup>), as discussed in a recent meta-analysis.<sup>6</sup>

The pathological underpinnings and potential therapeutic possibilities for cognitive impairment in long covid are also uncertain. The bulk of evidence to date is mechanistic (using basic science, animal models, or human tissue), observational (using longitudinal cohort studies), or hypothetical (reasoning from basic principles); this literature has been well summarised by the RECOVER Consortium.<sup>7</sup> Because of the methodological heterogeneity, even when individual studies have been rigorously conducted, it is difficult to know to what extent their findings can be extrapolated and generalised across those with long covid. A few randomised controlled trials of potential treatments (pharmacological and non-pharmacological) have been completed, and others are under way.<sup>7</sup>

Cognitive performance is typically conceptualised in terms of functional domains depending upon the task at hand. Domains are hierarchical and inter-related, ranging from more basic sensory and perceptual processes to executive functioning and cognitive

control.<sup>8</sup> Both psychometric studies and qualitative studies of the patient experience identify problems across one or more of these domains. The most frequent symptoms seem to affect memory, attention, and concentration<sup>9</sup> but discrete impairments are also seen in attentional and executive processing,<sup>10,11</sup> different types of memory,<sup>10,12</sup> visuospatial processing,<sup>13</sup> and language.<sup>12</sup> Many patients show deficits in multiple domains,<sup>12,14</sup> which may or may not correlate with self-reported symptoms.<sup>15</sup> Moreover, linked systemic symptoms such as fatigue, insomnia, and a general befuddled state frequently termed “brain fog” are commonly reported. This seems to wax and wane with physical fatigue.<sup>16</sup> A higher symptom burden is often associated with concomitant mood disorders or post-traumatic stress disorder, regardless of illness severity.<sup>15,17–19</sup>

Longitudinal cohort, case control, and qualitative studies have shown that while many individuals improve gradually over time, cognitive symptoms fluctuate unpredictably, causing uncertainty and (in some) anxiety.<sup>9,20–22</sup> These impairments can have profound impacts on an individual’s life, with significant ramifications for relationships, jobs, and normal daily activities.<sup>4,22</sup> This article explores the impact of these symptoms and offers a practical guide for GPs to help them approach cognitive dysfunction in individuals with long covid as indicated by the evolving and conflicting evidence base. An account from a patient’s perspective is given in box 1.

## Box 1: Patient experience

When I got covid in December 2020 I was worried about what might happen. It was before vaccines, and the news was full of statistics of the hospitalised and those who’d lost their lives. After my 14 day isolation I was relieved to get back to normal life, thinking I had dodged quite a bullet.

I was quickly aware that something wasn’t right. At the time of my infection I was a drama teacher in a secondary school. I remember being at work in January 2021 and finding it impossible to concentrate on what I had to do. Trying to focus made my head spin, and working on a computer screen was almost impossible. In the classroom I couldn’t process what was happening around me like I used to be able to, there was a sharpness lost, and that had a significant impact on both my teaching ability and classroom management. After several attempts at returning to work it became clear that I wasn’t able to continue, and I left teaching in January 2022.

Alongside my difficulties focusing there are problems with memory. Remembering things from one minute to the next is often difficult, and this is not something I ever had an issue with before covid. If I am mid-task or thought and am distracted (my husband asks a question, the phone rings, etc) I can completely forget what I was doing. I lose words, and as someone who works with

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words, that is both frustrating and at times frightening. My brain mixes up facts and names, and I find myself having to double check such things on a regular basis to avoid embarrassing situations or mistakes.

Like many elements of long covid, these problems fluctuate and are worse when I don't do so well with my pacing, or have more mental stimulus or physical activity than I am able to cope with. One big challenge is that, as this is a hidden condition, others forget it's there and so fail to accommodate it.

That covid has impaired my cognitive function in many ways is without question. I can only hope that, in time, a solution is found, and in the meantime I adapt to survive, and do what I can to manage the condition. It isn't easy!

## Questions patients ask

### Why did I develop cognitive problems?

Anybody who has been infected with the SARS-CoV-2 virus can develop long covid, including cognitive impairment, regardless of the severity of infection,<sup>23</sup> but a prospective cohort study of 4000 patients logging their symptoms through an app revealed an increased risk of developing long covid in older individuals, women, and those with a higher body mass index or greater burden of pre-existing comorbidities.<sup>24</sup> Moreover, systematic reviews and meta-analyses have shown that vaccination against SARS Co-V-2 reduces the risk of developing long covid.<sup>25 26</sup> Further associations have been seen in a cohort study of patients admitted to hospital between cognitive impairments and objectively assessed persistent impairments in smell or taste<sup>27</sup> and sleep apnoea,<sup>28</sup> while numerous, but relatively small cross sectional studies using objective clinical assessments have found strong reciprocal associations with fatigue or mood disorders.<sup>29-31</sup>

### What is causing my cognitive problems?

There is no straightforward answer to this question, which is understandably frustrating for patients.<sup>22</sup> Different areas of the brain are involved in different cognitive processes. Animal and neuroimaging studies in humans with persistent symptoms have shown alterations in the anatomy or functioning of some of these regions correlating with specific impairments,<sup>32-35</sup> providing a pathological link with symptoms. However, there are many mechanistic hypotheses. Neuropathological, biomarker, and neuroimaging studies have suggested ongoing viral infection in the brain,<sup>33 36</sup> viral activation of immune or inflammatory pathways resulting in neuronal destruction or impairment,<sup>35 37</sup> and dysregulated autonomic function as seen in other conditions.<sup>38</sup> Alternative proposals include microvascular damage caused by endothelial dysfunction and hypoxia related inflammation,<sup>39</sup> and parallels have also been drawn with cognitive difficulties experienced during chemotherapy treatment<sup>40</sup> or in other chronic inflammatory or autoimmune disorders.<sup>41</sup>

Seek to exclude non-specific cognitive blunting from other underlying causes. Alongside specific metabolic, toxic, or (patho)physiological causes (box 2), poor sleep, diet, smoking, alcohol, and recreational drug use, reduced activity levels, and low exposure to natural light may also contribute. These should therefore be established in the history and improved or mitigated if and where possible.

#### Box 2: Other contributors to cognitive impairment

- Alzheimer's disease/dementia
- Anxiety
- Vitamin B12 deficiency

- Chronic hypoxia (eg, chronic obstructive pulmonary disease)
- Chronic pain
- Depression
- Menopause/perimenopause
- Migraine
- Multiple sclerosis
- Myalgic encephalomyelitis
- Poor glycaemic control
- Parkinson's disease
- Schizophrenia
- Sleep apnoea
- Thyroid problems

#### Medications that can contribute to cognitive impairment\*

- Anticholinergics
- Anticonvulsants (eg, gabapentin/pregabalin)
- Antihistamines
- Antidepressants (eg, amitriptyline/nortriptyline)
- Antispasmodics
- Anxiolytics
- Chemotherapy
- Opioids
- Sedatives

\* Medication review is recommended (including over-the-counter medicines, supplements, and herbal remedies) to address polypharmacy and potential drug interactions

### What tests do I need for my cognitive function?

No specific test will diagnose or assess the severity of cognitive impairment in long covid, although multiple measures can provide an assessment of cognition more generally. Several instruments are in development.<sup>42-44</sup> These include mental evaluation that captures cognitive deficit in the context of other long covid symptoms. The approach to investigation is to exclude "red flag" symptoms that indicate the need for emergency referral,<sup>45</sup> consider and manage comorbidities and alternative causes, and then explore specific symptoms.

As with all investigations, consider how the result may alter management. A normal, appropriate brain imaging test may reassure those who are concerned but may also identify incidental findings that can lead to unnecessary intervention. Brain imaging using standard computed tomography or magnetic resonance imaging scanning is not routinely recommended in those with cognitive problems following covid-19, particularly those who describe the typical pattern of "brain fog" frequently seen in patients with long covid. However, imaging or targeted cognitive testing (see below) may be indicated in some patients to rule out other neurological conditions. These would typically include individuals with symptoms suggestive of intracranial pathology such as suspicious nausea and vomiting, postural headaches, focal motor or sensory changes, or visual disturbances, or those who may be at higher risk of an underlying neurological disorder. Examples of the latter group may include older individuals concerned about degenerative conditions, those with a family history of hereditary neurological disorders, or with symptoms potentially indicative of an underlying disorder—eg, bradykinesia or recurrent falls (suggestive of Parkinson's disease and progressive supranuclear palsy, respectively).

Guidelines from the National Institute for Health and Care Excellence on long covid suggest neuropsychometric testing after six months if cognitive function is not improving (and especially if worsening).<sup>46</sup> Most new symptoms spontaneously resolve within this timeframe. However, it may be helpful for patients to elicit the level of impairment relative to their “normal” state at presentation and monitor any change (usually improvement) over time. After this point, formal testing may be helpful as the proportion of individuals with long term persistent symptoms seems to increase with time.<sup>1</sup> Formal assessment may include the Montreal cognitive assessment (MOCA),<sup>47</sup> mini mental state examination,<sup>48</sup> or frontal assessment battery<sup>49</sup> (among others), which assess attention, working memory, visuospatial skills, executive functioning (MOCA), and verbal fluency (MOCA). However, the usefulness of such tests in assessing post viral change is currently unclear. Moreover, the tests are affected by an individual’s baseline cognitive function and previous education; thus individuals with higher baseline cognitive performance may notice reduced abilities relative to their usual level but still pass standard tests. The fluctuating nature of long covid also makes one-off assessments potentially inaccurate. Make patients aware of these issues when considering referrals for further neuropsychometric testing.

### How do people manage their cognitive problems?

Our engagement with patients in the LOCOMOTION patient advisory group and qualitative studies have highlighted practical strategies to cope with impairments. Many patients have found communicating the fluctuating nature and variable impact of their (largely invisible) symptoms particularly challenging. One technique is to explain energy levels in terms of battery life, bank balance, or the number of spoons remaining in a drawer. All three analogies describe energy as finite units used up by activities and therefore leaving the person unable to do all they want or need to do. Some activities can be rejuvenating and replenish the store. Planning days with a mixture of differently draining activities can help minimise fatigue and frustration and maximise performance.<sup>22</sup> Similarly, activity and symptom trackers can help identify triggers for mental fatigue that can be avoided or help people prioritise tasks and activities.

Other reported strategies focus on reducing an individual’s general cognitive load (a combination of simultaneous conscious and unconscious cognitive tasks). These “task loads” interact in complex ways but because working memory capacity is limited,<sup>50</sup> even distractions that a person is not consciously aware of can measurably degrade performance.<sup>51</sup> Box 3 outlines different approaches individuals have raised in qualitative interview and focus group studies to minimise their cognitive load.<sup>22,52</sup> Lessening overall cognitive load can improve functioning in specific domains while also lessening the distress of “failing” at simple cognitive tasks.

#### Box 3: Self-management strategies that can reduce cognitive load

- Limit distractions when performing tasks by controlling environmental stimuli such as noise and light
- Make and use lists
- Identify “homes” for things that might easily be lost (eg, glasses, watch, phone, keys, medications, handbag)
- Keep a regular routine that includes rest breaks
- Break down activities into smaller components
- Ask others to help by checking, reminding, and proofreading work
- Identify patterns in symptoms to help with scheduling activities
- Pace yourself to maintain steady levels of activity and avoid crashes

- Try group mindfulness classes, available at many long covid clinics
- Try cognitive exercises such as word puzzles or memory exercises

### What can my primary care team do for my cognitive symptoms?

Qualitative interview and focus group studies highlight that patients find the process of seeking help and support to be exhausting.<sup>22,53,54</sup> However, they also show how beneficial patients find a supportive encounter or relationship with a clinician who hears the patient’s story and responds empathically, even if they are unable to ease the physical symptoms.<sup>22,53,54</sup> Alongside this witnessing role, despite a lack of clear evidence, it makes theoretical sense to ensure optimal management of comorbid conditions such as diabetes, blood pressure, postural orthostatic tachycardia, menopause, insomnia, or depression. For example, the pro-inflammatory environment associated with impaired glycaemic control has been hypothesised to contribute to capillary dysfunction and exacerbation of long covid symptoms, including cognitive dysfunction.<sup>39,55</sup>

Community support from physical and occupational therapists may be helpful to support optimal day-to-day functioning.<sup>56</sup> However, physical rehabilitation should reflect the evidence from observational studies<sup>57</sup> and patient groups<sup>58</sup> that post-exertional symptom exacerbation (PESE) and post-exertional malaise (PEM) can be precipitated using traditional “graded exercise therapy,” which takes no account of the person’s energy levels and encourages participants to “push through” fatigue. Rather, physical interventions should incorporate “pacing”—that is, adjusting the level of exertion to accommodate energy levels as self-assessed with the “battery” or “spoons” metaphor described above.

World Health Organization guidance suggests that in individuals with PESE or PEM, red flags for such deteriorations should be established before commencing exercise—eg, using pulse oximetry or screening tools such as the De Paul symptom questionnaire-post exertional malaise (DSQ-PEM). Moreover, rehabilitative regimens should be personalised, grounded in realistic expectations, and be conducted in a safe and supportive environment.<sup>59</sup> Small interventional studies have shown objectively assessed improvements in fatigue, cognition, and overall functioning following in-person programmes that included resistance, endurance, and balance training alongside an education and pacing element<sup>60,61</sup>—although the latter study specifically focused on individuals who had been admitted to intensive care units during their acute illness.<sup>61</sup> Large scale observational or interventional studies of physical interventions for brain fog which reflect the heterogeneity of the long covid population are currently lacking.

Clinical trials are under way for a range of therapeutic agents in long covid, with a view to these relieving cognitive symptoms. Trials include antivirals, anti-inflammatory or immunomodulators, cardiac agents, cannabinoids, agents targeting receptors within the central nervous system (eg, aripiprazole and vortioxetine), anticoagulants, and others (summarised by the RECOVER consortium).<sup>7</sup> However, to date, no large scale randomised controlled trials support any particular therapeutic approach to treat cognitive impairment in long covid. Numerous small studies have shown variable benefit from use of nutritional supplements,<sup>62,63</sup> mindfulness supported by essential oils,<sup>64</sup> transcutaneous auricular vagus nerve stimulation,<sup>65</sup> hyperbaric oxygen therapy,<sup>66,67</sup> and acupuncture.<sup>68</sup> Patients also report symptom improvement following yoga techniques.<sup>69</sup> However, these results are inconsistent, subject to selection, information, and publication biases and potential performance effects during testing. Patients may wish to consider these approaches, but an important aspect of the GP’s role is to



ensure appropriate expectation management and discuss their lack of routine availability through the NHS.

Given the absence of definitive evidence on effective drug treatments, GPs can provide essential longitudinal support and encouragement for patients. This ongoing therapeutic relationship may help individuals optimise their physical condition, given the strong association between physical and mental symptoms in chronic conditions.<sup>70</sup> This might include education around a healthy, balanced lifestyle and attention to optimising sleep patterns, helping them develop their own management strategies—including discussions around energy preservation and pacing, discussing the potential harms of over-investigation and unproved treatments, and managing their expectations around recovery. Moreover, support and guidance around returning to work is vital. Many employers lack a formalised return-to-work policy, or phased returns are too structured to support the fluctuating nature of long covid. Communicating this to employers and supporting flexible returns may be helpful for patients. Patients may also be interested in taking part in research studies and might value being signposted to opportunities available to them.

### Will my cognitive problems get better, and what can be done if they don't?

A retrospective, nationwide cohort study of nearly two million healthcare records in Israel suggested that individuals who suffer persistent symptoms following mild covid-19 infection, including cognitive dysfunction, generally recover within 12 months.<sup>71</sup> Further longitudinal studies support this, suggesting that where cognitive symptoms after covid-19 have resolved, they have taken around one year to do so.<sup>12 20 72</sup> In particular, executive function commonly seems to resolve within a year.<sup>4</sup> Patients with long term persistent symptoms will need ongoing support, encouragement with self-management strategies, and active acknowledgment of the frustration and impact of their condition on daily life.

Patients with severe, progressive, or persistent cognitive impairment following covid-19, or those for whom the diagnosis is in doubt, will likely benefit from referral to a specialist multidisciplinary long covid service or cognitive disorders clinic.<sup>73</sup> Similarly, referral to rehabilitation services may help in the context of a comprehensive holistic neuropsychological rehabilitation programme that is team based and goal focused. This may focus on specific rehabilitative approaches such as respiratory physiotherapy or fatigue management strategies and may address cognitive and emotional difficulties to improve everyday function.<sup>74</sup>

#### Long covid patients' accounts of cognitive dysfunction and its impact (adapted from<sup>22 53 75</sup>)

One of the things I've realised is how many things I do in my normal day—and I'm not talking about work—that are cognitive, and that I didn't previously think of as such. For example, a trip to the supermarket, where the amount of sensory information—just staring at a row of things while looking for the food that you want, remembering where things are in the aisles, and planning your trip so that you don't have to walk backwards and forwards around the shop—all surprised me. It's not just “can I walk around the supermarket?” but the planning, getting there, choosing stuff, all of that which is really difficult.

*Rebecca (34)*

I can't cope with multiple inputs. If I'm trying to reply to a message on my phone and one of my boys starts speaking to me or there's something else happening as well—that just really fries my brain. Multi-tasking used to be my superpower, and I was able to do lots and lots of things. As a doctor, I would be dealing with one patient while hearing about another. I'd be remembering, doing something else, juggling lots and lots of things. And now I can't keep multiple plates spinning, I absolutely can't. I've got

to focus on just one thing or I make massive mistakes and it's like I forget my intentions all the time.

*Nadya (54)*

I can ask somebody a question and then I'll ask the exact same question two minutes after and not remember that I've asked. I can't remember significant things that have happened in the past either.

*John (48)*

I've had an in-depth conversation with somebody who isn't aware of how I am, and they've said to me, “you're going round in circles in your conversation” or “you're not making a lot of sense,” when I hadn't realised how repetitive I was being. But those same people can't seem to cut me any slack, or see how difficult it is. There doesn't seem to be the understanding—but it would be beyond my comprehension as well if I hadn't lived it.

*Stephen (61)*

Seven months in, I don't know whether I'm going to get my brain back. I'm really, really fearful for the future and whether I'm going to be able to get back to what I want to do. That's like your identity and yourself. Being an [allied health professional] is a big part of who I am, and if I've lost that, I've lost a huge part of me.

*Rachael (45)*

#### Resources for patients

- Healthtalk.org. Hear directly from people who have had a wide range of debilitating and sometimes confusing symptoms. These are people who know what it is like to have long covid. They talk about things they have found difficult and some of the things that have helped. <https://healthtalk.org/Long-Covid-In-Adults/overview>
- Headway. A charity for individuals suffering from a brain injury. Includes advice and support for recognition and management of cognitive dysfunction <https://www.headway.org.uk>

#### Research

At the time of writing there are 34 ongoing research studies funded by the NIHR recruiting patients with long covid in the UK. Individuals with cognitive symptoms may like to learn more about participating here: <https://bepartofresearch.nihr.ac.uk/results/search-results?query=long%20covid&location=>

#### Resources for professionals

- Fine JS, Ambrose AF, Didehbandi N, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of cognitive symptoms in patients with post-acute sequelae of SARS-CoV-2 infection. *PM R* 2022;14:96-111
- Silver JM MTSJ. Mild traumatic brain injury. Traumatic Brain Imaging. Washington, American Psychiatric Publishing; 2011. 239-64.

See also *The BMJ* article for general sources of support for healthcare professionals and individuals with long covid<sup>45</sup>

#### How patients were involved in the creation of this article

Patient members of the LOCOMOTION quality improvement collaborative contributed the comments in the box “Long covid patients' accounts of cognitive dysfunction and their impact.” ITB has lived experience of long covid and is a member of the patient advisory group for LOCOMOTION. The paper was read by four additional patients with long covid and modified in response to their feedback. This was largely concerned with ensuring we had adequately captured the patient experience with regard to the complexity and severity of symptoms. We subsequently included box 1 “Patient experience” to ensure the patient voice was adequately heard.

## How this article was created

This article is one in a series that offers guidance to general practitioners on persistent symptoms following covid-19. The series began with a general introduction<sup>45</sup> and has previously covered orthostatic tachycardia.<sup>76</sup> This paper on cognitive dysfunction draws on two sources: a literature search of PubMed conducted using the terms “post-acute covid-19”, and “long covid” and multiple terms relating to impaired cognition; and group discussions with front line clinicians and patient partners (the LOCOMOTION consortium<sup>77</sup>) who are members of a national quality improvement collaborative for long covid clinics in UK. In box 1 “Patient experience” and the box “Long covid patients’ accounts of cognitive dysfunction and their impact” we give examples of the impact of impairments raised by our patient advisory team and by participants from qualitative research studies previously conducted by one of the authors (EL). We have also provided a practical guide about how to approach cognitive dysfunction in long covid, designed using the established Quick Reference Handbook style guide used by the Association of Anaesthetists and Resuscitation Council UK.

The paper draws on the clinical experiences and wisdom of the LOCOMOTION consortium. All authors contributed to the narrative and snowball literature search and synthesis of key findings. EL and JLD wrote the first draft which was extensively amended by other authors. All authors offered feedback on the infographic. All authors read and approved the final manuscript. Trisha Greenhalgh provided editorial comments on a final draft.

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- Office for National Statistics. Updated estimates of the prevalence of long COVID symptoms: Office for National Statistics 2022. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/alldatarelatingtoprevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk>.
- Natarajan A, Shetty A, Delanerolle G, et al. A systematic review and meta-analysis of long COVID symptoms. *Syst Rev* 2023;12. doi: 10.1186/s13643-023-02250-0 pmid: 37245047
- Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. *Brain Behav Immun* 2022;101:135. doi: 10.1016/j.bbi.2021.12.020 pmid: 34973396
- Ziauddeen N, Gurdasani D, O'Hara ME, et al. Characteristics and impact of Long Covid: Findings from an online survey. *PLoS One* 2022;17:e0264331. doi: 10.1371/journal.pone.0264331 pmid: 35259179
- Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 2021;8:27. doi: 10.1016/S2215-0366(21)00084-5 pmid: 33836148
- O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long COVID among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* 2022;55:101762. doi: 10.1016/j.eclinm.2022.101762 pmid: 36474804
- Bonilla H, Peluso MJ, Rodgers K, et al. Therapeutic trials for long COVID-19: A call to action from the interventions taskforce of the RECOVER initiative. *Front Immunol* 2023;14:1129459. doi: 10.3389/fimmu.2023.1129459 pmid: 36969241
- Harvey PD. Domains of cognition and their assessment [published Online First: 2019/11/22]. *Dialogues Clin Neurosci* 2019;21:37. doi: 10.31887/DCNS.2019.21.3/pharvey. pmid: 31749647
- Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review [published Online First: 20210730]. *Brain Behav Immun* 2021;97:48. doi: 10.1016/j.bbi.2021.07.018. pmid: 34339806
- Delgado-Alonso C, Valles-Salgado M, Delgado-Álvarez A, et al. Cognitive dysfunction associated with COVID-19: A comprehensive neuropsychological study. *J Psychiatr Res* 2022;150:6. doi: 10.1016/j.jpsychires.2022.03.033 pmid: 35349797
- Zhao S, Shibata K, Hellyer PJ, et al. Rapid vigilance and episodic memory decrements in COVID-19 survivors. *Brain Commun* 2022;4:fcab295. doi: 10.1093/braincomms/fcab295 pmid: 35128398
- Cecchetti G, Agosta F, Canu E, et al. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. *J Neural* 2022;269:12. doi: 10.1007/s00415-022-11047-5 pmid: 35249144
- Delgado-Alonso C, Valles-Salgado M, Delgado-Álvarez A, et al. Cognitive dysfunction associated with COVID-19: A comprehensive neuropsychological study. *J Psychiatr Res* 2022;150:6. doi: 10.1016/j.jpsychires.2022.03.033 pmid: 35349797
- Andriuta D, Si-Ahmed C, Roussel M, et al. Clinical and imaging determinants of neurocognitive disorders in post-acute COVID-19 patients with cognitive complaints. *J Alzheimers Dis* 2022;87:50. doi: 10.3233/JAD-215506 pmid: 35431242
- Chen C, Hauptert SR, Zimmermann L, et al. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J Infect Dis* 2022;226:607. doi: 10.1093/infdis/jiac136 pmid: 35429399
- Premraj L, Kannapadi NV, Briggs J, et al. Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis. *J Neural Sci* 2022;434:120162. doi: 10.1016/j.jns.2022.120162 pmid: 35121209
- Titze-de-Almeida R, da Cunha TR, Dos Santos Silva LD, et al. Persistent, new-onset symptoms and mental health complaints in Long COVID in a Brazilian cohort of non-hospitalized patients. *BMC Infect Dis* 2022;22. doi: 10.1186/s12879-022-07065-3 pmid: 35135496
- Whiteside DM, Naini SM, Basso MR, et al. Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection part 2: Psychological functioning. *Clin Neuropsychol* 2022;36:47. doi: 10.1080/13854046.2022.2030411 pmid: 35098861
- Lamontagne SJ, Winters MF, Pizzagalli DA, Olmstead MC. Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment. *Brain Behav Immun Health* 2021;17:100347. doi: 10.1016/j.bbih.2021.100347 pmid: 34549199
- Del Brutto OH, Rumbea DA, Recalde BY, Mera RM. Cognitive sequelae of long COVID may not be permanent: A prospective study. *Eur J Neurol* 2022;29:21. doi: 10.1111/ene.15215 pmid: 34918425
- Huang Y, Ling Q, Manyande A, Wu D, Xiang B. Brain imaging changes in patients recovered from COVID-19: a narrative review. *Front Neurosci* 2022;16:855868. doi: 10.3389/fnins.2022.855868 pmid: 35527821
- Callan C, Ladds E, Husain L, Pattinson K, Greenhalgh T. 'I can't cope with multiple inputs': a qualitative study of the lived experience of 'brain fog' after COVID-19. *BMJ Open* 2022;12:e056366. doi: 10.1136/bmjopen-2021-056366 pmid: 35149572
- Houben S, Bonnechère B. The impact of COVID-19 infection on cognitive function and the implication for rehabilitation: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;19. doi: 10.3390/ijerph19137748 pmid: 35805406
- Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med* 2021;27:31. doi: 10.1038/s41591-021-01292-y pmid: 33692530
- Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review. *EClinicalMedicine* 2022;53:101624. doi: 10.1016/j.eclinm.2022.101624 pmid: 36051247
- Gao P, Liu J, Liu M. Effect of COVID-19 vaccines on reducing the risk of long COVID in the real world: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;19. doi: 10.3390/ijerph191912422 pmid: 36231717
- Damiano RF, Neto DB, Oliveira JVR, et al. ICHFMUSP COVID-19 study group. Association between chemosensory impairment with neuropsychiatric morbidity in post-acute COVID-19 syndrome: results from a multidisciplinary cohort study. *Eur Arch Psychiatry Clin Neurosci* 2023;273:33. doi: 10.1007/s00406-022-01427-3 pmid: 35633395
- L Mandel H, Colleen G, Abedian S, et al. Risk of post-acute sequelae of SARS-CoV-2 infection associated with pre-coronavirus disease obstructive sleep apnea diagnoses: an electronic health record-based analysis from the RECOVER initiative. *Sleep* 2023;46:zsad126. doi: 10.1093/sleep/zsad126 pmid: 37166330
- Vannorsdall TD, Brigham E, Fawzy A, et al. Cognitive dysfunction, psychiatric distress, and functional decline after COVID-19. *J Acad Consult Liaison Psychiatry* 2022;63:43. doi: 10.1016/j.jaclp.2021.10.006 pmid: 34799396
- Brown LA, Ballentine E, Zhu Y, McGinley EL, Pezzin L, Abramoff B. The unique contribution of depression to cognitive impairment in Post-Acute Sequelae of SARS-CoV-2 infection. *Brain Behav Immun Health* 2022;22:100460. doi: 10.1016/j.bbih.2022.100460 pmid: 35403066
- Bungenberg J, Humkamp K, Hohenfeld C, et al. Long COVID-19: Objectifying most self-reported neurological symptoms. *Ann Clin Transl Neurol* 2022;9:54. doi: 10.1002/acn3.51496 pmid: 35060361
- Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022;604:707. doi: 10.1038/s41586-022-04569-5 pmid: 35255491
- Manca R, De Marco M, Ince PG, Venneri A. Heterogeneity in regional damage detected by neuroimaging and neuropathological studies in older adults with COVID-19: a cognitive-neuroscience systematic review to inform the long-term impact of the virus on neurocognitive trajectories. *Front Aging Neurosci* 2021;13:646908. doi: 10.3389/fnagi.2021.646908 pmid: 34149394
- Guedj E, Million M, Dudouet P, et al. <sup>18</sup>F-FDG brain PET hypometabolism in post-SARS-CoV-2 infection: substrate for persistent/delayed disorders? *Eur J Nucl Med Mol Imaging* 2021;48:5. doi: 10.1007/s00259-020-04973-x pmid: 32728799
- Benedetti F, Palladini M, Paolini M, et al. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: A multimodal magnetic resonance imaging study. *Brain Behav Immun Health* 2021;18:100387. doi: 10.1016/j.bbih.2021.100387 pmid: 34746876
- Apple AC, Oddi A, Peluso MJ, et al. Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19. *Ann Clin Transl Neurol* 2022;9:6. doi: 10.1002/acn3.51498 pmid: 35043593

- 37 PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022;10:75. doi: 10.1016/S2213-2600(22)00127-8 pmid: 35472304
- 38 Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. *J Neurol Neurosurg Psychiatry* 2003;74(Suppl 3):-41. doi: 10.1136/jnnp.74.suppl\_3.iii31 pmid: 12933912
- 39 Østergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation. *Physiol Rep* 2021;9:e14726. doi: 10.14814/phy2.14726 pmid: 33523608
- 40 Fernández-Castañeda A, Lu P, Geraghty AC, et al. Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain. *bioRxiv* 2022;doi: 10.1101/2022.01.07.475453.
- 41 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21:-46. doi: 10.1038/s41579-022-00846-2 pmid: 36639608
- 42 Sivan M, Preston N, Parkin A, et al. The modified COVID-19 Yorkshire Rehabilitation Scale (C19-YRSm) patient-reported outcome measure for Long Covid or Post-COVID-19 syndrome. *J Med Virol* 2022;94:-64. doi: 10.1002/jmv.27878 pmid: 35603810
- 43 Munblit D, Nicholson T, Akrami A, et al. PC-COS project steering committee. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med* 2022;10:-24. doi: 10.1016/S2213-2600(22)00169-2 pmid: 35714658
- 44 COMET. Core Outcome Measures for Post-Covid condition/Long Covid. <https://www.comet-initiative.org/Studies/Details/1847>.
- 45 Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long covid—an update for primary care. *BMJ* 2022;378:e072117. doi: 10.1136/bmj-2022-072117 pmid: 36137612
- 46 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19.
- 47 Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:-9. doi: 10.1111/j.1532-5415.2005.53221.x pmid: 15817019
- 48 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:-98. doi: 10.1016/0022-3956(75)90026-6 pmid: 1202204
- 49 Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000;55:-6. doi: 10.1212/WNL.55.11.1621 pmid: 11113214
- 50 Macdonald JS, Lavie N. Visual perceptual load induces inattentive deafness. *Atten Percept Psychophys* 2011;73:-9. doi: 10.3758/s13414-011-0144-4 pmid: 21611856
- 51 Greig PR, Higham H, Nobre AC. Failure to perceive clinical events: an under-recognised source of error. *Resuscitation* 2014;85:-6. doi: 10.1016/j.resuscitation.2014.03.316 pmid: 24746782
- 52 Hossain MM, Das J, Rahman F, et al. Living with "long COVID": A systematic review and meta-synthesis of qualitative evidence. *PLoS One* 2023;18:e0281884. doi: 10.1371/journal.pone.0281884 pmid: 36795701
- 53 Ladds E, Rushforth A, Wieringa S, et al. Developing services for long COVID: lessons from a study of wounded healers. *Clin Med (Lond)* 2021;21:-65. doi: 10.7861/clinmed.2020-0962 pmid: 33479069
- 54 Kingstone T, Taylor AK, O'Donnell CA, et al. Finding the 'right' GP: a qualitative study of the experiences of people with long-COVID. *BJGP Open* 2020;4:bjgpopen20X101143.
- 55 Raveendran AV, Misra A. Post COVID-19 Syndrome ("Long COVID") and diabetes: challenges in diagnosis and management. *Diabetes Metab Syndr* 2021;15:102235. doi: 10.1016/j.dsx.2021.102235 pmid: 34384972
- 56 Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med* 2010;72:-52. doi: 10.1097/PSY.0b013e3181d14633 pmid: 20223924
- 57 Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG. Chronic fatigue and postexertional malaise in people living with long COVID: an observational study. *Phys Ther* 2022;102:pzac005. doi: 10.1093/ptj/pzac005 pmid: 35079817
- 58 Long COVID Physio. [www.longcovidphysio.org](http://www.longcovidphysio.org).
- 59 *Clinical management of COVID-19. Living guideline. (WHO/2019-nCoV/Clinical/2022.2). Licence: CC BY-NC-SA 3.0 IGO.* World Health Organization, 2022.
- 60 Daynes E, Gerlis C, Chaplin E, Gardiner N, Singh SJ. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis* 2021;18:14799731211015691. doi: 10.1177/14799731211015691 pmid: 33957805
- 61 Udina C, Ars J, Morandi A, Vilaró J, Cáceres C, Inzitari M. Rehabilitation in adult post-COVID-19 patients in post-acute care with Therapeutic Exercise. *J Frailty Aging* 2021;10:-300. doi: 10.14283/jfa.2021.1 pmid: 34105716
- 62 Cash A, Kaufman DL. Oxaloacetate treatment for mental and physical fatigue in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long-COVID fatigue patients: a non-randomized controlled clinical trial. *J Transl Med* 2022;20:-. doi: 10.1186/s12967-022-03488-3 pmid: 35764955
- 63 Rossato MS, Brilli E, Ferri N, Giordano G, Tarantino G. Observational study on the benefit of a nutritional supplement, supporting immune function and energy metabolism, on chronic fatigue associated with the SARS-CoV-2 post-infection progress. *Clin Nutr ESPEN* 2021;46:-8. doi: 10.1016/j.clnesp.2021.08.031 pmid: 34857243
- 64 Hawkins J, Hires C, Keenan L, Dunne E. Aromatherapy blend of thyme, orange, clove bud, and frankincense boosts energy levels in post-COVID-19 female patients: A randomized, double-blinded, placebo controlled clinical trial. *Complement Ther Med* 2022;67:102823. doi: 10.1016/j.ctim.2022.102823 pmid: 35341944
- 65 Badran BW, Huffman SM, Dancy M, et al. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. *Res Sq* [preprint]. 2022. <https://pubmed.ncbi.nlm.nih.gov/35765566/>
- 66 Bhaiyat AM, Sasson E, Wang Z, et al. Hyperbaric oxygen treatment for long coronavirus disease-19: a case report. *J Med Case Rep* 2022;16:-. doi: 10.1186/s13256-022-03287-w pmid: 35168680
- 67 Zilberman-Itskovich S, Catalogna M, Sasson E, et al. Hyperbaric oxygen therapy improves neurocognitive functions and symptoms of post-COVID condition: randomized controlled trial. *Sci Rep* 2022;12:-. doi: 10.1038/s41598-022-15565-0 pmid: 35821512
- 68 Lu L, Zhang Y, Tang X, et al. Evidence on acupuncture therapies is underused in clinical practice and health policy. *BMJ* 2022;376:e067475. doi: 10.1136/bmj-2021-067475 pmid: 35217525
- 69 Capela Santos D, Jaconianio S, Macedo S, et al. Yoga for COVID-19: An ancient practice for a new condition—A literature review [published Online First: 2022/12/17]. *Complement Ther Clin Pract* 2023;50:101717. doi: 10.1016/j.ctcp.2022.101717. pmid: 36525872
- 70 Pick A. *Is long covid a functional disorder?* Advance Rehab Sci Pract, 2023, doi: 10.1177/11795727221141193.
- 71 Mizrahi B, Sudry T, Flaks-Manov N, et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. *BMJ* 2023;380:e072529. doi: 10.1136/bmj-2022-072529 pmid: 36631153
- 72 Ferrucci R, Dini M, Rosci C, et al. One-year cognitive follow-up of COVID-19 hospitalized patients. *Eur J Neurol* 2022;29:-14. doi: 10.1111/ene.15324 pmid: 35285122
- 73 University College London Hospitals. Cognitive disorders clinic. <https://www.uclh.nhs.uk/our-services/find-service/neurology-and-neurosurgery/cognitive-disorders-clinic>
- 74 SIGN. SIGN: Brain rehabilitation in adults—a national clinical guideline 2013. <https://www.sign.ac.uk/media/1068/sign130.pdf>.
- 75 Ladds E, Rushforth A, Wieringa S, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res* 2020;20:-. doi: 10.1186/s12913-020-06001-y pmid: 33342437
- 76 Espinosa-Gonzalez ABMH, Greenhalgh T. Orthostatic tachycardia after covid-19: a disabling and under-recognised complication. *BMJ* 2023; [forthcoming] doi: 10.1136/bmj-2022-073488.
- 77 Sivan M, Greenhalgh T, Darbyshire J, et al. Protocol for mixed-method study by LONG COVID Multidisciplinary consortium: Optimising Treatments and services across the NHS (LOCOMOTION). *BMJ Open* 2022; [forthcoming] doi: 10.1136/bmjopen-2022-063505.