For the purposes of this study, subjective cognitive decline is defined as a self-perceived cognitive decline in cognitively normal people [[31](https://pmc.ncbi.nlm.nih.gov/articles/PMC11262122/#b31-2712-7672_2022_3_3_45)]. In line with this definition the sample was divided in two subgroups: those who complained about decreased cognitive functions and those who had no cognitive complaints.

**Literature**

Birle et al., 2020

Bland et al., 2024

Cambridge Cognition, 2015

Ceban et al., 2022

Eysenck & Brysbaert, 2018

Kwan et al., 2024

Liu, Wang, Xin, Jiang & Meng, 2024

Pais, Ruano, Carvalho & Barros, 2020

Schild, Scharfenberg, Kirchner et al., 2023).

WHO, 2021

Davids et al., 2021

**Other factors**

**The role of psychological factors in SCD**

Zamarian et al. (2024) discovered that SCD in everyday situations can be better explained by elevated anxiety and fatigue levels than by objective cognitive performance. In addition to anxiety (Almeria, Cejudo, Sotoca, Deus & Krupinski, 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) and fatigue (Bland et al., 2024; Delgado-Alonso et al., 2023; Zamarian et al., 2024), sleep disturbances (Zamarian et al., 2024) and depressive symptoms (Almeria et al., 2020; Brück et al., 2019; Costas-Carrera et al., 2022; Hill et al., 2016; Zamarian et al., 2024) have been found to be associated with subjective but not objective cognitive decline/impairment (Henneghan, Lewis, Gill & Kesler, 2022). Conversely, objective cognitive function has been found to be more closely related to perceived stress (Bland et al., 2024).

These findings highlight the intricate and often discordant relationship between subjective and objective cognitive performance, as well as their complex interactions with psychological factors such as anxiety, fatigue, sleep disturbances, and depressive symptoms. This complexity is particularly relevant in the context of **PCS, where many patients report persistent cognitive impairment despite normal objective cognitive test results.**

Patients with cognitive impairment within PCS often experience other psychiatric and health-related symptoms. However, results on associations with anxiety, depression, sleep, and fatigue are inconsistent (stolen)

[Gomzyakova](https://pubmed.ncbi.nlm.nih.gov/?term=%22Gomzyakova%20N%22%5BAuthor%5D): No significant correlations were found between the MoCA score and the levels of anxiety and depression according to HADS (p >0.05) among those who complained of memory and attention loss. However, no significant correlations were found between the MoCA scores and the anxiety and depression levels. Group with subjective cognitive decline had higher levels of depression and anxiety. According to the obtained results, subjective complaints about cognitive dysfunction in patients of outpatient units during the pandemic are mainly caused by the emotional state rather than the objective decline in cognitive functions.

Deng et al. (2021): Our results showed that the overall prevalence of depression, anxiety, and sleep disturbances among COVID-19 patients is 45%, 47%, and 34%, respectively.

Almeria et al. (2020): Anxiety and depression were associated with cognitive complaints, although no impairment was evidenced on neuropsychological tests in these patients.

Premraj et al. (2022): Fatigue, cognitive dysfunction (brain fog, memory issues, attention disorder) and sleep disturbances were the most prevalent features of neurological/neuropsychiatric post-COVID-19 syndrome, all identified in almost one third of patients three months after the onset of acute COVID-19 illness.

Badinlou et al. (2022): Results showed significant rates of significant depression (55%), anxiety (20.5%), and insomnia (60.9%) in our sample. All post-COVID impairments and fatigue dimensions were significantly associated with depression, anxiety, and insomnia. In conclusion, the current study outlines that individuals with a history of probable or confirmed SARS CoV-2 infection/infections are more likely to suffer from mental health problems.

Damiano et al. (2022): The present study provides original data highlighting the high prevalence of neuropsychiatric impairment in the long-term outcome of moderate or severe forms of SARS-CoV-2 infection. we found a high prevalence of psychiatric and cognitive impairments following SARS-CoV-2 infection, specifically common mental disorders, depression, anxiety, PTSD, executive and attentional cognitive impairments. These deficits seem unrelated to psychosocial stressors or clinical risk factors documented in the acute-stage of COVID-19.

Holdsworth et al. (2022): 69% reported ≥3 ongoing symptoms. Shortness of breath (61%), fatigue (54%) and cognitive problems (47%) were the most frequent symptoms, 17% met criteria for anxiety and 24% depression. 67% remained below pre-COVID performance status at 24 weeks. A specific, focal cognitive deficit was identified in those with ongoing symptoms of fatigue, poor concentration, poor memory, low mood, and anxiety. Symptoms of low mood, anxiety, and sleep disturbance were all described by more than one quarter of all patients.

Henneghan et al. (2022): Anxiety, depressive symptoms, fatigue, and sleep disturbance were not associated with objective cognitive impairment but were related to subjective cognitive impairment (p < 0.001).

**Why relevant to investigate subjective cognitive decline further**

As the aging population grows, the prevalence of individuals experiencing SCD continues to rise (Perez et al., 2024). Not only therefore has it gained increasing attention in recent years, but also due to its potential role as a preclinical marker of cognitive impairment, particularly in the context of neurodegenerative diseases such as Alzheimer’s disease (AD) (Jessen et al., 2014). A meta-analysis of longitudinal studies on SCD with a follow-up period of at least four years estimated that 27% of individuals with SCD progressed to MCI of 27 %, while 14% developed dementia (Mitchell et al., 2014).

In conclusion, although individuals with SCD perform within normal ranges on neuropsychological tests, they face an increased risk of developing objective cognitive impairment, such as MCI and AD (L i et al., 2022; Numbers et al., 2023; Rivas-Fern´andez et al., 2023). Therefore, identifying early and reliable biomarkers for the detection of SCD is crucial for maintaining cognitive health and delay or prevent its progression to AD (Abdulrab & Heun, 2008).

Research suggests a link between PCS and increased risk of MCI. Bohlken, Weber, Heller, Michalowsky & Kostev (2022) found that patients diagnosed with COVID-19 had a significantly increased risk of MCI – referred to as mild cognitive disease (MCD) in their study – compared to those with other acute upper respiratory infections. Additionally, Schild et al. (2022) objectively confirmed NCD in around 60% of individuals with PCS with SCD in their study. This is why the context of MCI is discussed here.

Zhao et al. (2022): Overall, the findings here show that COVID-19 survivors showed a significant reduction in their ability to sustain attention on a demanding task up to 9 months after COVID-19 infection, along with mild, but significantly worse, episodic memory for up to 6 months.

[Gomzyakova](https://pubmed.ncbi.nlm.nih.gov/?term=%22Gomzyakova%20N%22%5BAuthor%5D): Cognitive impairment is one of the main factors that disrupt daily social functioning and quality of life.

Blackmon et al. (2022): Neurocognitive complaints were common in patients recovering from COVID-19 in this series, regardless of disease severity; however, the rate of objective impairment was higher in hospitalized patients. These results emphasize the importance of assessing both subjective and objective complaints in determining prevalence of cognitive impairment in recovering patients and research participants.

Premraj et al. (2022): The prevalence of neurological and neuropsychiatric symptoms of post-COVID-19 syndrome were higher when assessed at or beyond six months (long-term) than when assessed between three and six months (mid-term). Fatigue, cognitive dysfunction (brain fog, memory issues, attention disorder) and sleep disturbances were the most prevalent features of neurological/neuropsychiatric post-COVID-19 syndrome, all identified in almost one third of patients three months after the onset of acute COVID-19 illness. Interestingly, these symptoms persisted and were even more common long-term (six or more months post infection) than when assessed mid-term (three to six months). Persistent symptoms may arise from a combination of biological and psychological mechanisms. For example, SARS-CoV-2 RNA may remain in brain tissue long-term, worsening neuronal loss over time [4,34–36]. Moreover, innate immune cell entry secondary to blood brain barrier dysfunction may prolong neuro-inflammation [34,37].

In their recent study, [Schild et al. (2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c73)) highlighted the challenges encountered in assessing cognitive deficits in patients with PCS necessitating a comprehensive and individualized analysis of both subjective complaints and objective impairment as well as their discrepancies. However, some sequelae of intensive care treatment may still escape these testing approaches, and certain persistent problems cannot be detected without psychophysiological methods. This suggests encouraging the use of additional neuropsychophysiological methods in specific patient groups.

There is agreement that subjective impairments should be taken seriously, and that changes in experience and behavior not apparent to the clinician should be examined, evaluated, and documented.

Long-term neurological disorders associated with PCS may involve encephalopathy, cerebral dysregulation, and ischemic stroke ([Hingorani et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c34)).

**Biological Mechanisms**

Numerous potential pathomechanisms have been implicated in PCS: these may include the continued presence of viral RNA and proteins and the persistence of inflammatory reactions in important organs, such as the lungs, heart, brain, or vascular system ([Bussani et al., 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c9)) causing thrombosis, micro or macrovascular changes, and, possibly even long-term damage to many kinds of tissue ([Jonigk et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c36)). Moreover, systemic alterations involving metabolism and immune changes, such as hyperinflammation or autoimmune reactions, may be permanent. In those with severe courses of COVID-19, who experience organ and respiratory dysfunction, persistent COVID-19 symptoms have been associated with dysregulated autoimmunity and immunodeficiency ([Garmendia et al., 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c27); [Sotzny et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c79)). Alterations in immune function have been observed in various other viral infections, including Epstein-Barr, Ebola, SARS-CoV-1, and MERS. Anomalies in the activation of immunological pathways have been linked to persistent symptoms over time ([Needham et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c55); [Proal & VanElzakker, 2021](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c65)).

Systemic alterations in transmitter systems have been found, such as the renin-angiotensin-aldosterone system (RAAS) and the Hypothalamic–Pituitary–Adrenal (HPA) axis ([Jensterle et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c35); [Maranduca et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c46)), that are essential in regulating blood pressure and in coordinating inflammatory responses of the body. Specifically, the SARS-CoV-2 virus obstructs the production of angiotensin-converting enzyme type 2 (ACE-2), part of the RAAS system, resulting in disrupted homeostasis ([Méndez-García et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c51)). Furthermore, the dysregulation of the immune system appears to play a central role in persistent changes following COVID-19, termed *Multisystem Inflammatory Syndrome in Children (MIC-S),* among pediatric populations ([Chakraborty et al., 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c12); [P.-I. Lee & Hsueh, 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c41)).

Some authors ([de Melo et al., 2021](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c18); [Käufer et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c38); [Schwabenland et al., 2021](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c75)) have hypothesized that sustained neurocognitive impairments after SARS-CoV-2 infection could be related to these mechanisms, as the latter may have repercussions on cognition or neuropathy. Peripheral inflammatory cytokines may cross the blood-brain barrier and modulate central nervous system (CNS) inflammatory processes resulting in impaired cognitive functioning in animal models ([Lee et al., 2009](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c40); [Marsland et al., 2015](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c47); [Zuliani et al., 2007](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c88)). In humans, abnormally high levels of the C-reactive protein and interleukin-6 have been associated with a decrease in specific cognitive abilities (e. g., spatial reasoning, short-term memory, verbal ability, learning, memory, and executive function) as well as with brain morphological changes in grey and white matter volumes, and hippocampus and cortical surface areas ([Marsland et al., 2015](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c47)).

Long-term neurological disorders associated with PCS may involve encephalopathy, cerebral dysregulation, and ischemic stroke ([Hingorani et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c34)). There may be direct viral damage to the CNS via the binding of the SARS-CoV-2 virus to specific receptors that allow them to pass the blood-brain barrier ([Heneka et al., 2020](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c33)). However, direct invasion into the brain or spinal column is not the most salient mechanism of long-term COVID-19-related changes ([Gerhard et al., 2022](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c28); [Kanberg et al., 2021](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c37)).

Given the extensive range of pathomechanisms involved and the need for clarity in the context of PCS, novel research initiatives have emerged, such as the transdisciplinary international consortium NeuroCOV (<https://www.neurocov.eu/>) and the RECOVER Initiative (Researching COVID to Enhance Recovery) in the United States ([Reese et al., 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c67); [Zhang et al., 2023](https://econtent.hogrefe.com/doi/full/10.1024/1016-264X/a000373#c86)). They are strategically studying the various phenotypes of PCS and specific mechanisms over time, utilizing multiple approaches such as epidemiology, molecular biology, machine learning, and social science.