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Persistent Neurocognitive Problems Related to COVID-19 in Children and Adolescents

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has caused persistent multisystemic symptoms. Data on the long-term effects of coronavirus disease-2019 (COVID-19) in children and adolescents are scarce. Persistent neurocognitive symptoms are important for the functionality of children in daily life. This review assessed the literature regarding the frequency, pathology, risk factors, and prognosis of the long-term neurocognitive effects of COVID-19 in the pediatric population. This review demonstrated that children and adolescents had various persistent neurocognitive problems related to COVID-19. The heterogeneity of studies prevents from drawing firm conclusions, as there were differences between study populations and designs in terms of disease severity and time of assessment. Because the pandemic is a recent event, long-term follow-ups to establish how long cognitive impairment persists after COVID-19 recovery are still impossible.

Keywords: COVID-19, SARS-CoV-2, cognition, children, long-COVID

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a type of coronavirus that has caused a coronavirus disease-2019 (COVID-19) pandemic with significant morbidity and mortality via direct or indirect effects (1). The risks of acquiring and transmitting SARS-CoV-2 tend to increase with age (2). Clinical studies have defined COVID-19 as a multisystemic infection that can affect various systems, such as cardiovascular, hematologic, renal, gastrointestinal, neurologic and hepatobiliary, and endocrinologic (3). Children and/or adolescents tend to generally have a symptomatic but mild COVID-19 course with few requiring intensive care treatment and a very low rate of mortality (1,4,5,6). Most of the children and adolescents with COVID infection in early period of the pandemic were hospitalized and a significant number of them required intensive care unit (ICU) care (6). Despite these generally positive prognostic features of infection, multisystem inflammatory syndrome in children (MIS-C), which is a rare post-infectious hyperinflammatory disorder associated with SARS-CoV-2 and can result in severe organ dysfunction, seems to occur approximately 2-6 weeks after recovery from COVID-19 infection (7). Compared to acute COVID-19, MIS-C has a higher prevalence of neurological but lower prevalence of respiratory symptoms (8). However, it has not been sufficiently revealed what has temporary or permanent effects in children and adolescents when viewed longitudinally.

Clinical studies have shown that COVID-19 could cause several sequelae, including nervous system and neurocognitive impairments, mental health disorders, and fatigue (9,10). To describe post-COVID symptoms or long-term effects of COVID-19, there are many terms in use (such as "long-COVID", "long-haul COVID", "post-COVID-19 syndrome", "chronic COVID syndrome", "post-acute sequelae of COVID-19") (11). While there is no globally accepted terminology, definition, or duration for these terms, the National Institute for Health and Care Excellence defined long-COVID, which is widely used in terminology, as a syndrome including both ongoing symptomatic COVID-19 (signs and symptoms persisting 4-12 weeks from acute COVID-19) and post-COVID-19 syndrome (signs and symptoms persisting ≥12 weeks from acute COVID-19) (2020 COVID-19 rapid guideline: Managing the long-term effects of COVID-19) (12). The persistent various multisystemic symptoms characterize long-COVID. The literature on the long-term symptoms of COVID-19 in children and adolescents compared with adults is limited (13). The few studies conducted on children and adolescents demonstrated the same symptoms of long-COVID reported in the adult population (14). The prevalence of long-COVID in children and adolescents, as defined by the presence of one or more symptoms more than four weeks following a SARS-CoV-2 infection, was 25.24%, with a much lower prevalence in studies including the control group (15,16) and with lower frequency of persistent sequelae in children/adolescents than in adults (17,18). Also, persistent symptoms seem higher among children diagnosed with MIS-C, indicating the importance of the COVID severity (19). In a recent review study of Izquierdo-Pujol et al. (18), it has been reported that 94% children/adolescents are symptomatic (compared with 99% of adults) and that the SARS-CoV-2 infection is mild in 99% of cases in children/adolescents (compared with 81% in adults). Also, they reported that post-COVID-19 condition was seen in 1-30% children/adolescents and 10-61% adults (18). This difference between two groups may be due to the lower frequency of SARS-CoV-2 infection and to the lower impact of the infection itself in children and adolescents (18). In children and adolescents, recent review studies have reported fatigue (11-20%), lack of concentration, and muscle pain as the most common post-COVID-19 symptoms (18) and mood symptoms (16%), fatigue (10%), and sleep disorders (8%) as the most prevalent clinical manifestations of long-COVID (15).

Cognitive function is consequential for children's functionality at school and at home. Cognitive abilities are substantial to children's learning capacity. The fundamental knowledge and skills acquired during early childhood set the course for learning in the following decades, if not for the whole life. Both social skills and academic performance predict children's possibility of being gainfully employed later in life (20). In children and adolescents, the data on the neurocognitive effects of COVID-19 are scarce, while a recent review has exhibited cognitive (memory, attention, and executive functions) impairments in adults with previous COVID-19 infection (21). This review investigates the literature about the neurocognitive effects of COVID-19 in the pediatric population. Also, possible neuropathological mechanisms and risk factors related to neurocognitive symptoms are discussed.

Neurocognitive Problems Related to COVID-19 in Children and Adolescents

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines six key domains of neurocognitive function, and each of these has subdomains: Complex attention (sustained attention, divided attention, selective attention, processing speed), executive function (planning decision-making, working memory, responding to feedback inhibition, flexibility), learning and memory (free recall, cued recall recognition, memory, semantic and

autobiographical long-term memory, implicit learning), language (object naming, word ending fluency, grammar, syntax receptive language), perceptual-motor function (visual perception, visuoconstructional reasoning, perceptual-motor coordination), and social cognition (recognition of emotions theory of mind insight) (22). For this part of this review article, literature published in English between January 2020 and May 2022 was searched on May 30, 2021 in PubMed and Google Scholar databases by two reviewers. Children and adolescents aged ≤18 who were diagnosed with COVID-19 with real-time polymerase chain reaction (RT-PCR) were included. We included patients with neurocognitive symptoms defined in DSM-5 following COVID-19. During scanning, the following keywords were used: (Coronavirus or COVID-19 or SARS-CoV-2 or long-COVID) and (infant or kids or young or children or adolescent or pediatric) and (cognition or neurocognition or cognitive or neurocognitive or cognitive decline or cognitive deficit or cognitive impairment or concentration or attention or attention deficit or processing speed or learning or memory or memory impairment or executive function or language or verbal fluency or perception or perceptual or visuospatial or orientation or confusion or delirium). We also scanned references of found articles. The studies found were categorized as author's name, study year, country of study, a type of article, collection mode, age range/mean age, sex, disease severity, time of assessment, neurocognitive test, and results. We assessed the cases according to the types of neurocognitive symptoms. The review and/or meta-analysis studies were also used for the content of this manuscript. We also examined symptoms affecting cognitive functions, for instance, sleep issues, fatigue, dizziness, and headache.

Nineteen studies were included in this part of the review. Most of the studies consisted of data obtained via online or electronic surveys or questionnaires. The time of assessment after diagnosis of COVID-19 was varying approximately 28-324 days. No evaluation based on neurocognitive tests was found in these studies. Characteristics of the included studies are demonstrated in Table 1.

Cognition/Neurocognition

Studies investigating cognitive/neurocognitive difficulties have reported different results, with a wide frequency range. Cognitive difficulties were found to be 10% in the evaluation made 1-3 months after the onset of the disease in children aged 8-15 years with a diagnosis of COVID-19 who were hospitalized (23). Another study, including children aged 0-18 who were hospitalized but evaluated longer than four months after the hospitalization, reported the frequency of cognitive difficulties as 5.4% (24). Similarly, in two meta-analyses

conducted on children and adolescents, cognitive difficulties were reported as 6.3% and 3%, respectively (11,15). In another meta-analysis including pediatric COVID-19 patients with MIS-C, neurocognitive symptoms such as headache, irritability, lethargy, or visual change were reported in 31.8% (25). These differences suggest that higher frequency may be associated with shorter follow-up time, disease severity, and possibly narrow age range, as symptoms may resolve over time and symptom persistence may increase with age. Lower prevalence of cognitive symptoms was associated with higher study quality and longer follow-up duration (11). Moreover, Blankenburg et al. (26) did not reveal any significant differences between seropositive and seronegative students regarding the prevalence of any neurocognitive symptom. Conversely, when compared with the controls, cognitive sequelae were significantly associated with the SARS-CoV-2 infection (27). The prevalence of persistent cognitive complaints seems to increase considerably with age (27).

Attention, Concentration and Executive Functions

In this review, Roge et al. (27) reported impaired attention in 16.9% of the patients who had no MIS-C and were evaluated 1-6 months after acute COVID-19. Also, they stated that inability to focus their attention (24.1%) was one of the most reported persistent symptoms in adolescents. Additionally, from the same country, attention problems were declared less frequent in hospitalized children evaluated 1-3 months after the onset of the disease (23). Limited results of these two studies suggest that attention problems may be seen or noticed in older children later during post-COVID period. However, it is seen that most of the studies have found concentration difficulties ranging between 0.4-80% (13,16,27,28,29,30,31,32,33,34,35). Compared to SARS-CoV-2 positive peers, children and adolescents in the control group may experience more concentration difficulties, as reported by Borch et al. (16). Independent of the disease, compared to pre-pandemic, poorer concentration, attention, task engagement and persistence, and greater impulsivity during the pandemic were found, with evidence of possible mild impacts (36). Interestingly, children with ADHD had no notable changes in their ability to pay attention pre-pandemic to pandemic (36). We did not find any study investigating the impact of SARS-CoV-2 infection on executive function in children and adolescents.

Language Functions

The effect of COVID infection on language problems within neurocognitive functions in children and adolescents has been less studied. Parents of children and adolescents

with SARS-CoV-2 infection reported different language/speech dysfunctions including word repetition (12.1%) (32), trouble finding the right words (32), speech disturbances (1.3%) (27), and trouble forming words (0.4%) (37). In line with these findings, in a meta-analysis study, speech disturbances were declared as 0.4% in children and adolescents with SARS-CoV-2 infection (15). Also, Buonsenso et al. (32) showed that the word repetition was seen most in 3-6 months after SARS-CoV-2 infection and unassociated with age and sex.

Memory and Learning

In one of the first published studies, a five-patient case series evaluated 6-8 months after clinical diagnosis of COVID-19 identified that three of five children displayed memory loss (13). In other studies, memory problems after infection were considerably investigated in children and adolescents, showing memory loss (13%) (30), memory impairment (18%, 10%) (27,33), short-term memory issues (32.7%) (32) and loss (0.6%) (37), difficulty remembering information (45.9%) (32), difficulty in doing everyday tasks (40%) (32), difficulty processing information (32.7%) (32), and forgetfulness (1.5%) (37). Despite no further analysis, and when characteristics of these studies have been considered, these results related to memory dysfunctions seem to present mainly in older ages and every phase of post-COVID period, leading more cases with these problems to accumulate. Despite the absence of studies investigating learning deficits after SARS-CoV-2 infections, both acute and chronic attention and memory impairments related to hippocampal and cortical damage and neuroinflammation in brain areas essential for fine motor function, memory and learning may indicate some learning deficits in both children and adults (38,39).

Perceptual-motor Function and Social Cognition

Generally, studies have not reported any perceptual-motor and social cognitive difficulties directly related to SARS-CoV-2 infection in children and adolescents. However, brain areas having roles in perception, motor function, and social cognition may be damaged, as reported in adult studies (38), suggesting difficulties in these neurocognitive domains after infection in the pediatric population.

Other Neurocognitive Symptoms (Confusion, Orientation, Delirium, Hallucination)

In this review, some studies investigated these variables rarely seen in children and adolescents. Confusion was reported in 4% of children aged 0-16 at 1 month (37), 7.3% of adolescents at least 3 months (40), and 0.41% of children and adolescents at least 5 months (28) after SARS-CoV-2 infection confirmed with the test, suggesting increased risk with

older age and in early phase of the post-COVID period. Also, Stephenson et al. (40) found that 7.3% of adolescents with positive test for SARS-CoV-2 reported disorientation at least 3 months after infection. Delirium, which is manifested by cognitive findings, is a rarely reported neurological condition due to COVID-19 infection in children and adolescents (41). Its development is closely related to the severity of the disease (41). The observation that cases with delirium secondary to an acute COVID-19 infection showed improvement after several weeks may lead to thinking of this problem as a long-COVID symptom (42). Also, it is claimed that delirium may be associated with long-term cognitive complications (43). Similar to very low frequencies of other neurocognitive symptoms, only one study by Zavala et al. (37) found that hallucination was reported as frequent as 0.2% among the 472 laboratory-confirmed SARS-CoV-2 RT-PCR-positive patients aged 0-16.

Pathological Mechanisms of Neurocognitive Problems

Despite clear evidence that post-COVID-19 condition is pathological in both children and adults, the pathological mechanisms of this disease remain unknown. The one or multiple organ/tissue damage, medical interventions, exacerbated immune response, viral persistence in certain tissues, olfactory neuroepithelium/sensory neurons infection, autoantibodies (particularly being generated according to the severity of the disease), re-activation of neurotrophic pathogens such as herpes viruses under conditions of COVID-19 immune dysregulation, SARS-CoV-2 interactions with host microbiome/virome communities, clotting/coagulation issues, dysfunctional brainstem/vagus nerve signaling, and ongoing activity of primed immune cells have been suggested as potential pathophysiological mechanisms of post-COVID-19 or long-COVID-19 symptoms (18,44). The exacerbated immune response may lead to delay or defects in the resolution of inflammation, which may explain the persistence of symptoms (45). The resolution of inflammation seems to be delayed, particularly in symptomatic cases and persistent symptoms decrease around 6 months post-infection (45). However, early postmortem studies revealed no evidence of CNS damage directly caused by COVID-19 (38,46). When examining genetic susceptibility to the symptoms of post-COVID-19 until March 2022, no studies were found that explored the potential link among them (18). A recent study conducted on seropositive adult patients with asymptomatic/mild disease reported that rs11385942 polymorphism of the leucine zipper transcription factor like 1 gene (coding a protein involved in the primary cilia function and the immunological synapse between T-cells and antigen-presenting cells) was

associated with disease severity but not with long-term symptoms (47). Moreover, Blankenburg et al. (48) reported no significant differences between the symptoms of the SARS-CoV-2- seropositive and seronegative children, suggesting that most of the symptoms are due to lockdown syndrome rather than viral infection. However, a review study by Behnood et al. (11) found more common persistent symptoms in PCR-positive children than in PCR-negative children. Although difficult, there seems to be a need to distinguish between long-term symptoms caused by SARS-CoV-2 infection and pandemic-related symptoms (49,50).

When evaluated in terms of neurocognitive symptoms associated with COVID-19, pathological mechanisms are still unclear. Crivelli et al. (10) expressed these possible mechanisms as the direct effects of cellular damage due to viral invasion, secondary inflammatory responses, decreased angiotensin-converting enzyme 2 (ACE2) activity that regulates neuroprotective and neuro-immunomodulatory functions, oxidative stress, hypoxia, sepsis, and/or multi-organ damage related to severe COVID-19. Also, they stated a possible association of the post-COVID-19 neurocognitive impairment with poorer pulmonary function and vascular pathology (elevated D-dimer levels) (10).

According to our current knowledge based on data from adult studies, neurocognitive impairment is unlikely to be due to COVID-19-related delirium (10). Recently, a potential pathomechanism was described based on structural similarities between the N-methyl-d-aspartic acid receptor (NMDAR) synonym NR1 (GluN1) and synonym NR2a (GluN2a) subunits and the SARS-CoV-2 non-structural proteins 8 and 9 , respectively, indicating an immune-mediated cross-reactivity to the NMDAR (51,52). Considering the roles of NMDAR in memory, learning, synaptic plasticity, this mechanism may be a explanation of neurocognitive impairments.

When evaluated in terms of post-COVID-19 or long-COVID neurocognitive symptoms, several factors, including hypoxemia, cerebral thrombotic/inflammatory endothelial damage, disruption of the blood-brain barrier (leading to parenchymal translocation of pro-inflammatory molecules, cytokines, and cytotoxic T-lymphocytes), microglial activation and astrogliosis are suggested as pathological mechanisms found generally in adult studies (53).

Studies generally conducted on adult patients found that SARS-CoV-2 was detected in brains from severely infected patients (54). There is no clarity yet on how the virus enters the brain and how it spreads in the brain (54). Possible mechanisms/routes of SARS-CoV-2 entry to the brain seem to be retrograde transport via sensory (olfactory, trigeminal, autonomic nervous system) nerve endings within nasal and buccal cavities, neuroinvasion via gastrointestinal tract, the virus associated with leukocytes entering the brain via receptors, interaction of virus entering blood from the infected lungs with the cerebrovasculature and/or at the blood-cerebrospinal fluid barrier, and the choroid plexus (54). Although there are no data to support any mechanism for the spread of SARS-CoV-2 in the brain, it can be argued that SARS-CoV-2 may interact with and spread through the ACE2, other facilitator receptors, or by adsorptive uptake by cells (54). Moreover, a meta-analysis study of neuroimaging findings revealed acute to subacute infarcts (24.0%), cerebral microhemorrhages (6.9%), acute spontaneous intracerebral hemorrhages (5.4%) and encephalitis/encephalopathy (3.3%) in adult patients with COVID-19 (55).

Risk Factors of Neurocognitive Problems

Although there is no study directly evaluating the risk factors of neurocognitive problems in children and adolescents, the results from the long-COVID studies give an idea about this issue. In a review study, risk factors associated with long-COVID in children and adolescents were stated as older age, female gender, severe COVID-19, overweight/obesity, comorbid-allergic diseases, other long-term comorbidities, and poorer physical and mental health before COVID-19 (11,15,28,56,57). Also, Asadi-Pooya et al. (17) reported older age, muscle pain at hospital admission, and admission to the ICU during acute infection as the predictors of post-COVID-19 condition in children and adolescents. Moreover, Blankenburg et al. (48) stated the associations of neurocognitive and pain symptoms with female gender and higher age. Conversely, in a meta-analysis study, persistent cognitive difficulties were associated with higher age but not with gender (11). This study also revealed that higher study quality was associated with lower prevalence of all symptoms, except the loss of smell and cognitive symptoms (11). However, fewer comorbidities, strong innate immune responses, reduced expression of ACE2 receptors, active thymic function, vaccines, past infections, nutrition, and/or the gut microbiome were stated as protective factors against severity and duration of COVID-19 and possibly long-COVID (15).

Prognosis of Neurocognitive Problems

Knowing the duration of long-COVID symptoms seems important to address the implications for the children and families. Since the disease is still very young, information about its course is limited. Although there is no study has directly examined the prognosis of neurocognitive problems, some pediatric studies revealed that most children recover within

2 weeks-5 months (16,31,58,59), indicating a need for future studies to draw a conclusion. This wide range of recovery time may be due to improvement of symptoms at different times (28). A possible steady decline in the prevalence of fatigue and smell disturbance over time was declared, whereas the prevalence of symptoms such as headache and sleep problems declined slower. This finding should be carefully interpreted because of recalling the symptom onset and duration at the single follow-up interview. However, Borch et al. (16) found that children in the control group had significantly more concentration difficulties, headache, muscle and joint pain, cough, nausea, diarrhea, and fever than SARS-CoV-2 infected, suggesting that these may be related to other factors (for example restrictions, lockdown of the pandemic, etc.) than SARS-CoV-2 infection.

COVID-19. The reports are conflicting regarding its prevalence, duration, and impact on daily life (14). Childhood is a critical period of life for acquiring social, behavioral, and educational development (31). Parents need to be informed about the cognitive effects of COVID-19. It is significant that teachers, psychiatrists, and pediatricians collaborate on cognitive impairments. Pediatric cases with neurocognitive signs raise concerns about the potential for health sequelae to affect child and family functioning over many life years (60). Early diagnosis is a substantial point for long-COVID in children. After COVID-19, children and adolescents may be followed up by outpatient services for a while. Doctors may assess the neurocognitive complaints. A multidisciplinary approach will be beneficial in this issue. More knowledge on long-term sequelae of COVID-19 in children and adolescents needs to be collected. Further studies are required to provide greater insight into the neurocognitive effects of COVID-19 on developing brain.

Conclusion

Clinical studies are still exploring the long-term effects of

Table 1. Characteristics of the included studies: Methodological summary and main results

Author, year, country (reference)	Type of article and collection mode	Age range or mean age (year), sex (F %)	COVID-19 cases (n severity)	Time of assessment (neurocognitive test)	Results Associated with Neurocognitive Symptoms
Ludvigsson 2021, Sweden (13)	Case report and systematic review, internet-based social media forum (parental reports)	9-15, 80%	n= 5 Mild, hospitalized	6-8 months after clinical diagnosis of COVID-19 (-)	All children in this study reported fatigue and pain. Four of the five children complained of headaches, difficulties concentrating, and dizziness. The parents reported that three of the children experienced memory loss and depression
Buonsenso et al. 2021, Italy (31)	Cross-sectional study, phone or inpatient (questionnaire)	11±4.4, 48%	n= 129 26% symptomatic, 74% symptomatic, 5% hospitalised, 2% PICU	163±114 days after microbiological diagnosis (-)	129 children diagnosed with COVID-19 complained of insomnia (18.6%), fatigue (10.8%), concentration difficulties (10.1%), headache (10.1%)
Brackel et al. 2021, Netherlands (30)	Cross-sectional study, online questionnaire	9-15, NR	n= 89 52.8% had a positive PCR test, 34.8% positive serology tests, and 38.2% diagnosed clinically 18% hospitalised	≥12 weeks after diagnosis of COVID-19 (-)	89 children attended this study. Fatigue was the most common long-term complaint (87%). Many patients reported some degree of cognitive dysfunction, with 45% suffering concentration difficulties, 13% reporting memory loss, and 2% describing brain fog. 38% of children complained of headaches
Buonsenso et al. 2022, UK and USA (32)	Cross-sectional (preprint), online survey (parental reports)	10.3±3.8, 56%	n= 510 12% symptomatic, 74% managed at home, 4% hospitalised, 9% attended hospital (not admitted)	>4 weeks after symptom onset (-)	Several parents reported a lack of concentration (60.6%), difficulty remembering information (45.9%), difficulty in doing everyday tasks (40%), difficulty processing information (32.7%), short-term memory issues (32.7%), word repetition (12.1%) in their children

Sterky et al. 2021, Sweden (24)	Brief report, phone questionnaire	0-18, 42%	n= 55 All severities, hospitalized	219 days (123-324) after hospital admission (-)	Of 55 patients, 3 were suffering from cognitive difficulties (5.4%)
Ashkenazi-Hoffnung et al. 2021, Israel (33)	Brief reports, clinical	Mean age: 12±5, 41%	n= 90 all severities, mild n= 82 (91.1%) moderate n= 6 (6.7%) severe n= 2 (2.2%)	Median of 112 days (range: 33-410) after COVID-19 diagnosis (-)	Following the disease, they reported some symptoms such as memory impairment (17.8%) and difficulty in concentration (8.9%)
Roge et al. 2021, Latvia (27)	Ambidirectional cohort study, phone (questionnaire)	Mean age: 10.0, 44.5%	n= 236 86.9% outpatients with mild disease, 13.1% moderate/severe disease requiring hospitalization, no MIS-C	1-6 months after acute COVID-19 (-)	They complained of cognitive sequelae [including difficulties to concentrate (16.9%), impaired attention (16.9%), impaired memory (10.2%)], speech disturbances (1,3%). After the 12-week cut-off point, 105 (44.5%) COVID patients had persistent symptoms. No statistical differences were seen among most reported persisting symptoms before and after the 12-week cut-off point. Cognitive sequelae were significantly associated with the COVID-19 experience compared to the controls. In older children, one of the most prevalent persistent symptoms was cognitive disturbances, as well as neurological sequelae. The prevalence of persistent cognitive complaints increased considerably according to the study's age groups, with the highest rates seen among teenagers. In adolescents, cognitive disturbances including difficulty in concentrating (27.8%) and an inability to focus their attention (24.1%) were the most reported persistent symptoms
Miller et al. 2021, UK (56)	Cohort study, electronic (weekly survey)	Age groups: <2, 2-11, 12-17, 41%	NR	≥28 days after symptom onset (-)	4,504 participants attended this study. 175 patients were COVID-19 positive. 22.2% of patients had neurological (including cognitive impairment/"brain fog") symptoms
Fink et al. 2021, Brazil (34)	Prospective cohort study, outpatient and inpatients validated instruments and clinic	8-18, 58%	n= 53 Mild [16/23 (70%)], moderate/ severe/critical pediatric COVID-19 [7/23 (30%)]	4.4 months (0.8-10.7) after COVID-19 diagnosis (-)	In 53 patients with symptomatic pediatric COVID-19, one of the most frequently reported symptoms is difficulty concentrating (4%)
Borch et al. 2022, Denmark (16)	Retrospective cohort study, electronic (questionnaire)	0-17, NR	n= 15,041 Asymptomatic, mild	Symptoms lasting >1 month (-)	One of the most common symptoms was concentration difficulties. Children in the control group aged 0-5 years experienced significantly more concentration difficulties than children in the SARS-CoV-2 group. Correspondently, 6-17-year-old controls were more prone to concentration difficulties than their SARS-CoV-2 positive peers

Kikkenborg Berg et al. 2022, Denmark (35)	Cross sectional study, case-control, electronic (survey)	15-18, 57.6%	n=6630 all severities	≥8 weeks after the positive SARS-CoV-2 test (-)	3,013 matched controls were excluded because of suspected SARS-CoV-2 infection. 6,630 (27.3%) responded in the case group and 21 640 (22.3%) responded and were eligible to participate in the control group. One of the most frequent symptoms in the long COVID group was trouble remembering or concentrating. Cases are included in the specified time periods if they had sufficient follow-up time since a positive SARS-CoV-2 test. For at least two months (5.6%), for at least three months (5.9%), for at least six months (5.2%), for at least nine months (4.9%), for at least twelve months (3.3%) patients reported often or almost always troubled to remember or to concentrate
Kikkenborg Berg et al. 2022, Denmark (61)	Cross sectional study, case-control, electronic (survey)	0-14, 10.2, 48.2%	n= 10997	≥8 weeks after the positive SARS-CoV-2 test (-)	Cases had higher odds of reporting at least one symptom lasting more than 2 months than did controls in the 0-3 years age group (40·0% vs. 27·2%), 4-11 years age group (38.1% vs. 33.7%), and 12-14 years age group (46.0% vs. 41.3%). Differences in Children's Somatic Symptoms Inventory-24 symptom scores between cases and controls were statistically significant but not clinically relevant. Among those aged 4-11 years, trouble remembering or concentrating was one of the most common; and among those aged 12-14 years, trouble remembering or concentrating was one of the most common. The prevalence of symptoms lasting at least 2, 3, 6, 9, and 12 months are presented. With increasing duration of symptoms, the proportion of children with those symptoms tended to decrease. In cases aged 12-14, more girls than boys had at least one symptom lasting more than 2 months (52.7% vs. 39.6%), and a similar pattern was seen in the control group. In the younger age groups, sex differences were only found for controls aged 4-11 years
Radtke et al. 2021, Switzerland (29)	Prospective cohort study, online (questionnaire)	6-16, 54%	n= 109 Asymptomatic and mild	>3 months after serologic testing (-)	4 of 109 seropositive children (4%) and 28 of 1246 seronegative ones (2%) reported at least 1 symptom lasting beyond 12 weeks. One of the most frequently reported symptoms lasting more than 12 weeks among seropositive children was difficulty concentrating (2%)
Blankenburg et al. 2022, Germany (26)	Cross sectional study, schools (12-question long-COVID-19 survey)	14-16, 55%	NR	>3 months after acute infection (-)	1,365 (88%) students were seronegative, and 188 (12%) were seropositive. Fisher's Exact test did not reveal any significant differences between seropositive and seronegative students regarding the prevalence of any neurocognitive symptoms reported. More than one-third of adolescents reported the presence of at least one neurocognitive, pain, or mood symptom, with tenseness, listlessness, and difficulties concentrating reported most commonly

Smane et al. 2021, Latvia (23)	Retrospective cohort study, clinical	8-15, 39%	n= 92 Hospitalized	1-3 months after COVID-19 onset (-)	Among the 92 patients, 47 (51%) reported persistence of at least one symptom. Persistent cognitive disturbances (memory, attention, and information processing problems) were present in 9 (10%)
Zavala et al. 2021, U.K. (37)	Retrospective cohort study, paper questionnaire	0-16, 49%	n= 387 All severities Among the positive cases, 32.2% were asymptomatic at the time of the RT-PCR test	At 1 month (-)	A total of 2456 children were invited, and 35.0% (859/2456) completed the questionnaire, including 38.0% (472/1242) laboratory-confirmed SARS-CoV-2 RT-PCR–positive cases and 32% (387/1214) SARS-CoV-2 RT-PCR–negative controls. Differences in neurological symptoms included confusion, which was only reported for symptomatic cases (5.6%). Most elicited symptoms were as common among symptomatic cases as among symptomatic controls. Among the 472 laboratory-confirmed SARS-CoV-2 RT-PCR–positive patients reported cognitive symptoms: Confusion (19/472), forgetfulness (7/472), short-term memory loss (3/472), trouble forming words (2/472), hallucinations (1/472). Of the 65 ongoing symptoms solicited, 3 clusters were significantly more common, albeit at low prevalence, among symptomatic cases (3-7%) than symptomatic controls (0-3%): neurological, sensory, and emotional and behavioral well-being.
Stephenson et al. 2021, England (57)	Cohort (preprint), paper questionnaire	11-17, 63%	n= 3065 non-hospitalized	14.9 weeks (13.1-18.9) after testing (-)	6804 adolescents (3065 who tested positive and 3739 who tested negative) completed the questionnaire (response rate of 13.4%). Among 3065 participants who tested positive for SARS-CoV-2 reported symptoms such as confusion, disorientation, or drowsiness (7.3%).
Osmanov et al. 2022, multinational (28)	Prospective cohort, telephone interview	≤18, 52%	n= 518 hospitalized	Median 256 (223-271) days (≥5 months) since hospital discharge (-)	At the time of the follow-up interview, parents of 24.7% of children reported at least one persistent symptom. Confusion/ lack of concentration (0.4%), Tingling feeling/"pins and needles" (0.4%), problems speaking or communicating (0.2%).

MIS-C: Multisystem inflammatory syndrome in children, COVID-19: Coronavirus disease-2019, RT-PCR: Real-time polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

Ethics

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Authorship Contributions

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