Post-COVID cognitive dysfunction: current status and research recommendations for high risk population

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Summary

Post-COVID cognitive dysfunction (PCCD) is a condition in which patients with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, usually three months from the onset, exhibit subsequent cognitive impairment in various cognitive domains, and cannot be explained by an alternative diagnosis. While our knowledge of the risk factors and management strategy of PCCD is still incomplete, it is necessary to integrate current epidemiology, diagnosis and treatment evidence, and form consensus criteria to better understand this disease to improve disease management. Identifying the risk factors and vulnerable population of PCCD and providing reliable strategies for effective prevention and management is urgently needed. In this paper, we reviewed epidemiology, diagnostic markers, risk factors and available treatments on the disease, formed research recommendation framework for vulnerable population, under the background of post-COVID period.

Keywords: Long COVID; Post-COVID cognitive dysfunction; Epidemiology; Diagnosis; Risk factors; Management

Introduction

As of January 25, 2023, more than 665 million confirmed cases of COVID-19, including more than 67 million deaths, have been reported globally by WHO (https://covid19.who.int/). The clinical manifestations of COVID-19 range from asymptomatic to fatal. Post-COVID-19 conditions are characterized by multi-organ structural and functional impairment, including cardiovascular, neurological, psychiatric, hematological, pulmonary, and dermatological injury.[1,2] Although COVID-19 primarily presents as a respiratory infection with flu-like symptoms, it is now considered a multi-organ disease, often involving the nervous system.

The effects of COVID-19 have been unparalleled, and long-term symptoms can lead to serious healthcare crises. Recent evidence indicates that approximately 80% of people who are infected with COVID-19 have one or more long-term symptoms.[3] A community-based study reported that 70% of individuals with ongoing symptoms, even at low risk of COVID-19 mortality, have impairment in one or more organs four months after the development of initial COVID-19 symptoms, with important implications for healthcare and public health.[4] WHO defines post-COVID condition as the prolonged effects of COVID-19 occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of symptoms and lasting for at least 2 months that cannot be explained by an alternative diagnosis.[5] Common symptoms include fatigue, shortness of breath, and cognitive dysfunction and generally have an impact on everyday functioning.[6] SARS-CoV-2 enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is ubiquitous in the body, including in the oral and nasal mucosa, lung, heart, gastrointestinal tract, liver, kidney, spleen, brain, and arterial and venous endothelial cells. The virus then replicates and matures, triggering direct tissue damage. Furthermore, endothelial damage, thromboinflammation, dysregulation of immune responses, and maladaptation of ACE2-related pathways may contribute to the extrapulmonary manifestations of COVID-19.[1,7]

Among the extrapulmonary effects of COVID-19, the effects on the brain should not be ignored.[8] Respiratory system inflammation causes inflammation of the central nervous system (CNS) though various mechanisms. First, CNS cytokines, chemokines, and reactive microglia dysregulate multiple neural cell types, disrupt

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myelin homeostasis and plasticity, impair hippocampal neurogenesis, and induce neurotoxic astrocyte reactivity, thereby impairing neural circuit function and cognition.[9] Second, anti-neural autoantibodies and T cells may cause autoimmune encephalitis in patients with COVID-19 contributing to ongoing immune-mediated injury.[10] Third, COVID-19 can trigger reactivation of latent herpesvirus infections, most prominently Epstein–Barr virus, which may induce further inflammation.[11] Fourth, SARS-CoV-2 triggers neurovascular dysfunction, including blood–brain-barrier (BBB) disruption with consequent leakage of fibrinogen and other pro-inflammatory molecules, and thrombosis can contribute to neural inflammation and injury.[12] Finally, in severe COVID-19, hypoxia and other metabolic disturbances associated with pulmonary and multi-organ dysfunction can cause CNS injury.[13,14]

The brain effects of post-COVID conditions often include cognitive impairment such as deficits in attention, executive function, memory, and learning.[15,16] Based on the existing evidence, we summarize the definition of post-COVID cognitive dysfunction (PCCD) as new cognitive impairment occurring at least three months after COVID-19 acute infection, which has a relatively characteristic cognitive profile characterized by attention/processing speed deficits with or without associated episodic memory and executive function deficits.[15,17] PCCD can include subjective cognitive complaints and objective dysfunction in neuropsychological examinations.[18] Cognitive dysfunction manifests as cognitive impairment in domains such as memory, language, orientation, application, attention, perception (visual, auditory, sensory), and executive dysfunction, suggesting an impact of COVID-19 on brain structure and function.[16,19] Cognitive complaints, referred to by patients as "brain fog" and described as a "fuzzy state of the brain", include a combination of cognitive symptoms, such as inattention, aphasia, and amnesia, that may be accompanied by fatigue, lack of motivation, and sleep disorders.[20] Structural and functional changes in the brain of patients after COVID-19 have been identified, and these have been found to correlate with cognitive examination scores.[2,21] However, cognitive complaints are not necessarily associated with structural damage to the brain, and may resolve.[7,19]

PCCD contributes substantially to the morbidity of post-COVID conditions, but it is difficult to diagnose and separate from other causes of the symptoms manifesting in an individual patient because neurocognitive longitudinal data for patients are scarce.[22] PCCD has a significant impact on daily functioning and quality of life and is associated with a considerable economic, health, and social burden. Based on the literature on COVID-19 (Panel 1), we reviewed the current status of the epidemiology, diagnosis, risk factors and management framework of PCCD and developed research recommendations to improve the understanding of this disease, reduce the damage to brain function, and provide a reference for the management of PCCD worldwide during and after the COVID-19 pandemic.

Current status of epidemiology

The incidence of PCCD has been extensively reported. A recent two-year retrospective cohort study including over one million COVID-19 patients found that the risk of cognitive deficit was higher than that in matched controls at six months, with a hazard ratio of 1.36 (1.33–1.39), and that the risk remained higher at the end of the two-year follow-up period.[23] Another longitudinal cohort study in China including 3233 COVID-19 survivors reported that severe COVID-19 was associated with higher risks of early-onset cognitive decline (six months after discharge), late-onset cognitive decline (12 months after discharge), and progressive cognitive decline than in controls, with an odds ratio (OR) of 4.87 (3.30–7.20), 7.58 (3.58–16.03) and 19.00 (9.14–39.51), respectively. Non-severe COVID-19 was associated with a higher risk of early onset cognitive decline, with an OR of 1.71 (1.30–2.27).[24] The increased risk of cognitive impairment, seizures, dementia, psychosis, and other neurocognitive conditions persisted for at least two years.[23]

Meta-analyses showed that the prevalence of PCCD varied from 7.2% to 59.2%. A meta-analysis showed that 22% of individuals diagnosed with COVID-19 developed cognitive impairment after three months or more.[15] In another meta-analysis involving 1,285,407 participants from 32 countries, PCCD occurred in 19.7% of survivors for up to 12 months after infection.[25] The cognitive domains exhibiting the greatest level of impairment were executive function, memory, and attention.[25–28] Another meta-analyses showed that in post-COVID condition, brain fog approximately accounted for 32%, memory impairment accounted for 17.5–35%, and attention impairment accounted for 22%.[19,25] In a recent review, 40% of patients exhibited problems with attention, memory, and sleep after three or more months of hospitalization for COVID-19.[29] There are several reasons that may explain the variations in the reported prevalence of symptoms: 1) the timing of the studies varies as these included patients between 3 months and 12 months after COVID-19 diagnosis; 2) the sample characteristics of the studies are heterogeneous in terms of age range, proportion of male and female patients, ethnic group, hospitalized patients and outpatients, disease severity, and comorbidities; 3) there is variation in the neuropsychological tests/batteries used in the studies and in the cognitive/symptom domains examined; 4) there is variation in the diagnostic tools and criteria used; 5) there is variation among the studies in local public health policy regarding quarantine and vaccination; 6) there is variation among the studies in factors such as the environment, population density, climate, and ecology. The prevalence of PCCD has also been reported in different countries in large cohort

studies (>1000 patients). Specifically, a multicenter study in Madrid, Spain found that among 1142 patients who had been infected with COVID-19, 9.6% experienced brain fog and 19% experienced non-respiratory symptoms such as memory loss.[30] A cohort study of 2005 participants (>60 years old) including COVID-19 survivors and their uninfected spouses in Wuhan, China, showed that 35.7% of severely infected patients had cognitive impairment including dementia and mild cognitive impairment (MCI) and 59.2% had cognitive decline at six months of discharge.[31] Furthermore, 12.45% of patients in the same cohort had cognitive impairment at 12 months after discharge.[24] A study of 2320 patients in the UK found that 46.7% and 44.6% of patients exhibited slowing down in thinking and short-term memory loss, respectively, at 1 year of discharge.[32] A cohort study of 2696 patients in Fars, Iran, found that 194 patients (7.2%) reported post-COVID syndrome-associated brain fog at least three months after discharge.[33] Fig. 1 shows the aforementioned four cohort studies on a world map. It should be noted that cohort studies on PCCD were mostly conducted at the province or city level, rather than at the national level, and only the cohort in China included unaffected control subjects. Despite the variations in design and demographics discussed above, the findings of these high-quality cohort studies can be tentatively summarized as follows: 1) most of these studies were conducted during the first wave of the COVID-19 pandemic in 2020; 2) the prevalence of general cognitive impairment (not domain-specific impairment) in patients decreased at 12 months compared to the prevalence at 5–6 months; 3) more severe COVID infection was associated with a lower probability of improvement in cognitive function; 4) short-term memory loss, attention deficit, and brain fog were the most commonly reported cognitive features, followed by fatigue. These findings highlight the urgent need for further large-scale long-term follow-up cohort studies of patient populations experiencing a substantial burden of symptoms based on common criteria and assessment tools in order to identify precision treatment strategies targeting specific phenotypes.

Current status of diagnosis

The clinical diagnostic framework for PCCD was developed according to the rapid guideline proposed by the UK National Institute of Health and Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) (www.nice.org.uk/guidance/ng188),[34,35] which includes:

1) Individuals with a history of suspected or confirmed SARS-CoV-2 infection, and

***Fig. 1:* Major PCCD cohort studies in the world.** PCCD cohort studies were mainly concentrated in the United Kingdom, Spain, Iran and China, but mostly in regional level, instead of national level. PCCD: post-COVID cognitive dysfunction. The map of the world was downloaded and reproduced from the website (http://bzdt.ch.mnr.gov.cn/index.html), with drawing review No.: GS(2020)4401, and supervised by Ministry of Natural Resources.

2) Symptoms of cognitive dysfunction occurring during or after COVID-19 infection that are present for more than 12 weeks and cannot be explained by an alternative diagnosis.

Diagnosis is based on neuropsychological tests, blood tests and brain imaging.

Neuropsychological tests

Objective and computerized cognitive assessment batteries can be conducted. Objective assessment includes a range of general cognitive screening tools and more extensive neuropsychological assessment batteries according to specific criteria. The Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are well-known scales in the clinical setting for general cognitive screening,[36] and have been used in studies of PCCD.[26] A cut-off value of 26 on the MoCA was defined as the threshold for distinguishing between healthy controls and MCI based on a large cohort.[37] A study of 8 patients at 6 months after the manifestation of COVID-19 symptoms found that MoCA total scores were still significantly lower than the cut-off score of 26/30.[38] On the contrary, a large sample study of 443 patients at approximately 9.6 months after the first infection found that patients had a higher MMSE median score than that of 1328 matched controls (29/30 vs. 28/30).[36] These results indicate the importance of the timing of cognitive evaluation relative to the onset of symptoms. The Telephone Interview of Cognitive Status-40 and the Informant Questionnaire on Cognitive Decline in the Elderly were used to assess general cognitive status and cognitive decline, respectively, in patients who had recovered from COVID-19.[31] It should be noted that many of these screening tools have limited sensitivity to cognitive decline in younger populations, which may have led to an underestimation of cognitive impairment. Studies have recommended more sensitive screening tools such as the Screen for Cognitive Impairment for Psychiatry[28] and THINC-integrated tool.[15] In addition, since PCCD is characterized by impairment in various cognitive function domains such as attention deficits and executive function deficits, with or without memory deficits, many neuropsychological assessment batteries have been used to evaluate different cognitive domains in PCCD, including attention (Digit Span Test-DST, Trail Making Test-TMT part A, Stroop Word reading and Color Naming), executive function (DST backwards, Corsi backwards, Stroop, TMT part B), episodic memory (Rey auditory verbal learning test, Free and Cued Selective Reminding Test, Rey–Osterrieth Complex Figure-ROCF), visuospatial function (Judgment Line Orientation, Visual Object and Space Perception Battery, ROCF copy), and language (Boston Naming Test, Verbal fluencies).[26,27,39–41] However, the diagnostic accuracy of these tests needs to be verified in large cohort studies. Neuropsychiatric assessment scales include the Hamilton Anxiety Scale, Hamilton Depression Scale, Hospital Anxiety and Depression Scale,[42] and International Neuropsychiatric Interview,[43] for the assessment of depression, anxiety and general psychiatric symptoms, which have been shown to be related to cognition in post-COVID conditions. Computerized cognitive assessment is an emerging method. IPad-based online neuropsychological tests, including the TMT, DST, Continuous Performance Test (CPT), and Sign Coding Test, were conducted to minimize contact between medical staff and patients with COVID-19, due to the fact that human-to-human transmission of SARS-CoV-2 was confirmed. The study showed that patients who recovered from COVID-19 performed worse in the second and third parts of the CPT.[44] Another study used a web-optimized assessment battery as part of the Great British Intelligence Test, a composite of 9 cognitive tests such as the DST and Spatial Span, in 81,337 participants who had recovered from COVID-19. Cognitive battery comprised tests were designed to enable variance in examining different aspects of cognition within the general population at a very large scale.[45] These tests have confirmed that COVID-19 has a multi-domain impact on human cognition, which persists into the early chronic phase.[45]

Blood tests

The most frequently used blood biomarkers for PCCD are neuroinflammation related markers, many of which are overlapped with pathological changes occurring in dementia and related cognitive disorders or are risk factors for these diseases.[29] Specifically, higher levels of IL-6 and CD70 were observed in the cognitive impairment subgroup.[32] The worse performance on an iPad-based CPT in patients recovered from COVID-19 was significantly associated with higher blood levels of C-reactive protein.[44] In addition, hospitalized patients with COVID-19 without a history of cognitive impairment showed higher serum levels of neuronal and glial degeneration biomarkers including NfL, GFAP, and UCHL1 than non-COVID controls with MCI or Alzheimer's disease (AD), and the biomarkers were associated with encephalopathy.[46] Therefore, these may be useful biomarkers for the diagnosis of PCCD. A recent study found persistently elevated levels of C–C motif chemokine 11 (CCL11), a molecule that mediates microglial activation, in both mild respiratory COVID mice and the serum of patients with PCCD, with a further mechanism of white-matter-selective microglial reactivity (myelin dysregulation).[9,22] Although the sample sizes for humans were relatively small (48 patients with PCCD vs. 15 patients with long-COVID without cognitive deficits),[9] CCL11 may be a potential biomarker for diagnosing PCCD, although this needs to be corroborated in large-scale clinical studies.

Brain imaging

Several clinical studies have evaluated brain imaging findings in patients with PCCD; however, the sample sizes were relatively small. An observational study involving 13 patients with COVID-19 who underwent brain magnetic resonance imaging (MRI) because of unexplained encephalopathic features, found enhancement in the leptomeningeal spaces in 8 patients and bilateral frontotemporal hypoperfusion in all 11 patients who underwent perfusion MRI.[16] A study examining the brain MRI scans of 13 patients in the subacute stage of COVID-19 found that in 4 of the patients, microembolic subacute infarcts were present bilaterally in the cerebellum and in the right corona radiate, left superior cerebellar peduncle, and right frontal cortex.[47] In the same study, FDG PET showed predominant frontoparietal hypometabolism in 10 out of the 15 patients, which highly correlated with worse MoCA scores. An MRI study using diffusion tensor imaging and 3D T1-weighted imaging of 60 previously hospitalized patients with COVID-19 suggested possible disruption of microstructural and functional brain integrity at follow-up at three months. Furthermore, global gray matter volume, volumes in the left Rolandic operculum, right cingulate, bilateral hippocampi, left Heschl's gyrus, and global white matter mean diffusivity were correlated with memory loss.[48] Another diffusion MRI study of 215 patients at 3–11 months after COVID-19 infection detected changes in the apparent diffusion coefficient (ADC) with the greatest changes observed in patients with cognitive or memory disorder and in those with encephalitis or meningitis, suggesting that ADC is a non-invasive marker of neuroinflammation in PCCD.[49] Several FDG PET studies in patients at 3–6 months after COVID-19 revealed residual pathological changes, primarily frontoparietal hypometabolism which extended to the limbic and subcortical regions, and no brain hypometabolism was detected after 7–9 months after COVID infection.[38,50] A large sample MRI study investigated 785 participants from the UK Biobank (401 post-COVID cases vs. 384 controls), and found a significant reduction in cortical thickness of the orbitofrontal cortex and parahippocampal gyrus, and greater reduction in global brain size in patients at approximately 4.7 months after COVID infection, associated with a greater cognitive decline than that observed in controls.[2] As indicated by the authors, these changes in the limbic regions may be the in vivo hallmarks of a degenerative spread of the disease through olfactory pathways or of neuroinflammatory events or loss of sensory input due to anosmia.[2] Another large sample MRI study (188 post-COVID cases vs. 483 controls) in Germany found that patients had a higher mean cortical thickness (adjusted $p = 0.002$) than controls at 9.6 months after SARS-CoV-2 infection.[36] Another multimodal imaging study in Spain involving 86 patients with post-COVID syndrome at 11 months after the first onset of symptoms found reduced grey matter volume in the cortical, limbic and cerebellar areas, which were correlated with cognitive dysfunction.[21] Hypoconnectivity and alterations in white matter diffusivity were also detected. Such inconsistencies in terms of structural and functional changes may be partly due to the timing of scanning, variations in local public health policy, and the dynamic changes in the brain after COVID infection.

In view of the uncertainties about the long-term effects of COVID-19, further longitudinal cohorts with large sample sizes that monitor the cognitive function domains and blood/imaging biomarkers during and after post-COVID conditions are needed to plot recovery trajectories and provide insights for the development of public health policies and patient management following recovery from COVID-19. Furthermore, the sensitivity and diagnostic accuracy of these scales and markers need to be tested and validated.

Differential diagnosis

The differential diagnosis of PCCD includes cognitive disorders with other causes, such as AD and vascular cognitive impairment. The most frequent cases of cognitive impairment are dementia and MCI due to AD, which mainly manifest as cognitive impairment in the episodic memory domain. The diagnosis of AD is based on the "ATN" biomarker diagnostic framework of NIA-AA,[51] using imaging or biofluid markers and includes amyloid pathology (A) detected by amyloid PET imaging or on cerebrospinal fluid (CSF) analysis, tau pathology (T) detected by tau PET imaging or on CSF analysis, and neurodegeneration (N) detected by FDG PET imaging or MRI showing hippocampus atrophy. In addition, mutations in PSENs and APP have been confirmed as genetic diagnostic markers for AD. Blood biomarkers such as Aβ42, Aβ40, pTau217, pTau181, and NfL, have also been examined for the diagnosis of AD,[52] although the cut-off values for each biomarker remain unclear and need to be determined based on large cohort studies of different ethnic groups. In contrast to AD, PCCD appears to involve attention deficits, although the multiple pathophysiological processes associated with COVID-19 may potentially cause cognitive impairment (hypoxia, neuroinflammation, systemic involvement), suggesting that several cognitive profiles may be expected in these patients, which helps explain the heterogeneous findings reported to date.[45,53]

Current status of risk factors and potential causes

The available evidence demonstrates an uneven distribution of PCCD, suggesting that certain individuals are more susceptible to the disease than others. To prevent and treat cognitive impairment due to COVID-19, it is essential to identify vulnerable populations. Preliminary

evidence has found a predisposition to cognitive manifestations after COVID-19 infection in populations with specific demographic/genetic risk factors, severe COVID-19, medication factors, environmental factors, and comorbidities.[15,33]

Demographic/genetic risk factors

Studies of cognitive function in patients with COVID-19 have found that middle age is associated with cognitive decline after COVID-19, although the results were inconsistent.[17,32] A post-hospitalisation COVID-19 study involving 2320 individuals (mean age 58.7 ± 12.5 years) found that mean age was highest (67.8 ± 11.4 years) among patients with moderate cognitive impairment relative to other clusters without cognitive impairment, indicating that older age is associated with a higher risk of cognitive impairment.[32] However, another study of 404 patients with post-COVID syndrome 16 months after acute onset of COVID-19 and involving two centers found that patients who displayed cognitive impairment were younger than those without cognitive impairment (mean age 46.65 ± 9.08 vs. 50.05 ± 9.05 at –1.0 SD, 45.76 ± 9.44 vs. 49.28 ± 9.04 at –1.5 SD).[17] This suggests a vulnerability to PCCD in the middle age population, which could have implications from a pathophysiological perspective that differ from ageing or neurodegenerative disorders.

Women showed trend level (56% vs. 36%, $p = 0.063$)[15] and significant (OR: 1.4, $p = 0.020$)[33] higher incidences of cognitive impairment after COVID-19 than men. Fragments of SARS-COV-2 may be hidden in reservoirs such as the kidneys or brain, triggering a chronic inflammation cascade with higher levels of inflammatory cytokines in women than in men, which may lead to brain fog.[54] Such sex-related differences were not observed in pediatric patients,[55] suggesting that sex hormones and their immunomodulatory activity play a role in post-COVID conditions in adult patients.

A study of post-discharge patients with COVID-19 in China found that low education level and socioeconomic status were risk factors for cognitive decline.[31] Education increases cognitive reserve, which represents a cumulative cerebral potential derived from cognitive engagement and stimulation in everyday life. Low cognitive reserve is associated with cognitive disorders.[56] In addition, factors related to low socioeconomic status, such as poverty, poor housing conditions, and lower-status occupations, are associated with more comorbidities and a lack of access to health care.[57]

Genetically, overexpression of ACE2 is associated with PCCD development. Neural tissue invasion involves SARS-CoV-2 spike protein binding to ACE2 receptors present on neurons, glial cells, and the capillary endothelium.[58,59] Upon invasion, SARS-CoV-2 stimulates reactive astrogliosis, microglial activation, and the neuroinflammatory cascade. Consequently, the BBB becomes compromised due to systemic inflammation followed by disrupted brain homeostasis and neuronal death, each of which can impair neural circuit function and thus cognition.[60] Presence of the APOE4 gene is another risk factor for PCCD. APOE4 allele carriers are at a heightened risk of severe COVID-19 infection,[61,62] BBB breakdown,[63] and cerebral microhaemorrhages,[64] which contribute to post-COVID cognitive decline and mental fatigue independent of AD pathology. Direct evidence for the role of ACE2 and APOE4 in PCCD is lacking and needs to be confirmed in large-sample studies.

Severe COVID-19 infection

Studies have confirmed that the severity of COVID-19 infection is associated with the development of cognitive impairment.[6,31] The incidence of cognitive impairment was higher in patients with severe COVID-19 than in those without severe COVID-19 (59.24% vs. 28.67%).[15] Furthermore, admission to the ICU, severe pulmonary dysfunction, and higher maximum D-dimer levels have also been associated with PCCD.[16,28,31] Higher levels of many inflammatory markers have been detected in the blood samples of patients with severe disease and patients admitted to the ICU than in blood samples of non-ICU patients. These markers include IP-10, MCP-1, IFN-γ, and IL-1β, and may initiate a cytokine storm by stimulating the T helper 1 (Th1) immune response.[65] Evidence of immune dysregulation may be relevant to the understanding of the mechanisms underlying PCCD. Coagulation abnormalities and thrombosis caused by acute cerebral ischemic hypoxia inhibit hippocampal synaptic transmission and aggravate neuronal apoptosis.[31]

Medication for COVID-19 treatment

Previous studies showed that raltegravir treatment was associated with cognitive impairment.[66] A small number of patients have also been reported to experience cognitive impairment with tolzumab.[67] In addition, benzodiazepines,[68] opioids,[69] and antipyretics[70] used in the supportive therapy of patients with COVID-19 have been associated with cognitive impairment. Therefore, the drugs used to treat COVID-19 may affect the incidence of cognitive impairment. Furthermore, patients with existing neuropsychiatric symptoms may self-administer antipsychotic medication, sleeping tablets, and other sedative drugs during the treatment of COVID-19 because of the increased difficulty in accessing medical support.[71] In these circumstances, healthcare providers are unable to assess patient medication dosage and side effects in a timely manner, which may lead to the development of cognitive impairment.[72,73]

Environmental factors

Isolation during COVID-19 results in lower social participation (e.g., living alone, little social support, small social network, low social frequency) with an increase in loneliness,[72] which leads to the onset or

worsening of cognitive impairment.[74] A follow-up study in China confirmed further impairment of cognitive function in 42% of patients with MCI, 54.3% of patients with AD, and 72.7% of patients with dementia with Lewy body after at least 6 months of isolation from COVID-19.[75] Another study from Argentina showed that 60% of families suspended visits to patients with dementia in nursing homes during the COVID-19 pandemic, and over 90% patients with dementia stopped previous cognitive and physical therapy.[73] A large number of nursing homes implemented strict visitation regimes to reduce infections and deaths, which also increased the burden on caregivers and made it more difficult for families of older adults to meet, increasing the risk of cognitive impairment.[76]

Comorbidities

The COVID-19 pandemic has increased the risk of comorbidities, such as pre-existing cognitive dysfunction and psychiatric diseases. People with dementia and AD are more likely to contract COVID-19,[77,78] and have more severe disease consequences than people without dementia.[79,80] An observational study in China found that patients with AD had a 2.29 times higher risk of contracting COVID-19 than the normal population, and patients with dementia had a 2.16 times higher risk of contracting COVID-19.[77] This may be attributed to patient poor understanding and adherence to protective procedures during the COVID-19 pandemic period, such as wearing masks and maintaining proper body distance. Another reason is that most of these individuals live in nursing homes, which have higher rates of COVID-19 infection than those in communities. Comorbidity risk factors for dementia, such as obesity, cardiovascular disease, hypertension, and diabetes, are also risk factors for COVID-19, which, in turn, exacerbate PCCD. Patients with COVID-19 may be prone to developing psychiatric symptoms such as depression and anxiety.[81] Meanwhile, the restrictions imposed in many countries to control the pandemic had neuropsychiatric effects on people with dementia, with forced social isolation leading to increased psychiatric symptoms,[82] which may result in more severe cognitive symptoms. In addition, such patients often present with atypical symptoms at the onset of COVID-19, such as altered mental status,[83] which may delay appropriate diagnosis and treatment, consequently worsening cognitive prognosis. It has also been reported that patients with pre-existing critical illness (such as respiratory failure or shock) in medical and surgical ICUs are at high risk for long-term cognitive impairment.[13] COVID-19 and pre-existing diseases can exacerbate each other in a vicious circle.

Other potential risk factors

In PCCD, vaccination reduced the risk of cognitive dysfunction, kidney disease/dysfunction, myalgia, and sleeping disorders or problems. Studies have shown that COVID-19 vaccines reduced the risk of PCCD in patients vaccinated before or after COVID-19 infection.[84,85] It has been postulated that vaccination may be associated with potential correction of dysregulated immune or inflammatory responses or the possible elimination of persistent viruses or viral remnants of SARS-CoV-2.[86] Furthermore, persistence of gut dysbiosis after disease resolution may be linked to long-COVID syndrome, particularly to its neurological manifestations. The gut microbiome of patients with post-acute COVID-19 syndrome is characterized by higher levels of *Ruminococcus gnavus* and *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii*.[87,88] Further studies should investigate whether microbiota modulation can facilitate prompt recovery from PCCD.

Current status of management

For the clinical rehabilitation and management of cognitive impairment in adults with post COVID-19 condition, the latest WHO living guidelines (September 15, 2022) suggest an approach based on the combination of education, skills training on self-management strategies, and cognitive exercises. The provision of assistive products and environmental modifications to support cognitive deficits, and the delivery of training in their use, may improve the individual's daily functioning (https://www.who.int/publications/i/item/WHO-2019-nCoV-Clinical-2022.2).

Medication

Currently, symptomatic treatments for cognitive disorders (particularly dementia and AD) include US Food and Drug Administration approved drugs, such as cholinesterase inhibitors and uncompetitive NMDA receptor modulators (memantine). In China, medications administered to patients with dementia include various adjuvants and traditional Chinese medicines, although the efficacy of many traditional compounds has not been tested in international randomized controlled trials.[89] Ongoing clinical trials are being conducted to test the safety and efficacy of potential drugs for the treatment of PCCD, including donepezil (IRCT20210816052203N1), famotidine (IRCT20090117001556N138), vortioxetine (NCT05047952), temelimab (NCT05497089) and atorvastatin (NCT04904536). A recent comprehensive review summarized the therapeutic drug trials for post-COVID conditions. Among these, temelimab and vortioxetine are proposed medications with a mechanism of improving cognitive functioning.[90] In addition, nirmatrelvir/ritonavir (Paxlovid), a disease-modifying therapy for COVID-19, is currently undergoing clinical trials, with cognitive function as a primary (NCT05595369) and secondary (NCT05668091, NCT05576662) outcome measure. Evidence has shown that luteolin, a natural flavonoid, may alleviate cognitive impairment by inhibiting mast cell and microglial activation,[91] and it has been

used as a dietary supplement co-ultramicronized with palmitoylethanolamide in clinical trial for post-COVID conditions, with cognitive function as a secondary outcome measure (NCT05311852, data not available). The drug dosages of the above ongoing clinical trials were listed in Table S1. However, to date, no drugs have been approved for the clinical treatment of PCCD.

Non-pharmacological treatment

Cognitive rehabilitation

Cognitive rehabilitation may help patients experiencing cognitive difficulties, and includes discussions of past and present events and topics of interest, music, and practical activities such as baking or indoor gardening, computer-based cognitive training, puzzles, word and number games, and reading.[92,93] Activities are broken down into individual steps so that patients do not feel overwhelmed. Patients are supported through cognitive exercises and compensatory tools and the use of electronic devices such as cell phones, computers, and application software during the COVID-19 pandemic,[94] and virtual reality devices is encouraged.[95] Internet-based and computer-based adaptive cognitive training systems with multiple cognitive domains have been effective in patients with vascular cognitive impairment and no dementia.[92] Cognitive rehabilitation can be domain-specific. Specifically, direct-attention training and metacognitive strategy training have been used to improve attention; internal (imagery, etc.) and external (notes, alarms) compensatory strategies have been used to improve memory; pragmatic conversational skills have been used to improve language; metacognitive strategies (self-monitoring, self-regulation) and explicit performance feedback have been used to improve executive functioning; and multimodal, computer-assisted cognitive retraining with an emphasis on patient-centered goal setting, has been used for comprehensive neuropsychological rehabilitation.[96]

None-invasive brain stimulation

Brain stimulation, another form of non-pharmacological treatment, has also been recently tested in clinical trials for PCCD. A study in Brazil investigated the therapeutic effects of high-definition transcranial direct current stimulation (tDCS) with rehabilitation for severe patients with post-COVID fatigue, and found that tDCS targeting the left primary motor cortex combined with a rehabilitation program was effective in reducing cognitive and psychosocial domains of fatigue.[97] Conversely, a study conducted in Spain found that eight sessions of tDCS targeting the left dorsolateral prefrontal cortex were effective for the treatment of physical fatigue but had no effect on cognition in post-COVID patients with fatigue.[98] Two studies conducted in Germany and Brazil proposed a 3-week and 4-week neuromodulation therapy course, respectively, consisting of tDCS-assisted cognitive training in PCCD, with cognitive performance as the primary outcome (NCT04944147, NCT05389592).[99] Another study in Hong Kong, China, is currently testing the effects of transcranial pulse stimulation (TPS) for young adults with depression after the COVID-19 pandemic, with cognitive function as a secondary outcome (NCT05006365).[100]

Lifestyle management

Some of the strategies for managing activities of daily living may also help patients manage the impact of attention, memory, and thinking impairment, such as physical activity interventions (squats, push-ups, sit-ups, dancing, stair climbing, yoga, or traditional tai chi, and walking or running on site)[101]; dietary interventions (vegetables, fruits, and whole grain products, adequate vitamin and mineral supplementation such as zinc, vitamins C, D, and A, adequate hydration, reasonable fat intake, and avoidance of excessive sugar and salt intake)[102,103]; social activity intervention (using telephone and internet to contact family and friends for psychological support, and enriching home living arrangements with simple household or gardening activities)[94]; sleep disorder management (limit thinking about stress in a specific daytime to reduce disruption of nighttime sleep). Furthermore, social media can be used to share feelings of stress and anxiety with family and friends while sharing positive messages, preferably without bringing communication devices into the bedroom. Going to bed when feeling sleepy, keeping light levels dim to encourage sleep, and choosing familiar and relaxing activities before sleeping, such as reading a book and yoga[104]; are recommended depending on the patient's condition during the COVID-19 pandemic. A 2-year multidomain large prevention clinical trial (FINGER) integrated intervention consisting of diet, exercise, cognitive training, and vascular risk monitoring and found that such intervention could prevent cognitive decline in at-risk elderly people.[105] A recent large-sample long-term prospective cohort study in China showed that a healthy lifestyle involving multiple domains, such as healthy diet, physical exercise, cognitive stimulation, social activity, less smoking, and alcohol use, is associated with slower memory decline, which offers strong evidence to protect older adults against memory decline.[106] Such an approach may be easily tested in patients with PCCD, including young adults. There are several ongoing trials on lifestyle management for treating PCCD worldwide, such as combined cognitive-behavioral treatment and psychoeducation (NCT05597722, NCT05167266), and Tai Chi digital therapy (NCT05419219), although the sample sizes are relatively small.

Research recommendations of PCCD in high risk population

Evidence regarding the specific management of PCCD remains scarce; therefore, a holistic and multidisciplinary

Expert consensus and recommendations
Epidemiology
● Pay attention to the extensive damage of cognitive function caused by long course COVID-19
● Clinicians carry out cognitive evaluation after COVID-19 infection
Clinical manifestation and diagnosis
● Consider diagnosing PCCD if symptoms of cognitive impairment appear after COVID-19, and improve the diagnosis via brain imaging, cognitive assessment and laboratory tests
● Follow up COVID-19 patients within 6 weeks or more after discharge to monitor the dynamic cognitive changes, and provide consultations when necessary
● Clinicians make a detailed history inquiry for patients with cognitive impairment during COVID-19 to determine the factors for aggravation, so as to give targeted treatment
Risk factors
● Strengthen the identification of risk factors for cognitive impairment of long course COVID-19, and effectively control the risk factors as far as possible
Treatment and management
● Strengthen clinical studies of non-drug treatment of PCCD
● Patients carry out moderate physical activities at home according to their own conditions during the isolation period
● Promote healthy and diversified diet (such as Mediterranean diet)
● Strengthen social activities, and medical and community service organizations provide patients with telephone support hotline and self-help guidance
● Advocate frequent cognitive training for the elderly at high risk of cognitive impairment during long course COVID
● Follow the regular sleep–wake cycle and properly conduct activities conducive to sleep
● Pay attention to people's mental health during COVID-19 and actively provide professional psychological consultation
● The society cooperate in various ways to provide mental health support for dementia patients and their caregivers

Table 1: **Recommendations for the diagnosis and management of PCCD.**

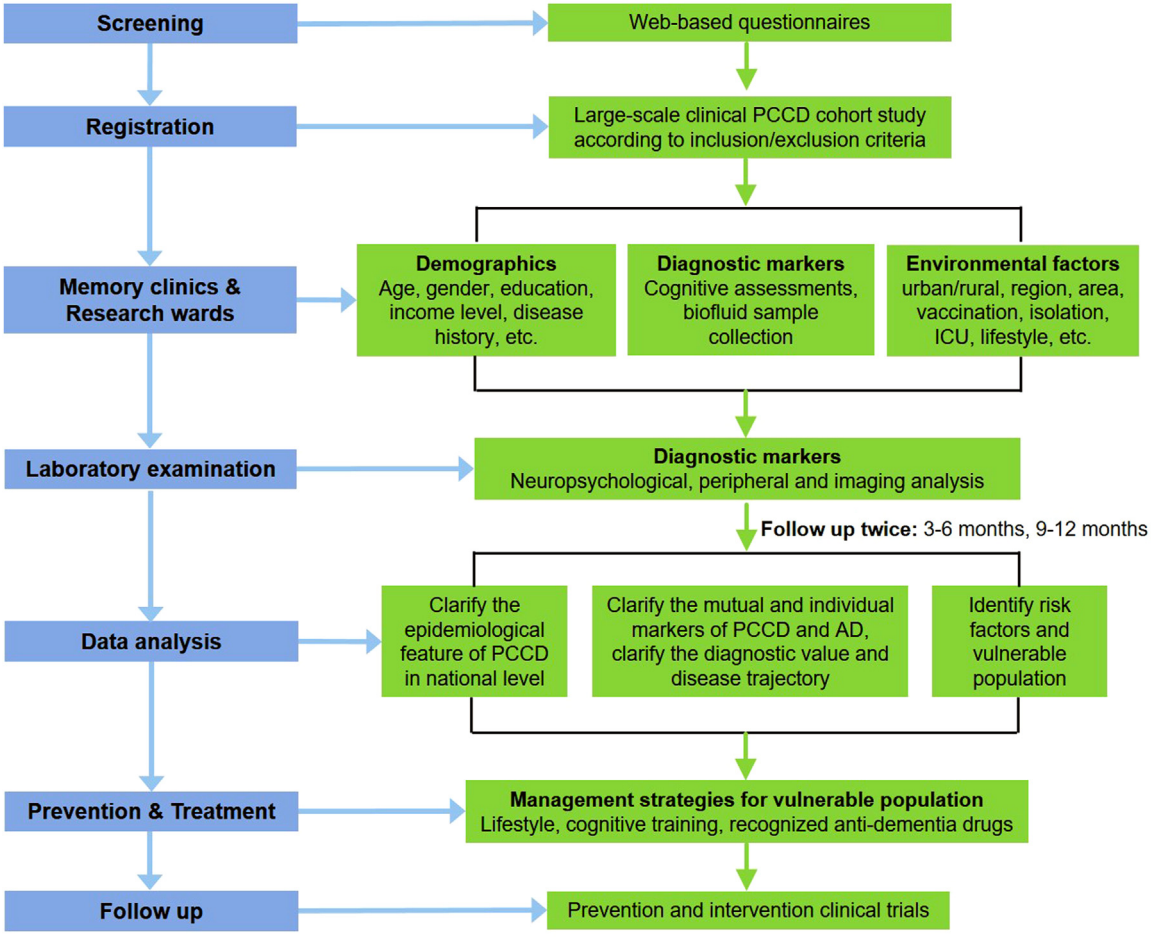

Fig. 2: **Research recommendation framework in high risk population.**

Panel 1: **Search strategy and selection criteria.**

References were identified by searches of PubMed between January 1, 2000 and January 25, 2023, and from relevant articles. We used the search terms of "long COVID", "post-COVID", "COVID long-haulers", "SARS-CoV-2", "cognitive dysfunction", "cognition", "brain fog", "vulnerable", "epidemiology", "risk factors". The final reference list was generated on the basis of relevance to the topics covered in this manuscript. For the cohort studies, we have only included studies with the sample size of more than 1000 subjects. For the clinical trials, we have searched clinicaltrials.gov website to include only clinical trials with sample size of more than 100 subjects, that would provide evidence of efficacy for drugs with the highest chance of becoming available for clinical use.

approach should be supported, including setting targeted, achievable goals and implementing validated screening tools.[34] In response to the limited PCCD data in the literature, Chinese experts have reached consensus on the diagnosis and management of PCCD[107] and issue key recommendations that are summarized in Table 1.

Moreover, Chinese experts have formed a research paradigm called the "cognitive unit", which integrates memory clinics, research wards, and laboratories to study the mechanisms, diagnostic markers, and management of dementia-related cognitive disorders.[108] It is important to focus on vulnerable populations with potential high-risk factors for the development of PCCD. For example, it has been recommended that appropriate rehabilitation should be started in the ICU as soon as sedation permit and clinical stability is achieved to prevent the long-term consequences of post-COVID conditions. Early mobilization improves functional, cognitive, and respiratory conditions in patients with severe disease in the ICU and may shorten hospital stay.[109] Based on this consensus and many literature reports, and following discussion, a research recommendation framework for populations vulnerable to PCCD has been developed (Fig. 2). We hope that this recommendation framework can help initiate more international collaborations, raise the awareness of clinicians and the public about this syndrome, improve prompt diagnosis and treatment, and standardize the management of PCCD, particularly in vulnerable populations.

Conclusions and future perspectives

There has been a gradual increase in the number of reports of PCCD, which seriously affects the quality of life of people infected with COVID-19. We propose establishing a global neurological COVID-19 registry, database, and surveillance system to generate useful data for the identification of vulnerable populations. We also suggest developing standardized PCCD diagnostic and treatment criteria and guidelines to provide a rational basis for the diagnosis and treatment of individuals vulnerable to PCCD and a greater focus on vulnerable populations by promoting appropriate public health and management systems in the future.

Contributors

JJ and MQ designed the framework of the manuscript. XW and MG collected and collated most of the data. MQ, XW, and MG wrote the manuscript. MQ, XW, and MG created the table. MQ created the figures. JJ, QW and YL participated in the critical revision of the manuscript for important intellectual content. All the authors reviewed and approved the final manuscript.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100836.

References

1 Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017–1032.
2 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(7907):697–707.
3 Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022;28(5):657–666.
4 Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. 2021;11(3):e048391.
5 Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22(4):e102–e107.
6 Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601–615.
7 Crook H, Raza S, Nowell J, Young M, Edison P. Long covid-mechanisms, risk factors, and management. *BMJ*. 2021;374:n1648.
8 Monje M, Iwasaki A. The neurobiology of long COVID. *Neuron*. 2022;110(21):3484–3496.
9 Fernandez-Castaneda A, Lu P, Geraghty AC, et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell*. 2022;185(14):2452–2468.e16.
10 Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature*. 2021;595(7866):283–288.
11 Meng M, Zhang S, Dong X, et al. COVID-19 associated EBV reactivation and effects of ganciclovir treatment. *Immun Inflamm Dis*. 2022;10(4):e597.
12 Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med*. 2022;28(11):2406–2415.
13 Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306–1316.
14 Thakur KT, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain*. 2021;144(9):2696–2708.

15 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;101:93–135.
16 Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268–2270.
17 Matias-Guiu JA, Herrera E, Gonzalez-Nosti M, et al. Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach. *Psychiatry Res*. 2023;319:115006.
18 Hugon J, Msika EF, Queneau M, Farid K, Paquet C. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. *J Neurol*. 2022;269(1):44–46.
19 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 Neurol Sci*. 2022;434:120162.
20 Shimohata T. Neuro-COVID-19. *Clin Exp Neuroimmunol*. 2022;13(1):17–23.
21 Diez-Cirarda M, Yus M, Gomez-Ruiz N, et al. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. *Brain*. 2022;146:214.
22 Venkataramani V, Winkler F. Cognitive deficits in long covid-19. *N Engl J Med*. 2022;387(19):1813–1815.
23 Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1,284,437 patients. *Lancet Psychiatry*. 2022;9:815.
24 Liu YH, Chen Y, Wang QH, et al. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China: a longitudinal cohort study. *JAMA Neurol*. 2022;79(5):509–517.
25 Zeng N, Zhao YM, Yan W, et al. A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action. *Mol Psychiatry*. 2023;28(1):423–433.
26 Crivelli L, Palmer K, Calandri I, et al. Changes in cognitive functioning after COVID-19: a systematic review and meta-analysis. *Alzheimers Dement*. 2022;18(5):1047–1066.
27 Becker JH, Lin JJ, Doernberg M, et al. Assessment of cognitive function in patients after COVID-19 infection. *JAMA Netw Open*. 2021;4(10):e2130645.
28 Miskowiak KW, Johnsen S, Sattler SM, et al. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. *Eur Neuropsychopharmacol*. 2021;46:39–48.
29 Liu W, Gauthier S, Jia J. Alzheimer's disease current status and perspective. *Sci Bull*. 2022;67:2494.
30 Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, et al. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: a multicenter study. *J Infect*. 2021;83(2):237–279.
31 Liu YH, Wang YR, Wang QH, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol Neurodegener*. 2021;16(1):48.
32 Group PCC. 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(8):761–775.
33 Asadi-Pooya AA, Akbari A, Emami A, et al. Long COVID syndrome-associated brain fog. *J Med Virol*. 2022;94(3):979–984.
34 *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. London: National Institute for Health and Care Excellence (NICE); 2020.
35 Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021;372:n136.
36 Petersen EL, Gossling A, Adam G, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: the Hamburg City Health Study COVID programme. *Eur Heart J*. 2022;43(11):1124–1137.
37 Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699.
38 Blazhenets G, Schroeter N, Bormann T, et al. Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients. *J Nucl Med*. 2021;62(7):910–915.
39 Delgado-Alonso C, Valles-Salgado M, Delgado-Alvarez A, et al. Cognitive dysfunction associated with COVID-19: a comprehensive neuropsychological study. *J Psychiatr Res*. 2022;150:40–46.
40 Garcia-Sanchez C, Calabria M, Grunden N, et al. Neuropsychological deficits in patients with cognitive complaints after COVID-19. *Brain Behav*. 2022;12(3):e2508.
41 Whiteside DM, Basso MR, Naini SM, et al. Outcomes in post-acute sequelae of COVID-19 (PASC) at 6 months post-infection Part 1: cognitive functioning. *Clin Neuropsychol*. 2022;36(4):806–828.
42 Calabria M, Garcia-Sanchez C, Grunden N, et al. Post-COVID-19 fatigue: the contribution of cognitive and neuropsychiatric symptoms. *J Neurol*. 2022;269(8):3990–3999.
43 He D, Yuan M, Dang W, et al. Long term neuropsychiatric consequences in COVID-19 survivors: cognitive impairment and inflammatory underpinnings fifteen months after discharge. *Asian J Psychiatr*. 2023;80:103409.
44 Zhou H, Lu S, Chen J, et al. The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res*. 2020;129:98–102.
45 Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. *eClinicalMedicine*. 2021;39:101044.
46 Frontera JA, Boutajangout A, Masurkar AV, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-COVID subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. *Alzheimers Dement*. 2022;18(5):899–910.
47 Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain*. 2021;144(4):1263–1276.
48 Lu Y, Li X, Geng D, et al. Cerebral micro-structural changes in COVID-19 patients–an MRI-based 3-month follow-up study. *eClinicalMedicine*. 2020;25:100484.
49 Caroli A, Capelli S, Napolitano A, et al. Brain diffusion alterations in patients with COVID-19 pathology and neurological manifestations. *Neuroimage Clin*. 2023;37:103338.
50 Meyer PT, Hellwig S, Blazhenets G, Hosp JA. Molecular imaging findings on acute and long-term effects of COVID-19 on the brain: a systematic review. *J Nucl Med*. 2022;63(7):971–980.
51 Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–562.
52 Thijssen EH, La Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol*. 2021;20(9):739–752.
53 Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *eClinicalMedicine*. 2021;31:100683.
54 Ortona E, Malorni W. Long COVID: to investigate immunological mechanisms and sex/gender related aspects as fundamental steps for tailored therapy. *Eur Respir J*. 2022;59(2):2102245.
55 Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study. *Eur Respir J*. 2022;59(2):2101341.
56 Almeida-Meza P, Steptoe A, Cadar D. Markers of cognitive reserve and dementia incidence in the English Longitudinal Study of Ageing. *Br J Psychiatry*. 2021;218(5):243–251.
57 Politi J, Martín-Sánchez M, Mercuriali L, et al. Epidemiological characteristics and outcomes of COVID-19 cases: mortality inequalities by socio-economic status, Barcelona, Spain, 24 February to 4 May 2020. *Euro Surveill*. 2021;26(20):2001138.
58 Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*. 2020;11(7):995–998.
59 Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552–555.
60 Steardo L, Steardo L Jr, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol*. 2020;229(3):e13473.
61 Kuo CL, Pilling LC, Atkins JL, et al. APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort. *J Gerontol A Biol Sci Med Sci*. 2020;75(11):2231–2232.
62 Ostendorf BN, Patel MA, Bilanovic J, et al. Common human genetic variants of APOE impact murine COVID-19 mortality. *Nature*. 2022;611(7935):346–351.

63 Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*. 2020;581(7806):71–76.
64 Kurki SN, Kantonen J, Kaivola K, et al. APOE epsilon4 associates with increased risk of severe COVID-19, cerebral microhaemorrhages and post-COVID mental fatigue: a Finnish biobank, autopsy and clinical study. *Acta Neuropathol Commun*. 2021;9(1):199.
65 Yazdanpanah N, Rezaei N. Autoimmune complications of COVID-19. *J Med Virol*. 2022;94(1):54–62.
66 Izcovich A, Siemieniuk RA, Bartoszko JJ, et al. Adverse effects of remdesivir, hydroxychloroquine and lopinavir/ritonavir when used for COVID-19: systematic review and meta-analysis of randomised trials. *BMJ Open*. 2022;12(3):e048502.
67 Borah P, Deb PK, Chandrasekaran B, et al. Neurological consequences of SARS-CoV-2 infection and concurrence of treatment-induced neuropsychiatric adverse events in COVID-19 patients: navigating the uncharted. *Front Mol Biosci*. 2021;8:627723.
68 Kotfis K, van Diem-Zaal I, Williams Roberson S, et al. The future of intensive care: delirium should no longer be an issue. *Crit Care*. 2022;26(1):200.
69 Neelamegam M, Zgibor J, Chen H, et al. The effect of opioids on the cognitive function of older adults: results from the Personality and Total Health through life study. *Age Ageing*. 2021;50(5):1699–1708.
70 Kumar A, Chattopadhyay A, Gupta S. Neuropsychiatric manifestation of the drugs used in the treatment of SARS-2-CoV-2019 (COVID-19) infection and their management: an overview and practice implications. *Asian J Psychiatr*. 2022;73:103101.
71 Levaillant M, Wathelet M, Lamer A, Riquin E, Gohier B, Hamel-Broza JF. Impact of COVID-19 pandemic and lockdowns on the consumption of anxiolytics, hypnotics and antidepressants according to age groups: a French nationwide study. *Psychol Med*. 2021:1–7.
72 Velayudhan L, Aarsland D, Ballard C. Mental health of people living with dementia in care homes during COVID-19 pandemic. *Int Psychogeriatr*. 2020;32(10):1253–1254.
73 Simonetti A, Pais C, Jones M, et al. Neuropsychiatric symptoms in elderly with dementia during COVID-19 pandemic: definition, treatment, and future directions. *Front Psychiatry*. 2020;11:579842.
74 Manca R, De Marco M, Venneri A. The impact of COVID-19 infection and enforced prolonged social isolation on neuropsychiatric symptoms in older adults with and without dementia: a review. *Front Psychiatry*. 2020;11:585540.
75 Chen ZC, Liu S, Gan J, et al. The impact of the COVID-19 pandemic and lockdown on mild cognitive impairment, Alzheimer's disease and dementia with Lewy bodies in China: a 1-year follow-up study. *Front Psychiatry*. 2021;12:711658.
76 Bethell J, Aelick K, Babineau J, et al. Social connection in long-term care homes: a scoping review of published research on the mental health impacts and potential strategies during COVID-19. *J Am Med Dir Assoc*. 2021;22(2):228–237.e25.
77 Zhou J, Liu C, Sun Y, Huang W, Ye K. Cognitive disorders associated with hospitalization of COVID-19: results from an observational cohort study. *Brain Behav Immun*. 2021;91:383–392.
78 Wang H, Li T, Barbarino P, et al. Dementia care during COVID-19. *Lancet*. 2020;395(10231):1190–1191.
79 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430–436.
80 Godeau D, Petit A, Richard I, Roquelaure Y, Descatha A. Return-to-work, disabilities and occupational health in the age of COVID-19. *Scand J Work Environ Health*. 2021;47(5):408–409.
81 Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. 2020;7(7):611–627.
82 Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: systematic review of the current evidence. *Brain Behav Immun*. 2020;89:531–542.
83 Ward CF, Figiel GS, McDonald WM. Altered mental status as a novel initial clinical presentation for COVID-19 infection in the elderly. *Am J Geriatr Psychiatry*. 2020;28(8):808–811.
84 Nehme M, Braillard O, Salamun J, et al. Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2. *J Gen Intern Med*. 2022;37(6):1585–1588.
85 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(19).
86 Marshall M. The four most urgent questions about long COVID. *Nature*. 2021;594(7862):168–170.
87 Liu Q, Mak JWY, Su Q, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut*. 2022;71(3):544–552.
88 Ancona G, Alagna L, Alteri C, et al. Gut and airway microbiota dysbiosis and their role in COVID-19 and long-COVID. *Front Immunol*. 2023;14:1080043.
89 Jia L, Quan M, Fu Y, et al. Dementia in China: epidemiology, clinical management, and research advances. *Lancet Neurol*. 2020;19(1):81–92.
90 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.
91 Theoharides TC, Cholevas C, Polyzoidis K, Politis A. Long-COVID syndrome-associated brain fog and chemofog: luteolin to the rescue. *Biofactors*. 2021;47(2):232–241.
92 Tang Y, Xing Y, Zhu Z, et al. The effects of 7-week cognitive training in patients with vascular cognitive impairment, no dementia (the Cog-VACCINE study): a randomized controlled trial. *Alzheimers Dement*. 2019;15(5):605–614.
93 Sikkes SAM, Tang Y, Jutten RJ, et al. Toward a theory-based specification of non-pharmacological treatments in aging and dementia: focused reviews and methodological recommendations. *Alzheimers Dement*. 2021;17(2):255–270.
94 Society PaMHBoCG, Association AsDBoCEHC, Association GPGoPBoCM, Association GPWGoPAoCMD, Health PCoMHftEoCAoM. Expert advice on mental health and psychosocial support for patients with cognitive impairment and their caregivers during the prevention and control of COVID-19. *Chin J Psychiatr*. 2020;53(2):89–94.
95 Jung AR, Kim D, Park EA. Cognitive intervention using information and communication Technology for older adults with mild cognitive impairment: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2021;18(21):11535.
96 Cicerone KD, Goldin Y, Ganci K, et al. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Phys Med Rehabil*. 2019;100(8):1515–1533.
97 Santana K, Franca E, Sato J, et al. Non-invasive brain stimulation for fatigue in post-acute sequelae of SARS-CoV-2 (PASC). *Brain Stimul*. 2023;16(1):100–107.
98 Oliver-Mas S, Delgado-Alonso C, Delgado-Alvarez A, et al. Transcranial direct current stimulation for post-COVID fatigue: a randomized, double-blind, controlled pilot study. *Brain Commun*. 2023;5(2):fcad117.
99 Thams F, Antonenko D, Fleischmann R, et al. Neuromodulation through brain stimulation-assisted cognitive training in patients with post-COVID-19 cognitive impairment (Neuromod-COV): study protocol for a PROBE phase IIb trial. *BMJ Open*. 2022;12(4):e055038.
100 Cheung T, Ho YS, Yeung JW, et al. Effects of transcranial pulse stimulation (TPS) on young adults with symptom of depression: a pilot randomised controlled trial protocol. *Front Neurol*. 2022;13:861214.
101 Jimenez-Pavon D, Carbonell-Baeza A, Lavie CJ. Physical exercise as therapy to fight against the mental and physical consequences of COVID-19 quarantine: special focus in older people. *Prog Cardiovasc Dis*. 2020;63(3):386–388.
102 Angelidi AM, Kokkinos A, Katechaki E, Ros E, Mantzoros CS. Mediterranean diet as a nutritional approach for COVID-19. *Metabolism*. 2021;114:154407.
103 Jolliffe DA, Camargo CJ, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2021;9(5):276–292.
104 Altena E, Baglioni C, Espie CA, et al. Dealing with sleep problems during home confinement due to the COVID-19 outbreak: practical recommendations from a task force of the European CBT-I Academy. *J Sleep Res*. 2020;29(4):e13052.
105 Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263.

106 Jia J, Zhao T, Liu Z, et al. Association between healthy lifestyle and memory decline in older adults: 10 year, population based, prospective cohort study. *BMJ*. 2023;380:e072691.
107 Expert Group CIaDCoCMDA, Jia JP. Consensus on diagnosis, treatment and management of cognitive impairment after COVID-19. *Sci Sin Vitae*. 2022;52(12):1905–1914.
108 Jia JP, Gong M. ["Cognitive unit" is a diagnosis and treatment pattern suitable for the clinical practice of cognitive disorders in China]. *Zhonghua Yi Xue Za Zhi*. 2020;100(9):645–647.
109 Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *J R Soc Med*. 2021;114(9):428–442.