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STATE OF THE ART REVIEW

Cognitive and mental health outcomes in long covid

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ABSTRACT

Roughly one in five adults who meet criteria for long covid present with objective or subjective cognitive dysfunction or elevated symptoms of depression or anxiety lasting ≥12 weeks from an acute covid illness. These neuropsychiatric sequelae have considerable functional consequences at the level of the individual, society, and the broader economy. Neuropsychiatric long covid symptoms are thought to be causally diverse, and a range of risk factors as well as biological, psychological, and environmental mechanisms have been hypothesized to contribute to symptom development and persistence. When present, objective cognitive deficits tend to be modest for most individuals, with some evidence suggesting increased risk of dysfunction and decline specifically for older adults with a history of severe acute illness. Longitudinal data suggest a delayed emergence of psychiatric symptoms may occur in the weeks and months after an acute covid illness. Emerging research points to the early recovery period as a potential window of opportunity for intervention to alter patient trajectories, though evidence based treatment remains lacking.

Introduction

Long covid refers to a range of chronic, systemic, and often disabling health conditions associated with SARS-CoV-2 infection.[1 2] By September 2024, 5.3% of the US general population reported symptoms lasting three or more months after acute SARS-CoV-2 infection,[3] whereas the World Health Organization (WHO) estimates that 10–20% of people infected by SARS-CoV-2 worldwide go on to develop long covid.[4] Long covid can manifest as profound fatigue, breathlessness and other respiratory conditions, muscle and joint pain, cardiac abnormalities, and a variety of other symptoms resulting from damage to multiple organs and systems.[5 6] Among the range of symptoms experienced by those with long covid, cognitive and mental health concerns (commonly referred to as neuropsychiatric symptoms), such as "brain fog," concentration and memory difficulties, depression, and anxiety are especially common,[7-9] affecting approximately 20.4% of long covid patients.[10] Neuropsychiatric symptoms often persist longer than other long covid symptoms,[8 11-14] are associated with functional limitations[7 11 15 16] and ultimately pose considerable burden on individuals, health systems, and the economy.[17]

While high quality studies have advanced our understanding of long covid, including neuropsychiatric symptoms, there are methodological challenges inherent to a novel, rapidly expanding field. Distinct long covid symptom phenotypes have been identified (such as mental/cognitive, cardiac/renal, multidomain).[18 19] Studies examining long covid as a unitary syndrome may obscure the specific risk factors and mechanisms underlying distinct phenotypes.[20] An additional challenge relates to conducting research in the setting of evolving definitions of long covid. Variation in recruitment strategies and the potential for selection bias may skew our understanding of neuropsychiatric sequelae. Careful consideration must also be given to selecting the most appropriate control groups (that is, no covid, prior asymptomatic illness, well recovered). Reliance on subjective ratings rather than objective cognitive testing and differing definitions of cognitive impairment may contribute to discrepant findings across studies. Variable consideration has been given to factors such as acute illness severity, comorbidities, and demographic characteristics.[21 22] The evolving nature of viral variants along with cultural and temporal shifts in pandemic-related social and behavioral restrictions, vaccination rates, prior infections, and medical practices all demand careful consideration in study design and interpretation. Meta-analyses may produce similar results as they draw on a similar pool of studies while being simultaneously vulnerable to the methodological shortcomings of the parent literature.

This review provides an up-to-date assessment of the functional and economic consequences, nature, severity, and trajectory of neuropsychiatric long covid sequelae. It identifies current knowledge regarding risk factors and proposed mechanistic pathways for symptom development and persistence, and outlines evidence to guide treatment interventions while also highlighting directions for future research.

Epidemiology

The reported prevalence of long covid varies widely by study, time, and data source. Even among high quality studies, data range from conservative estimates of 6.2% of adults who ever had covid-19 to 45% across prospective epidemiologic studies, cross-sectional health surveys, electronic health records (EHR), and systematic reviews and meta-analyses.[23-26] Reported prevalence estimates may be inflated due to methodological limitations, including self report bias and skewed study populations (that is, surveys may overestimate prevalence due to recall bias). This raises concerns that high-end estimates may not reflect the true population-level risk.

Leveraging pre-covid health status, global estimates suggest 6.2% of symptomatic covid-19 survivors

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experience at least one of three common symptom clusters at three months after acute infection: persistent fatigue with pain or mood swings, cognitive problems, or respiratory issues.[27] In the US, data from the Medical Expenditure Panel Survey estimated that, by March 2023, 6.9% of all adults had ever had long covid.[28] The US Centers for Disease Control and Prevention's (CDC) Household Pulse Survey reports a fluctuating prevalence of long covid, ranging from a height of 7.6% in summer 2022 to a low of 5.3% at the most recent survey in August-September 2024.[3]

On a global scale, the cumulative incidence of long covid has steadily increased, with estimates of 65 million cases in 2020, 211 million in 2021, 337 million in 2022, and 409 million in 2023.[29] In the US, data from the NIH-funded RECOVER study covering March 2020 to January 2024 reported the excess incidence of long covid—after accounting for background levels of similar symptoms—at 5-6% among adults.[30] Incidence rates have demonstrated relative temporal stability with slight transient increases following the emergence of new variants.[30]

Methods

A literature review was conducted by two of the authors (EA and TDV). We searched PubMed and MedLine databases for studies published from January 2020 to end of June 2024 using the following search terms: ("long covid" or "post-covid" or "covid long-haulers" or "post SARS-CoV-2" or "post-covid-19 condition" or "post-acute sequelae of covid-19" or "chronic covid") AND ("cognition" or "cognitive dysfunction" or "mental health outcome" or "mental disorder" or "mental health" or "function" or "depression" or "anxiety" or "post-traumatic stress disorder" or "return to work" or "sick leave" or "workforce connection" or "employment"). We also identified articles cited within select publications. We opted not to include search terms only related to long covid fatigue, as fatigue frequently co-occurs with other neuropsychiatric symptoms of interest as well as physical symptoms of long covid such as pulmonary dysfunction.[31]

We included systematic reviews, meta-analyses, large randomized controlled trials, high quality population-based observational and prospective studies (which we considered as low risk of bias), and clinical guidelines. We also permitted smaller, well designed trials and clinical cohorts to inform our discussion of functional outcomes, mechanistic pathways, and symptom management. We focused on studies assessing outcomes at least three months after the initial SARS-CoV-2 infection where data permitted. As this is not a systematic review, final decisions on study entry were made through a consensus meeting. We excluded studies in animals, children, or specific patient populations and studies that did not explicitly report on cognitive and mental health outcomes associated with covid-19. Case reports and case series were also excluded.

Nomenclature and definition of long covid

A reliable diagnostic marker for long covid is currently lacking, as is a consensus definition or generally agreed set of diagnostic criteria. Hence, a range of terms exist to characterize long covid, including post-covid-19 condition or syndrome (PCC or PCS), post-acute sequelae of SARS-CoV-2 infection (PASC), long-haul covid-19, or chronic covid-19.[32] Definitions from national and international organizations differ on clinical criteria, particularly regarding the initial diagnosis of covid-19 (suspected, probable, confirmed with SARS-CoV-2 testing, clinically diagnosed), timing since symptom onset, and duration of symptoms required for long covid diagnosis (see table1).

Table 1 | Definitions of long covid

Definition	Criteria for diagnosis	Symptom duration requirement	Requirement for confirmed SARS-CoV-2 infection	Strengths	Weaknesses
WHO: Post-Covid-19 Condition (PCC)[4 33]	Probable or confirmed SARS-CoV-2 infection with persistent unexplained symptoms	≥2 months	Probable or confirmed	Captures a broad range of cases; accommodates evolving evidence	Loose criteria may include unrelated symptoms; possible overdiagnosis
CDC and US Department of Health and Human Services[34]	Persistent symptoms following covid-19	≥4 weeks	Not explicitly required	Early identification of cases; useful for public health tracking	May capture transient postviral symptoms rather than chronic cases
UK NICE: Long covid / Post-Covid-19 Syndrome (PCS)[35]	Symptoms persisting or emerging post-covid-19	≥12 weeks	Not explicitly required	Focuses on prolonged symptoms, reducing false positives	May exclude individuals with significant symptoms at earlier time points
National Academies of Arts and Sciences (US)[36]	Chronic condition post-SARS-CoV-2 infection, relapsing/remitting or progressive	≥3 months	Recognized or unrecognized infection of any severity	Includes asymptomatic and untested cases; considers chronic disease patterns	Broad inclusion may reduce specificity; difficult to apply in clinical settings

While broader definitions, such as those from the WHO and National Academies, enhance case identification and public health monitoring, they risk overdiagnosis by including individuals with uncertain infection histories or unrelated symptoms. In contrast, the CDC and the UK National Institute for Health and Care Excellence (NICE) definitions apply more stringent criteria, prioritizing specificity for clinical and research use but potentially overlooking early or mild cases. These inconsistencies impact prevalence estimates, clinical diagnosis, and policy development, underscoring the need for harmonized criteria and objective biomarkers to improve diagnostic reliability and research comparability.

Functional and economic outcomes

The impact of cognitive and mental health symptoms associated with long covid is challenging to separate from that attributable to other long covid symptoms or the broader covid-19 pandemic. However, existing evidence highlights the specific contribution of neuropsychiatric distress to functional limitations (that is, ability to work and perform everyday tasks)[7 16 37-40] and associated economic burden[17 41] among affected individuals.

The Canadian COVID-19 Antibody and Health Survey reported that, among >26 000 adults with post-covid-19 condition, 28.0% (95% CI 20.4 to 36.6%) of those with post-covid mood dysfunction (that is,

sadness, pessimism, hopelessness, or depression) indicated that these symptoms often or always limited their daily activities.[42] This rate was nearly identical to that of survey participants with pre-existing chronic mental health conditions who rated their functioning as often or always limited after their covid-19 illness (28.1% (95% CI 21.2 to 35.8%)). Rates of functional limitations were even greater among those reporting post-covid stress or anxiety (34.2% (95% CI 25.9 to 43.3%)) and post-covid cognitive dysfunction (38.0% (30.1% to 46.5%)) relative to other symptoms. A cross-sectional observational study spanning 31 post-covid clinics in the UK found that fatigue, depression, and perceived cognitive difficulties were significant determinants of occupational and psychosocial functioning among 3754 patients seeking treatment for long covid.[43] It is now appreciated that older adults, those hospitalized for covid-19, and those who experienced neurological complications during an acute covid illness tend to experience more pronounced post-covid functional limitations.[44 45] For example, 1865 out of the 52 759 participants in the Neuro-COVID Italy trial who were hospitalized with covid-19 experienced newly diagnosed neurologic conditions during the acute or post-acute illness phase. While the majority with neurologic symptoms (64.6%) had good functional outcome at 6.7 month follow-up, a considerable proportion with stroke (47.6%), encephalitis (25%), encephalopathy (24.4%), or Guillain-Barré syndrome (23.7%) encountered substantial challenges performing basic activities of daily living.[44] Additionally, more than half of those with subjective post-covid cognitive dysfunction (56.2%) also reported mild but persistent functional limitations.[44]

Adverse changes in employment status are a common post-covid concern. In an early international online survey of 3762 primarily non-hospitalized patients participating in post-covid support groups, 45.6% (95% CI 43.2 to 48.0%) reported reduced work capacity compared with pre-illness levels. Of working respondents, 86.2% (84.4 to 88.0%) reported that cognitive dysfunction affected their ability to work.[7] A recent meta-analysis of 19 studies including 21 155 patients from 14 countries concluded that long covid cognitive dysfunction was associated with reduced work capacity and effectiveness as well as increased workplace absenteeism.[38] Of the 60.9% who successfully returned to work three months after infection, up to 49.3% required changes in their work assignments or hours.[38] A longitudinal, prospective cohort study in the UK revealed that 26.9% of 2469 previously hospitalized patients had changed their occupations within two to three years after their infection, primarily due to health related considerations.[14] Interestingly, both subjective cognitive symptoms and objective deficits in reaction time and cognitive control were key predictors of occupational change, thus illustrating the pivotal role of cognitive health in maintaining post-covid employment.

Beyond individual health-related concerns, the economic impact of the global SARS-CoV-2 pandemic and long covid in particular, is substantial.[17] The Organization for Economic Co-operation and Development estimated an approximate 0.5% drop in gross domestic product across eight countries in 2024 due to long covid.[46] In the US alone, the workforce impact of long covid was estimated to be 1.5 billion work hours lost and more than $152.6 billion in economic impact in 2024.[46] Previous reports estimated annual lost wages ranging from $101 to $430 billion,[47] potentially reaching nearly $1 trillion if symptoms persist for at least five years.[48] The direct cost of treating covid-related mental health issues (that is, depression and anxiety) has been estimated at roughly $20 000 per person per year, resulting in an estimated cost of $528 to $544 billion over five years.[41 48] Factoring in reduced quality of life, the overall economic toll of long covid is projected at $2.6 trillion.[17]

Mechanisms

The mechanistic pathways of long covid neuropsychiatric symptoms are complex and multifactorial. While many studies have explored pathways related to acute neurological complications, fewer have examined the mechanisms behind persistent cognitive dysfunction and mental health symptoms. Most research has focused on biological mechanisms linked to SARS-CoV-2 infection and its sequelae, with less attention given to indirect and/or psychosocial mechanistic pathways for neuropsychiatric symptoms.

Direct neuroinvasion by SARS-CoV-2, peripheral inflammation and related immune responses, endothelial disruption, and vascular processes such as thrombosis, ischemia, and hypoxia have been reported as potential mechanisms of long covid in humans (see fig 1).[49-52] Early research investigated whether SARS-CoV-2 might infect the brain through the olfactory pathway, replicate within neural or glial cells, and cause brain dysfunction.[53] However, evidence remains limited.[50] Some studies indicate that long covid neuropsychiatric dysfunction may result from an overproduction of cytokines, with the related hyperinflammatory response weakening the blood-brain barrier, allowing viral particles, cytokines, and immune cells to enter the central nervous system, potentially altering brain function.[54 55] Increased permeability of the blood-brain barrier has been observed during acute SARS-CoV-2 infection and thereafter, including among those with persistent cognitive complaints.[56 57]

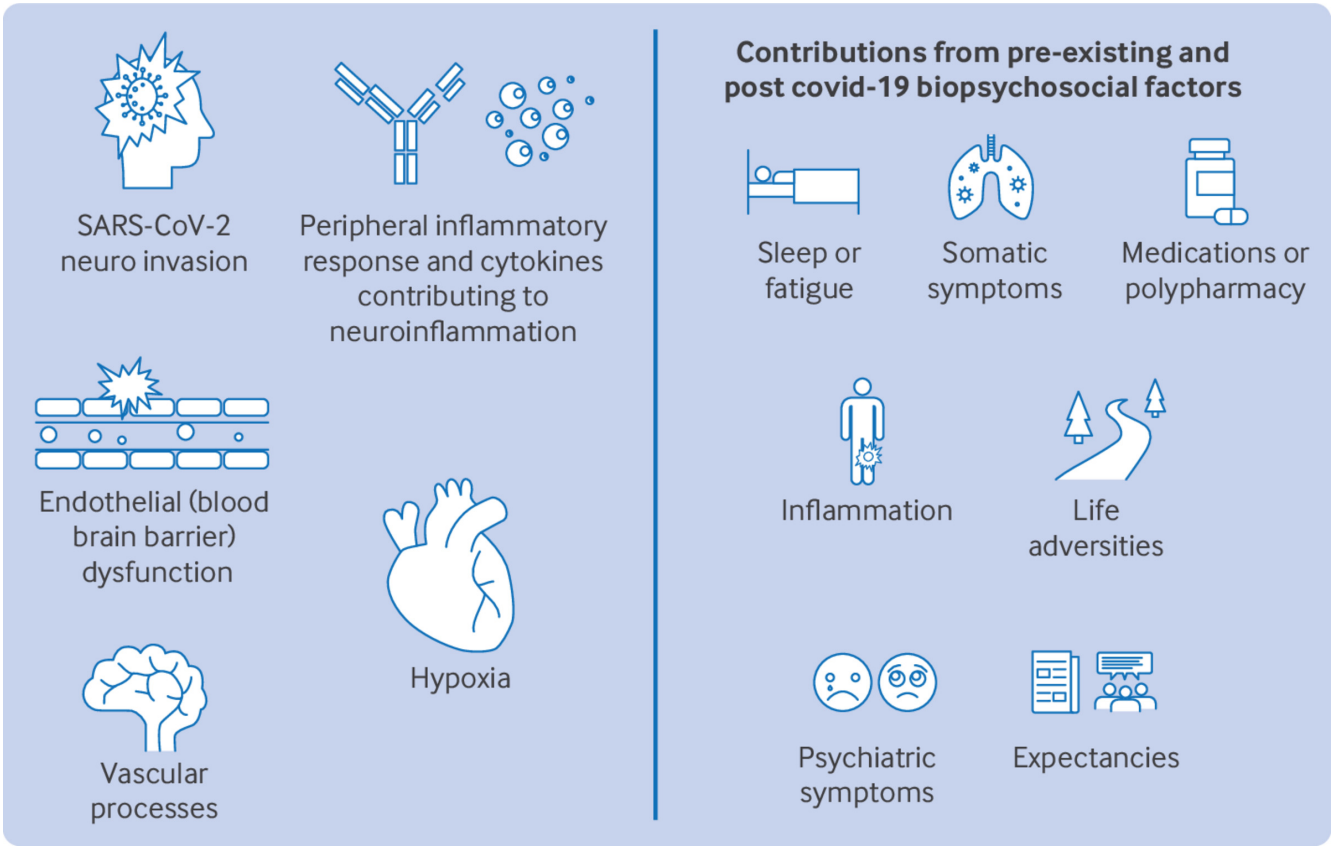

Fig 1 | Potential mechanisms of long covid

Proinflammatory and hypercoagulable states associated with covid-19 can increase the risk of serious vascular complications such as ischemic stroke and related cognitive dysfunction.[58-60] Microvascular injury in the absence of stroke has been observed in the brains of individuals who died of covid-19.[61] Hypoxia and hypoxemia may further contribute to brain dysfunction via a pathway of metabolic alterations, cell apoptosis, and neural systems dysfunction. Preliminary data have linked post-covid-19 cognitive complaints to cerebral hypoxia among non-hospitalized patients seven months after acute infection.[62]

Severity of acute illness is associated with various inflammatory markers.[63-67] In the general population, inflammation is associated with greater cognitive and psychiatric dysfunction.[68-71] Higher aggregate systemic inflammation during acute covid-19 has predicted both depressive symptoms and cognitive performance following hospital discharge.[72-74] Several studies point to specific immune profiles related to long covid neuropsychiatric outcomes. For instance, a cohort study of 2320 individuals found that moderate physical and cognitive symptoms five months after hospitalization were associated with elevated levels of interleukin-6 and CD70 compared with those with mild symptoms.[75] Inflammatory proteins, including those associated with endothelial repair, neural growth regulation, and cell turnover, have also been significantly elevated in those with severe covid-19 and persistent long covid cognitive and mental health symptoms.[76]

Although these remain promising areas for future investigation, the mechanisms underlying long covid-related neuropsychiatric dysfunction remain speculative. Biomarkers of neuronal injury post-covid, when identified in the blood, cerebrospinal fluid, and plasma, are not consistently associated with long covid cognitive and mental health outcomes.[77-79] Neurofilament light chain (NfL), a marker of axonal injury, has emerged as a potential biomarker for long covid-related neuronal damage, with higher levels correlating with post-covid cognitive deficits.[80] However, some studies have failed to establish an association between NfL and long term neuropsychiatric symptoms, underscoring the need for further investigation.[81] Structural, functional, and diffusion-weighted magnetic resonance imaging (MRI) as well as nuclear medicine imaging techniques (18F-DG-PET/CT, 18F-Amyloid PET/CT, and SPECT) have also been used to assess individuals with neuropsychiatric long covid symptoms. While individual studies have demonstrated associations with cognitive performance, subjective cognitive complaints, and mental health symptoms, consistent patterns of brain abnormalities have not been established, nor have reproducible links between imaging findings and clinical presentations.[82]

In addition to pathways associated directly with SARS-CoV-2 infection, a complex range of co-occurring and pre-existing biopsychosocial factors may contribute to the manifestation and persistence of long covid neuropsychiatric symptoms. Individual-level factors, including fatigue, sleep disruption, physical discomfort and pain, autonomic dysfunction (such as postural orthostatic tachycardia syndrome), polypharmacy, substance use, and comorbidities can influence the neuropsychiatric symptom profile in affected individuals.[83] In addition, evidence from correlational and experimental paradigms demonstrate that covid-related expectancies are associated with longer symptom duration and the presence of unexplained symptoms, suggesting

that individual beliefs and societal messaging may pose a nocebo effect in vulnerable individuals.[84-87]

Limited data suggest that, in a proportion of individuals with long covid, symptoms may reflect a somatic symptom disorder.[88 89] Long covid and somatic symptom disorder share several predisposing, precipitating, and perpetuating factors including demographic characteristics, psychiatric comorbidities, and adverse childhood experiences.[88 90 91] In a cohort of >2800 predominantly middle aged, white, female healthcare workers, childhood abuse showed a dose-dependent relationship with risk of developing post-covid condition, with moderate or severe childhood abuse (reported by 53.2%) linked to a 24% and 42% increased likelihood, respectively.[92] Early life trauma was hypothesized to have resulted in immune system dysregulation and pro-inflammatory states that heightened susceptibility to both contracting covid-19 and developing long covid. A small single center observational study (n=50) also found that 64% of individuals with persistent neurological symptoms after a mild covid-19 illness met DSM-5 criteria for somatic symptom disorder.[93]

Clinical data from adults presenting with cognitive concerns after non-severe acute covid-19 illness demonstrate elevated rates of heightened somatic preoccupation often paired with clinically significant symptoms of depression and anxiety.[94 95] This symptom pattern has remarkable overlap with that seen in individuals reporting cognitive concerns attributed to post-concussion syndrome.[95] Further, the stability of the long covid psychological profile over several phases of the pandemic has been interpreted to suggest that, rather than being driven by disease or pandemic-related environmental stressors, a proportion of individuals with long covid may have a pre-covid vulnerability to experiencing emotional distress and maladaptive somatic focus.[94 95]

Notably, the presence of a somatic symptom disorder does not preclude the existence of demonstrable physical dysfunction. Given the non-specific nature of long covid symptoms and a lack of diagnostic markers, identifying both physical and psychological manifestations of long covid may be important for guiding treatment and optimizing patient outcomes. While somatic symptom disorder is a treatable psychiatric condition,[96] it remains uncertain whether such approaches will benefit those with long covid. Importantly, data indicate that those presenting for long covid-related clinical neuropsychological services show relatively low rates of invalid symptom presentation (such as amplification) on formal symptom validity testing.[94] Further, given patient reports of stigmatization and concerns of "gaslighting" by healthcare professionals, enacting approaches to avoid social stigmatization and patient alienation are particularly important in this patient population.[97 98]

Neuropsychiatric symptoms in long covid

Risk factors

Numerous factors have been examined in relation to long covid neuropsychiatric symptoms. Perhaps the most replicated finding with regard to risk is that a greater proportion of women than men report cognitive dysfunction and psychiatric symptoms following covid-19 and meet criteria for long covid.[45 99-102] Age has been found to modify the relation between covid-19 and later outcomes, though findings are conflicting. Multiple studies point to a greater prevalence of long covid-related neuropsychiatric symptoms in younger and middle-aged adults.[103-105] Conversely, recent systematic reviews and meta-analyses have concluded that older age increases the risk for negative neurocognitive[9 45] and mental health outcomes.[106]

The association between severity of acute illness and neuropsychiatric symptoms after SARS-CoV-2 infection is complex. Data from patient registries, large epidemiologic studies, and meta-analyses indicate that greater severity of acute illness, typically indexed by the need for hospitalization, is associated with poorer cognitive and mental health outcomes.[45 107-110] However, findings are not uniform, and neuropsychiatric symptoms are also reported at high rates among individuals who experienced less severe acute illness, particularly in treatment-seeking cohorts.[95 105 111-113] There are also data indicating that rates of neurocognitive symptoms and new-onset mental health disorders after hospitalization for covid-19 are similar among those hospitalized for non-covid illness of matched severity, suggesting that factors related to severe illnesses and hospitalization rather than unique characteristics of SARS-CoV-2 infection may drive such outcomes.[83 114]

A series of studies demonstrated that vaccination is associated with lower risk for long covid, including cognitive dysfunction[45 115 116] and mental health symptoms.[117] Data on the risk of neuropsychiatric outcomes by covid-19 variant is mixed. While persistent or increased rates of psychiatric and cognitive diagnoses were reported with the emergence of the later delta and omicron variants,[58] evidence suggests more recent SARS-CoV-2 variants confer lower risk of long covid[118] and are linked to smaller cognitive deficits.[44 115]

A range of pre-existing physical health comorbidities (such as cardiovascular disease, obesity, hypertension, sleep apnea) are related to poorer neuropsychiatric outcomes following an acute covid-19 illness.[45 119 120] Many of these serve as independent of covid-19 risk factors for cognitive dysfunction. Pre-existing mental health conditions and subjective cognitive dysfunction have also emerged as risk factors for more severe acute covid-19 as well as for the development and persistence of long covid neuropsychiatric and somatic symptoms[121 122] in hospitalized and non-hospitalized patient groups.[113 121-125] Several studies with pre-existing and early neuropsychiatric data reveal a dose-dependent relationship between early neuropsychiatric symptoms and the risk of developing persistent symptoms following covid-19.[122 126]

Cognitive outcomes

Several methods have been used to capture cognitive outcomes associated with long covid, including diagnostic codes documented in electronic health records (EHRs) or assessed via self-reports. While EHR data provide insights into prevalence and symptom trajectories, they present methodological limitations, including missing data, non-participation bias, inconsistent coding practices, and variability in how cognitive outcomes and exposures are recorded.[127] These factors can lead to underreporting, misclassification, and a lack of granularity regarding cognitive impairments. Cognitive screening instruments, used to assess global cognitive skills, may lack sensitivity to detect subtle declines or distinct domains of dysfunction. Studies utilizing comprehensive, well validated cognitive test batteries are considered the gold standard[128 129] as they provide greater specificity, capturing both the nature and severity of cognitive dysfunction post-covid, and serve as more proximal markers of brain function, reducing the risk of misinterpretation inherent in broader EHR-based studies.

EHR data suggest that SARS-CoV-2 infection increases the risk of cognitive disorder diagnosis. For example, a study of >1.5 million US veterans with covid-19 (compared with >5.8 million contemporaneous no-covid-19 controls) found heightened risk for diagnoses of memory dysfunction (hazard ratio 1.77 (95% CI 1.68 to 1.85)) and Alzheimer's disease (HR 2.03 (1.79 to 2.31)) at one year post-illness.[105] A large international study (n=1 487 712) compared

patients with covid-19 with a contemporaneous cohort of matched patients with other respiratory infections: it found an increased risk of cognitive deficit (HR 1.36 (1.33 to 1.39)) and dementia (HR 1.33 (1.26 to 1.41)) remained at two years post-infection in those with a history of covid-19.[58]

Data from subjective symptom reports suggest cognitive dysfunction is one of the more common long covid symptoms.[9 10] The exact prevalence remains difficult to ascertain given the aforementioned methodological challenges and the overlap between cognitive complaints and other long covid symptoms (for example, depression, myalgic encephalomyelitis/chronic fatigue syndrome).[130 131] Rates may also be changing over time due to the shifting nature of the covid-19 pandemic.[36] At one end of the spectrum, a large, cross-sectional international online survey from 2020 involving primarily non-hospitalized (>91%) covid-19 support group participants reported a 58.4% prevalence (95% CI 56.5% to 60.2%) of cognitive dysfunction six months after infection.[7] In contrast, a Dutch intensive care unit (ICU) registry of 301 patients found that only 16.2% reported cognitive symptoms at one year after infection,[132] a rate notably lower than the typical prevalence among ICU survivors before the pandemic (that is, 45% at >6 months).[133]

A recent systematic review and meta-analysis of 43 studies of those with a history of covid-19 and/or long covid underscores the wide variability in prevalence of subjective cognitive dysfunction, with reports ranging from 15% to 80% at 12 or more weeks after diagnosis and an overall prevalence of 18%.[99] Finally, in one of the few studies to have statistically adjusted for pre-covid-19 health status and differentiated between covid-19 history and long covid, an estimated 2.2% (95% uncertainty interval (UI) 0.3% to 7.6%) of individuals who experienced a symptomatic SARS-CoV-2 infection and 35.4% (9.4% to 75.1%) of those with long covid reported cognitive difficulties three months after acute illness.[27]

In an effort to delineate the cognitive profile associated with long covid, there has been an emphasis on objective assessment via validated procedures as well as harmonization of the neuropsychological criteria for the definition of cognitive impairment.[103] This approach was prompted by concerns regarding response and ascertainment bias (that is, more persons with debilitating long covid symptoms may enroll in online surveys), potential over- or under-estimation of cognitive functioning,[134] the absent to modest relationship between severity of covid-19 illness and subjective cognitive symptoms, and findings indicating that subjective evaluation is often closely tied to and may be confounded by factors such as mood, anxiety, and fatigue.[135 -137]

Despite substantial research (see table 2 for key studies), a consistent cognitive profile associated with long covid has not emerged. Specific cognitive domains, such as attention/concentration,[142 147] executive functioning,[115 138 147 148] processing speed,[107 146 148] and memory[115 147] have each been identified as the most prominent areas of cognitive dysfunction associated with long covid. A recent systematic review of 34 studies employing objectively measured cognitive outcomes at least 12 weeks post-illness reported deficits in learning or recall in 8% to 27% of individuals, with executive dysfunction in 5% to 21%, and word finding deficits in 9% to 16%.[149] It is important to acknowledge that several studies reported no cognitive differences between those with persistent symptoms relative to recovered patients or healthy controls.[142 150]

Table 2 | Summary of select cognitive outcome studies

Study reference	Study design	Sample size and characteristics	Time to assessment (average)	Findings	Conclusions
Becker et al 2023[138]	Prospective cohort	G1: 417 covid-19; 8% hospitalized; 15% ED G2: 151 contemporaneous HC	From diagnosis: 11 months	G1>G2: executive functioning (OR 2.2 (CI 1.0 to 4.7)) G1=G2: attention, working memory, processing speed, language, immediate recall, delayed recall, recognition (ORs P>0.05)	Increased odds of executive dysfunction
Cheetham et al 2023[139]*	Prospective cohort	G1: 1737 covid-19; 8.4% hospitalized G2: 495 long covid G3: 1598 contemporaneous HC	From symptom onset: 42 weeks	G2<G3: composite accuracy (adjusted P<0.05), composite within-task reaction time variability (adjusted P<0.05) G2=G3: composite average reaction time (adjusted P>0.05)	Lower cognitive accuracy and greater reaction time within task variability, but not reaction times; effect sizes generally small
Crivelli et al 2022[140]	Cohort	G1: 45 covid-19; 31% hospitalized G2: 45 contemporaneous HC	From acute illness: 142 days	G1<G2: memory (Cohen's d=0.73, P=0.016), attention (Cohen's d=1.27, P<0.001), executive function (Cohen's d=1.48, P<0.001), language (Cohen's d=0.88, P=0.002) G1=G2: visuospatial skills (P>0.05)	Large deficits in executive functioning and attention; smaller effects for memory and language; no deficits in spatial skills
Delgado-Alonso et al 2022[141]	Cross-sectional	G1: 50 long covid with cognitive complaints; 36% hospitalized; 10% ICU G2: 50 contemporaneous HC	From post-infection: 9.1 months	G1≤G2: attention and processing speed (Cohen's d=0.04 to 0.40, P=0.005 to 0.863), executive function (Cohen's d=0.26 to 0.53, P=0.004 to 0.016), episodic memory (Cohen's d=0.32 to 0.58; P=0.003 to 0.103)	Deficits on select tests of attention, executive function, and episodic memory; effect sizes generally small
Graham et al 2021[142]*	Prospective cohort	100 non-hospitalized with clinical manifestations of covid-19 compatible with IDSA guidelines: G1: 50 BC SARS/covid-19 G2: 50 contemporaneous BC SARS negative	From symptom onset: G1: 4.7 months G2: 5.8 months	G1<normative data: attention (−0.85 SD, P<0.001), working memory (−0.70 SD, P=0.007) G1=G2: all cognitive domains (P≥0.15)	Lower attention and working memory compared to matched US population means but not differing from post-acute non-covid viral syndrome
Hampshire et al 2024[115]*	Observational cohort, community-based	G1: 2580 long covid (ongoing) G2: 1350 prior long covid (symptoms resolved ≥12 weeks) G3: 46261 contemporaneous HC	From infection: >12 weeks	G1<G3: global cognition (−0.42 SD) G1<G3: memory, reasoning, and executive functioning (−0.33 to −0.20 SD) G2<G3: global cognition (−0.2 SD)	Larger cognitive deficits in participants with long covid and resolved long covid compared to HC
Lamontagne et al 2021[143]*	Observational	G1: 50 covid-19; 2% hospitalized comprising three subgroups: G1a: 15 acute covid-19 G1b: 17 PASC (1–4 months post diagnosis G1c: 15 long covid (>4 months post diagnosis) G2: 50 contemporaneous HC	From infection: 123.6 days	G1b<G2: executive control/conflict reaction time ($\eta 2$=0.09, P=0.01) G1b=G2: alerting, orienting (P>0.05) No group differences: alerting, orienting (P>0.05)	Small executive control deficits exclusively in those 1–4 months post diagnosis, not observed in those ≥4 months post diagnosis
Matias-Guiu et al 2023[103]	Case-control	G1: 404 long covid†; 26.5% hospitalized; 4.2% ICU G2: 145 HC	From infection: 484.6 days	G1 *v* G2: attention and processing speed (z=−0.61 to −0.65, ±0.88 to 1.37), executive function (z=−0.41 to −0.53, ±0.81 to 0.89), visuospatial (z=0.08 to −0.06, ±1.23 to 0.86), language (z=−0.07 to 0.0, ±0.81 to 0.62), episodic memory (z=0.04 to −0.33, ±1.22 to 0.96)	Cognitive deficits mainly in attention/processing speed and executive functioning
Ortelli et al 2022[144]*	Case-control	G1: 74 patients with long covid† G2: 29 HC	From PCS onset: 126.4 days	G1 <G2: sustained attention (P<0.0001) G1 <G2: executive attention (P=0.036)	Deficits in sustained and executive attention

Table 2 | Summary of select cognitive outcome studies *(Continued)*

Study reference	Study design	Sample size and characteristics	Time to assessment (average)	Findings	Conclusions
Poletti et al 2022[145]	Prospective Cohort	G1: 312 covid-19; hospitalized: 86% of whom 4% in ICU G1a: 92 assessed at 1 month G1b: 122 assessed at 3 months G1c: 98 assessed at 6 months G2: 165 pre-pandemic inpatients with MDD G3: 165 pre-pandemic HC	From discharge: 1 to 6 months	G1a=G1b=G1c: global cognitive index (P=0.08) G1>G2: global cognitive index, verbal memory, working memory, psychomotor coordination (P<0.001) G1=G2: verbal fluency, processing speed, executive functioning (P>0.05) G1<G3: global cognitive index, psychomotor coordination, verbal fluency, processing speed, executive functioning (P<0.001) G1=G3: verbal memory, working memory (P>0.05)	Global cognition was stable post-covid; Those infected had poorer global cognition, psychomotor coordination, verbal fluency, processing speed, and executive functioning than HCs but better global cognition, verbal memory, working memory, and psychomotor coordination than MDD
Zhao et al 2024[146]*	Cross-sectional	G1: 270 long covid‡; 20.4% hospitalized G2: 63 recovered covid-19; 11.1% hospitalized G3: 113 contemporaneous HC	From diagnosis: G1: 325.7 days G2: 385.6 days	G1<G3: cognitive slowing reaction times (P<0.001), mean accuracy (P<0.001) G1 *v* G2: cognitive slowing reaction times (P<0.001), mean accuracy (P=0.034)	Moderate to severe cognitive slowing, compared to both HC and those recovered from covid-19

Study inclusion criteria: 1) Use of objective neuropsychological tests or batteries (excluding screening measures), 2) use of data from healthy/no-covid controls rather than published norms (and providing either group performance or deficit prevalence data), 3) cognition assessed a mean of ≥12 weeks from positive covid-19 test/acute illness/hospital discharge, etc., and 4) a total sample size of at least 50.

"Time to assessment" refers to the covid-19 group.

BC SARS = bio-confirmed SARS-CoV-2 infection during acute illness; ED = treated in emergency department; G = group; HC = healthy control; OR = odds ratio; IDSA = Infectious Diseases Society of America; MDD = diagnosis of major depressive disorder; PASC = post-acute sequelae of SARS-CoV-2 infection.

* Denotes use of computerized cognitive test instruments/platform.

† Post-covid-19 syndrome defined by WHO criteria.

‡ Post-covid diagnosed according to NICE criteria.

Overall, the long covid literature indicates that when present, the magnitude of objective neurocognitive dysfunction tends to be mild.[90 151] In one of the first large (n=12 689) studies of objective cognitive outcomes, Hampshire and colleagues demonstrated that those with a history of covid-19 scored lower on an online cognitive questionnaire after illness compared with pre-pandemic controls.[109] Those who had been ventilated produced a cognitive composite score −0.47 standard deviations (SD) below demographic expectations, with diminishing effect sizes observed for those who did not require mechanical ventilation (−0.26 SD), hospitalization (−0.13 SD), or any medical assistance (−0.07 SD). Participants in the COVID Symptom Study Biobank with symptoms persisting ≥12 weeks demonstrated similarly modest deficits (β=−0.22) relative to covid-negative controls on a smartphone application assessing cognitive accuracy while not differing from those who had recovered from covid-19.[139]

As the majority of covid-19 cases are now of mild to moderate severity, there is particular concern about the cognitive consequences of these milder acute illnesses.[151 152] A meta-analysis of data published through June 2023 examined cognitive outcomes across 54 studies (>75% of which focused on individuals with long covid or post-acute sequelae of SARS-CoV-2 infection (PASC)) at an average six months from mild to moderate acute covid illness while also exploring mental health outcomes.[152] A small but statistically significant overall effect was observed, with the covid group performing more poorly than healthy controls and/or normative data (g=−0.36 (95% CI −0.45 to −0.28)). The largest effect was observed for cognitive screening measures such as the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE) (g=−0.56 (−0.75 to −0.36)) followed by processing speed (g=−0.44 (−0.57 to −0.32)) and global cognition (g=−0.40 (−0.71 to −0.09)). Larger effect sizes were observed in the presence versus absence of fatigue (g=−0.35 *v* g=0.02), depression (g=−0.41 *v* g=−0.24), anxiety (g=−0.35 *v* g=−0.22) and with greater illness severity. The authors conclude that, absent the presence of psychiatric symptoms, those with mild to moderate acute illness are unlikely to demonstrate clinically meaningful post-covid cognitive deficits. If replicated, these findings suggest that mental health symptoms may serve as a primary target of intervention for long covid neuropsychiatric symptoms.

Cognitive performance validity testing (PVTs) is recommended in long covid clinical care and research as it is a standard of practice for neuropsychological assessment and provides objective evidence regarding the credibility of an examinee's cognitive scores.[21 153] Clinically, the use of PVTs is essential in demonstrating the veracity of low cognitive scores and guiding appropriate care and determinations (such as benefits eligibility). Applying PVTs in research allows for the exclusion of invalid data that could skew study findings. Studies have generally found PVT failure rates in long covid samples mirror that of non-litigating adults seeking neuropsychological services. For example, of 247 adults evaluated for long covid-related cognitive concerns approximately six months after their acute illness, just 6.4% failed a single PVT and 7.6% failed one or more PVT.[154] The latter group had higher rates of external incentives for poor performance.

Mental health outcomes

The global covid-19 pandemic was associated with an increase in mental health symptoms such as depression and anxiety.[58 105] While some studies indicate that this phenomenon was transient and symptoms returned to pre-pandemic levels by as early as mid-2020,[155] other studies suggest the prevalence of psychiatric symptoms increased over the early years of the pandemic.[156] Against this backdrop, psychiatric symptoms have emerged as a significant contributor to long covid-related disability.[145]

Studies have generally reported increased rates of psychiatric diagnoses following an acute covid-19 illness. A systematic review of 151 studies published through September 2021 estimated depression and post-traumatic stress disorder (PTSD) prevalences to be 18.3% and 17.9%, respectively, when assessed between four and 20 weeks from covid symptom onset.[9] UK BioBank data from one year after illness similarly demonstrated increased incidence of mental health diagnoses among 26 101 individuals with a history of covid-19 compared with 380 621 contemporary controls (hazard ratio 1.54 (95% CI 1.42 to 1.67)).[157] Electronic health record data from the US Department of Veterans Affairs have shown comparably elevated risk (1.43 (95% CI 1.38 to 1.47)) for a mental health disorder composite one year after covid-19 among 154 068 affected individuals compared with roughly 11 million contemporaneous and historical covid-negative controls. While hospitalization generally increases risk for psychiatric diagnoses both independent of and in the context of covid-19,[105 158 159] several studies report that rates of psychiatric complications after hospitalization for covid-19 do not differ from those observed following hospitalization for a similarly severe non-covid illness.[83 160]

Evidence from studies examining rates of elevated psychiatric symptoms, rather than formal diagnoses, is mixed, and few have focused on symptoms persisting ≥12 weeks. A systematic review of 23 studies published through October 2021 included individuals with symptoms persisting ≥4 weeks and found marked variability in the prevalence of elevated psychiatric symptoms.[113] Rates of anxiety ranged from 6.8% to 47.8%, depression from 4.6% to 35.9%, and PTSD from 13.0% to 42.8%. A review of 33 studies assessing 6743 people one to six months after a covid diagnosis found no compelling evidence of poorer mental health outcomes relative to the general population, with 12.2% reporting PTSD, 11.1% reporting anxiety, and 10.4% reporting depression at >12 weeks after illness.[161] The most informative data to date come from a nationally representative US sample of 25 122 adults.[162] A higher prevalence of moderate symptoms of depression (16.8% *v* 7.1%; adjusted odds ratio (AOR) 1.96 (95% CI 1.51 to 2.55)) and anxiety (16.7% *v* 6.3%; AOR 2.21 (1.53 to 3.19)) was observed in those with long covid of ≥3 months duration compared with non-long covid controls.

Neuropsychiatric symptom trajectories

Given the evolving nature of the pandemic, it is perhaps not surprising that considerable heterogeneity exists with respect to the reported longitudinal course of cognitive and mental health outcomes associated with both symptomatic covid-19 and long covid. Thus far, studies have variably demonstrated remission of neuropsychiatric issues over time, symptom persistence or fluctuation, delayed emergence of such issues, or a deteriorating clinical picture for at-risk populations.

Leveraging pre-pandemic data from a prospective population-based cohort of adults in Ecuador, declines in MoCA cognitive scores at six months were observed among those with a prior covid-19 illness (n=52) while scores of unaffected individuals (n=41) remained stable (β=−1.37 (95% CI −2.14 to −0.61), P<0.001). MoCA scores rebounded in the covid group by 12 months' follow-up, suggesting cognitive recovery (β=0.66 (−0.11 to 1.42), P=0.092).[163] Conversely, a cohort study of adults age ≥60 years who had been hospitalized for covid-19 in Wuhan, China, early in the pandemic compared their cognitive functioning against that of unaffected spouses and raised concern for the possibility of progressive cognitive decline over time. At six and 12 months after discharge, a greater proportion of covid survivors with severe acute illness demonstrated mild cognitive impairment (26.5% and 26%, respectively) or dementia (10% and 15%, respectively) compared with those with milder illness and controls (<5.4% across time points), whose rates of cognitive dysfunction did not differ from each other. Survivors of severe illness were also more likely to show declines across assessments.[110 164] However, deterioration may be time limited. When followed from 12 to 30 months after discharge, covid survivors showed less steep cognitive decline relative to control groups, and a small proportion (8%) improved over this period.[165] Wang and colleagues have similarly demonstrated increased risk of receiving an Alzheimer's disease diagnosis among older adults in the year following a covid illness compared with those with other respiratory illnesses.[166] However, findings are not consistent across research teams,[167] and a recent meta-analysis found that, although dementia risk is elevated among older adults after covid-19, this risk does not exceed that observed for other respiratory infections.[168]

Most definitions of long covid permit both persistence of early symptoms as well as a delayed emergence of symptoms after the initial covid-19 illness. A meta-analysis including both hospitalized and non-hospitalized patients reported increased prevalence of anxiety and depression among studies assessing symptoms ≥6 months after covid relative to 3-6 months after acute illness, whereas rates of subjective cognitive dysfunction remained stable across assessment periods.[13] Although these are cross-sectional data, they could suggest that psychiatric symptoms are more likely to emerge rather than persist post-infection. Longitudinal studies tend to support this contention. In a prospective, longitudinal cohort study of hospitalized patients comparing psychiatric symptoms and cognitive performance at 6-12 months versus 2-3 years after illness, depression and anxiety both worsened over time in those with early symptoms while they also emerged as new symptoms in previously unaffected individuals. Degree of recovery by six months predicted persistence of later depression, anxiety, and subjective cognitive dysfunction, whereas only early cognitive scores predicted later cognitive test performance.[14] Further, a prospective cohort study of digitally acquired cognitive test data from the UK Biobank demonstrated persistent cognitive deficits at nearly two years after infection, particularly in those with more severe acute illness and exclusively among those reporting unresolved covid symptoms.[139] Improvements in psychological distress partially mediated the observed cognitive recovery, suggesting a potential target for early intervention.

Symptom management

Given the phenotypic variability of long covid neuropsychiatric presentations, a patient-centered or individualized treatment approach is recommended.[35 137] Clinical care ideally occurs in a multidisciplinary clinical settings with access to medical providers, mental health specialists (such as neuropsychologists, rehabilitation or health psychologists), speech language pathologists, and physical and occupational therapists with expertise in long covid (see fig 2).[169-171] Logistical challenges are associated with establishing such programs, and many individuals with long covid are not able to access these services even in high-income countries.[172 173] In

response, ongoing trials are exploring methods to expand and refine long covid care via a range of care delivery models.[174]

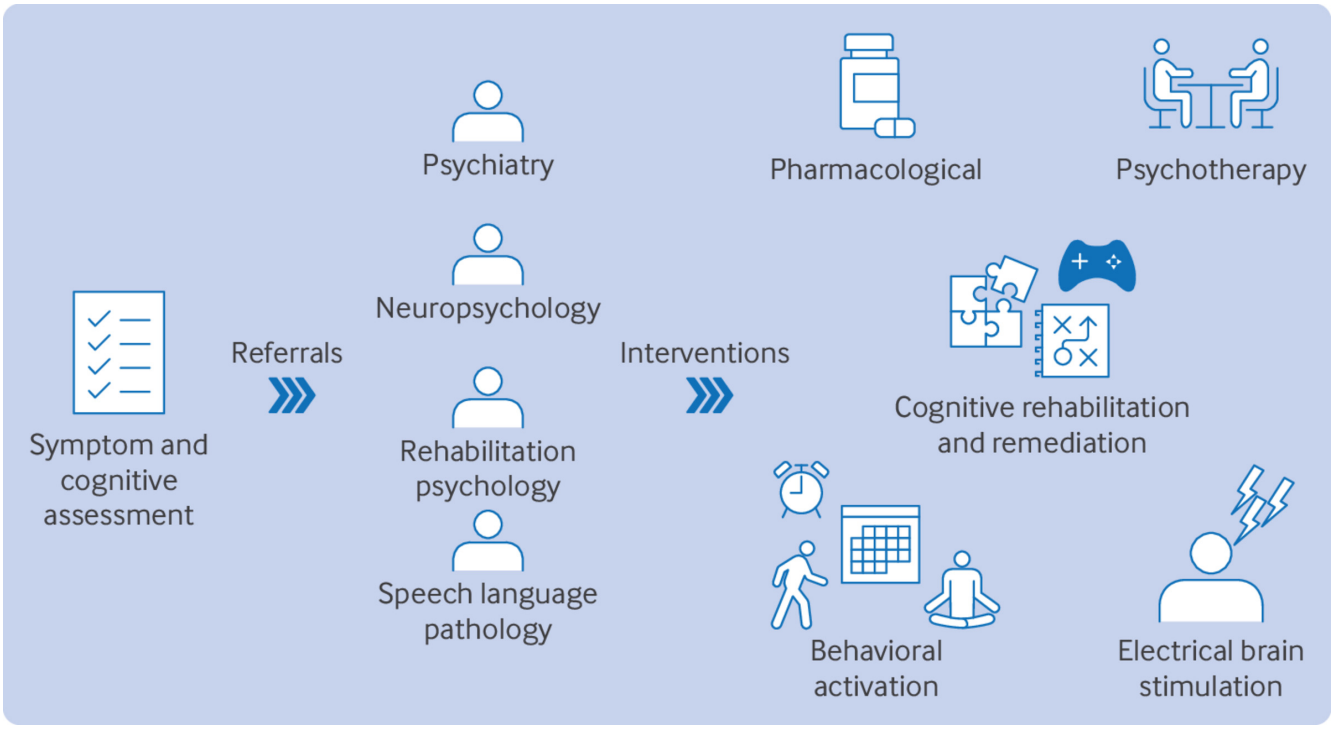

Fig 2 | Optimal clinical care of patients with long covid

Before initiating management of neuropsychiatric symptoms, a thorough assessment should gather information on acute covid-19 symptoms, vaccination status, symptom course, pre-existing conditions and symptoms, and potential contributing factors.[175] Workups to reveal or rule out other causes of cognitive dysfunction or mental health symptoms may be useful (such as thyroid functioning, vitamin B12 levels, polysubstance use). It is recommended that neuropsychiatric symptoms and functioning be assessed using validated measures that allow for tracking of progress over time.[170 176 177] Although a Delphi consensus study failed to identify optimal tools for long covid neuropsychiatric assessment,[177] the GAD-7,[178] PTSD Checklist for DSM-5,[179] Cognitive Failures Questionnaire,[180] and the Montreal Cognitive Assessment-Telephone version[181] were most highly rated. The NeuroCOVID International Neuropsychology Taskforce has recommended a harmonized, flexible set of tools for assessing both subjective and objective cognition in adults with long covid, including incorporation of cognitive performance validity testing.[176] The American Academy of Physical Medicine and Rehabilitation (AAPMR) and long covid neuropsychology experts have issued similar guidance concerning instruments for use in this population.[170 175]

Limited evidence exists to guide management of long covid neuropsychiatric symptoms. The quality of existing studies is generally weak, with most evidence stemming from case reports and small open label trials. A 2023 scoping review found only four of 17 mental health intervention studies were controlled trials,[182] and a 2024 review reported just 7% of psychological trials specifically targeted long covid-related mental health concerns.[183] Encouragingly, the 2022 National Health Interview Survey found most US adults with long covid-related depression (71.8%) or anxiety (65.1%) had received mental health treatment in the prior year, though they were more likely to report cost related barriers compared with other US adults without long covid (adjusted odds ratio 2.12 (95% CI 1.65 to 2.73)).[162]

Interventions for cognitive dysfunction recommended by the WHO and/or AAPMR include cognitive rehabilitation, self management strategies, use of compensatory and assistive technology, and environmental modifications.[137 170] Suggestions for addressing mental health symptoms include cognitive behavioral therapy (CBT), with additional components of acceptance and commitment therapy (such as validating the patient experience), mindfulness approaches, physical activity, and peer support as well as consideration of pharmacological intervention. Providing psychoeducation regarding biological, psychological, and social contributions to symptoms and their persistence is also emphasized.

Of the relatively few non-pharmacological trials in long covid, most have applied CBT principles and/or multidisciplinary programs and have targeted symptoms of anxiety, depression, and cognitive concerns.[184] A randomized clinical trial compared CBT versus usual care to tackle severe fatigue in 114 adults with long covid.[185] The intervention significantly improved both fatigue (Cohen's d=0.69) and subjective cognitive functioning (Cohen's d=0.68) at six months' follow-up. In one of the largest intervention trials to date, an eight week structured online group physical and mental health program was compared with care as usual among 585 formerly hospitalized individuals with physical and/or mental health symptoms of long covid.[186] The intervention was associated with improved symptoms of depression (adjusted mean difference 1.39 (95% CI 0.06 to 2.71)) but not subjective cognitive dysfunction, with benefits that persisted at 12 months. Other promising non-pharmacological approaches include neuromodulation via direct current stimulation (tDCS), transcranial pulse stimulation, or transcranial magnetic stimulation.[187] The ongoing NIH-funded RECOVER-NEURO randomized clinical trial is comparing the efficacy of computerized

cognitive rehabilitation with and without goal management training and tDCS to improve cognitive functioning in adults with long covid.[188]

There is little controlled evidence to guide the choice of medications. However, an eight week randomized controlled trial found that selective serotonin reuptake inhibitors (SSRIs) effectively reduced depressive symptoms in those with long covid-related depression, including among those with pre-covid psychiatric symptoms.[189] SSRIs are hypothesized to affect long covid depressive symptomatology via effects on covid-related inflammation (see Mazza et al[189] for an in-depth discussion). Low dose naltrexone (LDN) has been widely used to target long covid fatigue, with studies suggesting more widespread benefit. An opiate antagonist, LDN is hypothesized to target both immunomodulatory and anti-inflammatory pathways that are thought to play an etiological role in long covid symptom development and persistence.[101] In a single-center study, 52 patients treated with LDN showed improvement in subjective ratings of concentration among other outcomes.[190] Similarly, in a retrospective study, 62.7% of patients treated with LDN (n=59) reported improvement in at least one long covid neurocognitive symptom.[191] Finally, a 16 week, randomized, placebo controlled, phase II trial of LDN is underway in Canada and includes mood and anxiety symptoms as secondary outcomes.[192]

Emerging treatments

A 2022 review of clinicaltrials.gov, a trial registry by the US National Library of Medicine, and the International Clinical Trials Registry, showed 41 long covid mental health interventional trials, ranging from nutritional supplements to CBT and neurorehabilitation.[193] Several promising ongoing pharmacological interventions are evaluating C1 esterase inhibitor, atorvastatin, donepezil, vortioxetine, nirmatrelvir/ritonavir (Paxlovid), and marrow stromal cell infusion.[194] Given the extremely rapid pace of covid-19 research, it is expected that more pragmatic treatment guidelines will continue to emerge. Further, the heterogeneous nature of long covid suggests that it may be well suited to a precision medicine approach wherein treatment is tailored to individual patient phenotypes based on their risk factors, illness and treatment characteristics, symptom manifestation, etc.[195]

Guidelines

As an evidence based pathway for managing long covid neuropsychiatric symptoms has yet to emerge, NICE, WHO, and AAPMR have published guidelines for providing long covid care in community settings.[35 137 169 170] Most recently in February 2025, the CDC issued an updated Clinical Overview of Long COVID.[196] Common themes across guidelines include the importance of applying a person-centered approach and establishing a supportive and collaborative therapeutic milieu while also referring patients to specialists. The NICE, WHO, and AAPMR guidelines note the importance of using validated instruments to capture cognitive functioning and mental health symptoms, and both WHO and AAPMR specifically note the importance of assessing for other factors that may contribute to a patient's symptom presentation (such as fatigue, mental health symptoms, comorbidities, polypharmacy).[137 170] WHO, AAPMR, and CDC recommend implementing psychological and behavioral treatment strategies with an existing evidence base built on the treatment of other post-viral illnesses and medical conditions with high rates of mental health and cognitive sequelae (such as post-treatment Lyme disease syndrome, fibromyalgia).[137 169 170] Such interventions share the goals of improving psychiatric distress, functioning, and quality of life while emphasizing functionality rather than causality in the treatment process.[197] WHO and AAPMR provide more detailed guidance specific to the management of neuropsychiatric symptoms relative to other guidelines.

Conclusions

About five years after the onset of the covid-19 pandemic, a reliable diagnostic marker for long covid is lacking, as is a consensus definition or generally agreed upon set of diagnostic criteria. The nature and trajectories of post-covid neuropsychiatric symptoms, their risk factors and mechanistic pathways, and their socioeconomic impact are only beginning to come into view. Long term cognitive and mental health sequalae of covid-19 remain prevalent, with nearly one in five affected adults demonstrating or reporting persistent cognitive, mood, or anxiety symptoms at ≥12 weeks after an acute covid illness. While objective cognitive deficits are largely modest in magnitude, both cognitive and psychiatric symptoms serve as substantial contributors to reduced functioning and employment among those with long covid. Some patient populations, such as older adults with more severe acute illness, may be at particular risk for persistent long covid-related cognitive dysfunction, while those with pre-existing neuropsychiatric symptoms may be at heightened risk for long covid-related mental health symptoms. Evidence based treatments are lacking, and existing guidelines recommend interventions with empirical support for use in other patient populations. Additional work aimed at understanding the full complement of antecedent, illness, and psychosocial mechanisms of long covid-related neuropsychiatric symptoms will be critical for the development of effective treatment strategies.

Knowledge synthesis

- There is no reliable diagnostic marker for neuropsychiatric symptoms of long covid
- Methodological heterogeneity and the evolving nature of the pandemic have contributed to discrepant findings concerning long covid-related neuropsychiatric symptoms
- These symptoms are associated with functional, occupational, and economic burden and may be more pronounced in elderly people and those who had severe acute covid-19
- Potentially interactive pathways include immune and inflammatory responses, endothelial disruption, and vascular processes. Symptoms may also arise due to, or be complicated by, co-occurring symptoms, conditions, and interventions. For a subset, they may reflect a manifestation or exacerbation of pre-existing symptoms or vulnerabilities and may be influenced by early life adversities and expectancies
- Risk factors include female sex, vaccination status, emergence of new variants, and physical and psychiatric comorbidities. Increased age and severity of acute illness are generally associated with greater objective cognitive dysfunction, while less severe acute illness and younger age are common features among those presenting for neuropsychiatric treatment
- Cognitive testing provides a more direct measure of brain function relative to symptom reports, and recommended instruments and batteries have been developed
- A consistent cognitive profile has not emerged. When deficits are present, effect sizes tend to be small to moderate across domains of attention, processing speed, executive functioning, and memory and more pronounced in the context of severe acute illness, fatigue, and psychiatric symptoms
- There is evidence for symptom remission, persistence, fluctuation, and delayed emergence, which is consistent with current case definitions of long covid. Preliminary data suggest the early recovery

period may reflect a window of opportunity for mitigating negative long term neuropsychiatric outcomes

- Clinical care should take a person-centered approach, gather a comprehensive history, consider contributing factors, use validated screening and assessment instruments, and refer to specialists
- Providers should aim to form a trusting therapeutic alliance that validates the patient experience while providing psychoeducation, implementing interventions with empirical evidence from other health conditions, and focusing on functioning rather than causality
- Interventions may include cognitive rehabilitation and compensatory strategies, psychotherapy (such as CBT, ACT), mindfulness, physical activity, peer support, and pharmacotherapy (such as SSRIs, LND). These, as well as non-invasive brain stimulation and a range of pharmacological agents, are under active investigation as potential tools to address neuropsychiatric symptoms of long covid

Questions for further research

- What are the optimal diagnostic criteria for identifying long covid?
- How are pre-existing neuropsychiatric symptoms, conditions, and risk factors best conceptualized within the framework of long covid?
- Can identifying phenotypic profiles characterizing the cognitive and mental health features of long covid, in combination with other risk factors or biomarkers, aid in the effective personalization of long covid care?
- What are the most efficacious pharmacological, psychological, behavioral, and brain stimulation treatments for addressing cognitive and mental health symptoms in long covid?
- What is the optimal time in the recovery process to intervene in order to prevent or ameliorate neuropsychiatric long covid symptoms?
- How can providers and researchers reduce stigma associated with experiencing and seeking care for cognitive and mental health symptoms of long covid?

How patients were involved in the creation of this article

We have drawn on the clinical experience of addressing the cognitive and mental health concerns of patients within a covid-19 multidisciplinary care model that incorporates neuropsychology, rehabilitation psychology, and psychiatry services. The perspectives of long covid patients and caregivers were shared with author MM, whose moderated discussion of patients' lived experience with long covid is freely available online.[198] A patient with long covid and associated cognitive and mental health concerns provided a critique of our review before submission. Their input highlighted issues related to the challenges of living with symptoms for which there may not be a clearly identifiable cause or definitive diagnostic test. Their input led us to highlight concerns regarding stigma from society and the potential for patients to feel dismissed by care providers. Our patient shared the importance of supportive provider communication. This specifically included the value of providers acknowledging that much remains to be learnt about treating long covid-related neuropsychiatric symptoms and the value of sharing the scientific basis for implementing interventions that are lacking evidence in long covid but have been shown to improve symptoms or functioning in other health conditions.

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