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REVIEW

Long-term central nervous system (CNS) consequences of COVID-19 in children

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ABSTRACT

Introduction: Neurological/neuropsychiatric symptoms are commonly reported by children/young people with long COVID, especially headache, fatigue, cognitive deficits, anosmia and ageusia, dizziness, mood symptoms, and sleep problems. However, reported prevalence estimates are highly variable due to study heterogeneity and often small sample size; most studies only considered short-term follow-ups; and, apart from mood and sleep problems, neuropsychiatric conditions have received less attention. Considering the potential debilitating effects of neurological/neuropsychiatric conditions, a comprehensive review of the topic is timely, and needed to support clinical recognition as well as to set the direction for future research.

Areas covered: The authors discuss neurological/neuropsychiatric manifestations of long COVID in pediatric populations, with a focus on prevalence, associated demographic characteristics, and potential pathogenetic mechanisms.

Expert opinion: Children/young people may develop persistent neurological/neuropsychiatric symptoms following acute SARS-CoV-2 infection, which may affect daily functioning and well-being. Studies in larger samples with longer follow-ups are needed to clarify prevalence and symptom duration; as well as less investigated risk factors, including genetic predisposition, ethnicity, and comorbidities. Controlled studies may help separate infection-related direct effects from pandemic-related psychosocial stressors. Clarifying pathogenetic mechanisms is paramount to develop more targeted and effective treatments; whilst screening programs and psychoeducation may enhance early recognition.

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1. Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified as a new strain of coronavirus in late 2019 [1]. The outbreak was declared a pandemic by the World Health Organization (WHO) in March 2020, due to the rapid global spread of the disease [2]. As of June 2023, the WHO reported over 768 million confirmed cases and over 6.9 million deaths globally. Further, over 13 million vaccinations doses have been administered across the globe, with higher rates in America, Europe, and Australia (≥100 administered doses per 100 individuals) and lower rates in Africa (ranging between 20 and 100 doses per 100 individuals) [2].

Transmission of COVID-19 is primarily due to exposure to respiratory droplets from either asymptomatic or symptomatic individuals who are infected with COVID-19 [3]. Clinical manifestations of COVID-19 vary greatly. About one-third of infected individuals are believed to remain asymptomatic [3], as it has been estimated based on viral testing of passengers of chartered evacuation flights from Wuhan, China [3,4]. Those who become symptomatic commonly experience fever, cough, fatigue, and dyspnea [5]. In severe cases, acute respiratory failure, septic shock, and multiple organ failure may develop, requiring mechanical ventilation and intensive care [3].

Clinical presentation and symptom severity vary according to socio-demographic factors. For instance, infection rates have been much lower in children and young people than in adults, and child infections only account for 1.2% of worldwide cases [6]. In contrast to other respiratory diseases, when infected, children tend to either remain asymptomatic or develop mild symptoms [6,7]. However, due to this, a greater number of infected children may not be recognized and tested as compared to adults, which may also result in less accurate official statistics. It is not known why children tend to display milder symptoms of COVID-19. It has been suggested that they may have fewer risk factors (e.g. age-related changes in clotting function or comorbid medical conditions), or additional protective factors (e.g. related to immunity and microbiota) [8,9].

Although most children remain asymptomatic or only experience mild symptoms, there have been cases of COVID-related multisystem inflammatory syndrome (MIS-C) in

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Article highlights

- Children and young people tend to remain asymptomatic or only experience mild symptoms of acute COVID-19 but can develop persistent symptoms (long COVID).
- Symptoms of long COVID include neurological and neuropsychiatric manifestations, most often headache, fatigue, cognitive deficits, anosmia and ageusia, dizziness, mood symptoms and sleep problems.
- Studies to date have provided inconsistent data on prevalence and symptom duration; as many were limited by the small sample size, lack of comparative data, and short follow-up.
- Infection-related mechanisms, such as chronic systemic inflammation, oxidative stress, and immune-mediated processes are considered to play a prominent role in the development of neurological symptoms, whilst pandemic-related factors (e.g. concerns about exposure and impact of restrictions) may be more relevant for neuropsychiatric conditions (e.g. anxiety and sleep problems).
- Further studies are needed to clarify pathogenetic mechanisms, differences with adults, and duration/course of more persistent symptoms.

communities with high incidence of COVID-19 [6]. This is an inflammatory syndrome characterized by multi-organ involvement, which may manifest few weeks after the acute infection [10,11]. Children who develop MIS-C are typically above 5 years of age and present with severe extrapulmonary symptoms, e.g. gastrointestinal, cardiovascular, and mucocutaneous [12]. Neurological symptoms can also be present and include headache, seizures, lethargy, and encephalopathy [10]. Those with MIS-C are more likely than those without to require intensive care, yet, they are often able to recover [6].

Children and young people may also experience persistent symptoms (Long COVID or post-COVID-19 syndrome) [13]. Definitions of long COVID vary across the literature. Following a Delphi process and consensus meeting, a research definition of long COVID or post-COVID 19 condition was proposed in April 2022, indicating that a diagnosis can be made when at least one physical symptom persists more than 12 weeks in children/young people with a confirmed SARS-CoV-2 infection, and cannot be explained by an alternative diagnosis. However, the National Institute for Health and Care Excellence (NICE) guidelines indicate that the term 'long COVID' includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) [14,15]. Further, there is increasing recognition that long COVID can also manifest in previously asymptomatic individuals [16,17]. Prevalence estimates vary across the literature. For instance, the CloCk study, a large UK cohort study, reported that 14% of infected children and young people experienced persistent symptoms at 15 weeks. However, reported prevalence estimates range from 1.6% to 70% depending on study design, sample size, definition, and method of identification [9,18].

Similarly, to adults, symptoms of long COVID in children and young people frequently include fatigue, headache, muscle, or joint pain, impairment of smell or taste, and dyspnea [9]. However, respiratory symptoms and altered sense of taste or smell appear to be less common in children [19]. Since the first conceptualization of long COVID, the list of manifestations identified in children has been extended to up to 40 different symptoms [16,19]). In their review, Fainardi et al. (2022) [16] summarized common clinical manifestations of long COVID according to the main physiological system involved. Although the range of the reported prevalence estimates varied greatly, the most commonly identified symptoms (with prevalence up to 70–80%) were fatigue, concentration difficulties, headache, abdominal pain, stomachache, smell and taste alterations, and sore throat. Other symptoms (with prevalence up to above 30%) included myalgia, sleep disturbances, skin rashes, persistent fever, loss of appetite/weight, dyspnea, and chest tightness. Finally, less frequent symptoms included palpitations, diarrhea, vomiting, dizziness, irritability and mood changes, cough, and nasal congestion [16]. Similarly, a systematic review reported that symptoms such as mood changes, fatigue, sleep disorders, headache, respiratory, and cognitive symptoms were the most common (although all with pooled prevalence below 20%) [19]. Despite the great variation in reported prevalence estimates, which may reflect the heterogeneity and small sample size of many of the included studies, it is important to be aware that clinical presentations in the pediatric population are highly heterogenous and may be atypical, as also highlighted by the NICE guidelines [14].

It is not known why some individuals develop long COVID, but clinico-demographic characteristics have been identified as potential risk factors. For instance, a prospective cohort study of 518 PCR-positive children reported that 44.7% had pre-existing comorbidities, most commonly food allergy (13%), asthma (9.7%), and gastrointestinal problems (9.7%) [20]. Allergies and intestinal problems have also been reported with similar rates in a smaller study [21]. Similar to adults, older age and female sex have also been associated with long COVID in the pediatric population [19].

In sum, neurological and neuropsychiatric symptoms can manifest in children both in the context of acute COVID-19 and post-acute sequalae, such as MIS-C and long COVID [10,16]. For instance, children and adolescents may experience neurological (e.g. anosmia and headache) and neuropsychiatric symptoms (e.g. anxiety and depression) as acute and/or persistent manifestations [22]. This review focuses on manifestations of long COVID [22]. Before describing the symptoms in more detail, we will present the suggested underlying biological mechanisms. Pandemic-related factors may also be contributing factors to some of these clinical manifestations, as discussed in symptom-specific sections.

2. Neuropathophysiology of SARS-CoV-2

SARS-CoV-2 infects cells by binding to the Angiotensin-Converting Enzyme 2 (ACE2), which thus acts as entry point or 'receptor' for the virus [23,24], and undergoes spike protein priming via the transmembrane protease serine 2 (TMPRSS2) [24]. ACE2 and TMPRSS2 are expressed by a large variety of cells, including ciliated epithelial cells and oligodendrocytes [23,25]. ACE2 is part of the cellular pathways regulating blood pressure, wound healing, and inflammation. Thus, SARS-CoV-2 binding and subsequent ACE2 downregulation may promote vasoconstriction and inflammation, which can cause tissue

damage [26]. How COVID-19 may cause neurological manifestations is not well understood [25].

Several respiratory viruses, from influenza to SARS-CoV viruses, have neurotropic features and can cause neurological complications in vulnerable individuals [27,28]. Therefore, initial hypotheses suggested that SARS-CoV-2 may share some of the same pathogenetic mechanisms [27], such as olfactory nerve entry, vascular endothelial infection, and leukocyte-mediated migration through the blood-brain barrier (BBB) [25]. For instance, influenza A virus can cause neurological complications in both children and adults and, animal studies have shown that it can reach the central nervous system (CNS) through axonal transport along the olfactory nerves or sensory neurons of the vagus nerve in the lungs [28,29]. Further, it can sometimes be detected in the blood of infected individuals, which is associated with clinical severity, and reach the CNS by passing through the BBB (hematogenous route) [30]. Previous studies have indicated that CoV viruses, such as SARS-CoV, which was responsible for the SARS epidemic, may have neurotropic and neuroinvasive capabilities [28]. Although the exact mechanism of entry into the CNS is not well established, the virus has been detected in the cerebrospinal fluid (CSF) of infected individuals [31,32]. SARS-CoV-2 is genetically and structurally very similar to SARS-CoV and binds the same receptor [33,34]. Therefore, it might, in theory, share neuropathogenic characteristics, but this has not been confirmed [28].

For instance, it has been suggested that SARS-CoV 2 can cause hypo/anosmia by infecting olfactory epithelial neurons [28]; however, ACE2 was not identified in these neurons but in epithelial support cells [35]. Thus, these symptoms may be caused by the indirect effect of the infected epithelium on neuronal activity [36]. Conversely, ACE2 has been identified in sensory neurons, including those that innervate the lungs, and postmortem studies identified SARS-CoV-2 in the trigeminal sensory ganglia of infected individuals [36,37]. Thus, further work is needed to elucidate potential viral-neuronal interactions. For instance, it has been suggested that functional interactions might occur and affect neuronal function in the absence of neuronal infection [36]. Further, SARS-CoV-2 has been detected in the CSF of some individuals with meningoencephalitis and encephalitis in the context of COVID-19 infection [28,38]; but not in all cases [39–41]. This may be due to the limited sensitivity of CSF testing for SARS-CoV-2, especially at the beginning of the pandemic [25]. Alternatively, these presentations may be caused by pathogenetic mechanisms secondary to the systemic infection, such as inflammation, hypoxia, and altered neurotransmission [25,39]. When an individual is infected, immune cells are activated and release pro-inflammatory cytokines. An overactive immune response to SARS-CoV-2 can cause a massive cytokine release or 'cytokine storm,' which can induce irreversible damage to organs [42].

There is also evidence that SARS-CoV-2 genomic RNA consists of multiple open reading frames (ORFs) and supports the expression of accessory ORF proteins. These may play an important role in evading the immune response of the host and promoting viral proliferation [43,44]. For instance, they can inhibit the innate immune response; promote the release of proinflammatory cytokines and organ damage; and induce apoptosis and autophagy of host cells. Although their exact number and role is still a matter of debate [45], they may represent potential targets for developing antiviral drugs and vaccines [43,44].

Overall, multiple potential neuropathological mechanisms may be differentially involved according to the distinct clinical manifestations and their timing (e.g. acute infection versus long COVID) [46]. For instance, inflammatory cytokines, hypoxia, oxidative stress, metabolic, and electrolyte alterations may underlie presentations such as confusion, encephalopathy, and seizures [39]. Additional mechanisms may include exacerbation of underlying risk factors, coagulation derangement, and side effects of medication [25,27]. Further, post-infectious, immune-mediated mechanisms, may mediate complications such as Guillain-Barré. Conversely, nonspecific and milder symptoms, such as 'brain fog,' fatigue, and sleep problems, which are often observed in long COVID, may represent epiphenomena of systemic involvement and inflammatory response [46].

Intriguingly, a Positron Emission Tomography (PET) study of adults with long COVID has identified brain hypometabolism in the olfactory gyrus and connected fronto-temporo-limbic regions, cerebellum, and brainstem. Hypometabolism was associated with functional complaints such as hyposmia/anosmia, memory difficulties, and insomnia [47]. Although this study was conducted in adults, it suggests that post-infection mitochondrial dysfunction, oxidative stress, and altered cerebral autoregulation may lead to reduced brain glucose metabolism and contribute to the persistence of symptoms [46,47]. Another suggested mechanism involves the dysfunction of the autonomous nervous system. For instance, a small physiological study identified vagus atrophy and increased latency of the sympathetic skin response in adults with long COVID [48]. Thus, dysautonomia may warrant further investigations in larger, and even younger, samples.

It is also important to notice that many studies have investigated persistent symptoms in both non-hospitalized individuals with history of mild acute infection, and in survivors of critical illness requiring intensive care [46]. Symptoms such as fatigue, attention difficulties, anxiety, and depression may be present in both groups, however, they considerably differ in terms of severity and complexity of presentation, need for prolonged medical care, and outcomes [46,49]. It has been suggested that long-lasting neurological symptoms in survivors of critical illness might be better understood in the context of Postintensive Care Syndrome (PICS), i.e. as a consequence of severe respiratory illness and prolonged intensive care treatments [49,50].

In sum, the biological underpinnings of COVID-related CNS manifestations are not fully known but likely involve multiple contributing mechanisms, according to the symptoms and their timing. Chronic systemic inflammatory response, oxidative stress, and immune-mediated processes are thought to play a major role in the pathogenesis of neurological symptoms in the context of long-COVID [25,27, 39].

Table 1. Studies of long COVID in children and young people.

Study	Study design (country)	N long COVID	N Controls	Age mean (SD) or range	Sample source	COVID infection confirmation	Symptom assessment method	Prevalence
Ashkenazi-Hoffnung et al., (2021) [73]	Prospective cohort study (Israel)	90	0	12 (5)	Children <18y attending Long COVID specialist clinic	PCR or serology	Structured clinical evaluation >4 weeks after diagnosis, including physical examination, blood tests, ECG, chest X-ray	−17.8% memory impairment −8.9% difficulty in concentration −28.9% headache −25.6% anosmia-ageusia −71.1% fatigue −18.9% dizziness −33.3% sleep problems −2.2% tics exacerbation
Bartley et al., (2021) [51]	Case series (U.S. A.)	3	0	NI (Adolescents)	Individuals <21 hospitalized following COVID-19 infection and requiring neuropsychiatric consultation (psychosis and neurological signs)	PCR/serology	Clinical assessment plus CSF analysis, MRI.	1/3 showed persistent severe memory and concentration difficulties at 6 months
Blankenburg et al., (2022) [52]	Cross-sectional survey study	1365 seropositive	188 seronegative	Median age 15	Students attending secondary schools participating in SchoolCOVIDD19 study	Antibody test	Survey including questions from Symptom-checklist-90-R and Somatic Symptom Scale	Self-rated severe/very severe in seropositive −7.3% memory loss −11.3% headache Rated as 'multiple times': −29.2% sadness −33.1% insomnia No significant differences between groups, apart from lower level of sadness in seropositive adolescents.
Brackel et al., (2021) [74]	Cross-sectional (the Netherlands) survey of pediatricians	89	N/A	2–18	Dutch pediatricians surveyed about their experience with long COVID in children	52.8% confirmed via PCR, 34.8% via positive serology tests and 38.2% via clinical assessments	Survey questions covering: (1) occurrence of pediatric long COVID, (2) clinical manifestations, (3) severity, and (4) wider multidisciplinary team involvement	−45% concentration difficulties −13% memory loss −2% brain fog −38% headache −87% fatigue −3% dizziness
Brasseler et al., (2022) [75]	Single-site retrospective cohort study (Germany)	84	0	6–17	Children <18 with suspected long COVID attending infectious disease outpatient clinic	PCR	Ear nose and throat specialist and additional investigations if needed.	Of the 24 children who met criteria for long COVID, 6 showed restrictive eating behavior and 5 met diagnostic criteria for anorexia nervosa
Buonsenso et al., (2021) [17]	Cross-sectional (Italy)	129	0	11 (4.4)	Children <18 with confirmed COVID-19 attending Gemelli Hospital (Rome, Italy), without severe neurocognitive disability	PCR	In-house questionnaire for caregivers and interview with pediatricians (on average 4 months from infection)	-10.1% lack of concentration −10.1% headache − 4.6% anosmia −3.1% ageusia −10.9% fatigue −18.6% insomnia −3.1% hypersomnia
Buonsenso et al., (2022) [53]	Cross-sectional (mostly UK and US)	510	0	10.3 (3.8)	Online parent-survey for children with COVID >4 weeks	58.2% of parents reported positive PCR, lateral flow test, or clinical diagnosis.	Long COVID Kids Rapid Survey 2	At 7+ months ($N = 320$): −78.8% headache −79.1% fatigue −47.2% dizziness −51.6% irritability −10.6% tics

(*Continued*)

Table 1. (Continued).

Study	Study design (country)	N long COVID	N Controls	Age mean (SD) or range	Sample source	COVID infection confirmation	Symptom assessment method	Prevalence
Elvan-Tuz et al., (2022) [54]	Multicenter prospective cohort study (Turkey)	10157	0	10–18	Children attending pediatric infection clinics	PCR	Smell awareness questionnaire one month after infection	−12.5% anosmia, of whom 84% also had ageusia
Guido et al., (2022) [76]	Cross-sectional (Italy)	322	0	1.5–17	Children <18y attending outpatient clinic for COVID-19 follow-up	NI	In-house COVID-19 symptom checklist, psychological questionnaires (The Multidimensional Anxiety Scale for Children-2 Self Report, The Children's Depression Inventory, The Trauma Symptom Checklist for Children-A, The Child Behavior Checklist), medical examination	At 3–5 months: −9% attention problems −0.3% memory problems −7.5% headache −2.2% anosmia −6.5% ageusia −6.8% fatigue −0% dizziness −13% sleep problems −16.6% irritability −0.9% anxiety − 0.3% obsessions-compulsions −10.6% eating problems −0.3% auditory hallucinations
Javed & Shad (2021) [77]	Case report (+ review of two previously published cases)(US)	1	0	17	Adolescent presenting with new onset psychosis 3 weeks post-infection	PCR	Clinical assessment	Duration of psychosis 7 weeks, ongoing treatment, no relapse at 11 months
LaRovere et al., (2021) [55]	Multicenter case series (US)	1695	0	2.4–15.3	Health records of individuals (<21 years) hospitalized with confirmed COVID-19 infection	PCR/antibody test	Chart reviews	22% had demonstrated neurological involvement including encephalopathy (<1%) or Guillain-Barre' (<1%). 40% of survivors to life-threatening neurologic involvement were discharged with new deficits.
Ludvigsson (2021) [78]	Case reports (Sweden)	5	0	9–15	Self-reported cases with persistent symptoms >2 months	Clinical diagnosis only	Clinical assessment	At 2 months: −4/5 poor concentration −4/5 headache −4/5 dizziness −5/5 fatigue
Meeder et al., (2022) [56]	Case series (U.S. A.)	2	0	16–17	Adolescents presenting to hospital with new onset psychosis and mania	PCR	Clinical assessment plus blood tests and imaging	Both required admission and ongoing psychotropic medication
Molteni et al., (2021) [57]	Prospective cohort study (UK)	1734 with confirmed COVID infection	1734 matched COVID-negative sample	5–17	Online parent-survey of UK school-aged children	Parent-reported PCR or lateral flow test	Online parent-survey	Up to 56 days ($N = 25$ confirmed cases): −80% headache −84% anosmia −76% fatigue <1% of seronegative group had symptoms for at least 28 days
Ngo et al., (2021) [58]	Retrospective case series (U.S.A.)	5	0	1.4–15	Children <18 admitted with neuropsychiatric symptoms in the context of COVID-19 or MIS-C	PCR/serology	Clinical assessment plus blood tests, CSF analysis, EEG, MRI	3/5 presented with acute psychosis. No psychosis at discharge (8–26 days) but persistent anxiety in 1/3.

(*Continued*)

Table 1. (Continued).

Study	Study design (country)	N long COVID	N Controls	Age mean (SD) or range	Sample source	COVID infection confirmation	Symptom assessment method	Prevalence
Osmanov et al., (2021) [20]	Prospective cohort study (Russia)	518	0	Median age 10.4	Children <18 admitted to hospital with confirmed COVID-19	PCR	International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) COVID-19 Health and Wellbeing Follow-up Survey for Children	-<1% ack of concentration/confusion −3.5% headache −4.7% disturbed smell −3.42% disturbed taste −10.6% fatigue −1.03% dizziness −5.19% insomnia −2.99% hypersomnia
Parisi et al., (2022) [59]	Survey of pediatricians (Italy)	267	N/A	NI	NI	NI	Survey questions on timing of anosmia and ageusia	−33.2% anosmia, of whom 5.9% even after acute infection −27.8% ageusia, of whom 5.4% even after acute infection
Pavone et al., (2021) [60]	Case series (Italy)	2	0	12–13	Referred for acute onset of psychiatric symptoms	PCR	Children's Yale-Brown Obsessive-Compulsive Scale	Both cases showed acute onset of OCD and tics 2 weeks post-infection. These persisted at two months in one case
Radtke et al., (2021) [61]	Longitudinal cohort study (Switzerland)	109	1246	6–16	Schools randomly selected in the canton of Zurich; classes then randomly selected from schools	Serology	Online questionnaires including the Health Behavior in School-Aged Children (HBSC)	Difficulty concentrating >12 weeks: 2% seropositive, 1% seronegative Headache >4 weeks: 5% seropositive, 3% seronegative Tiredness >12 weeks: 3% seropositive, 10% seronegative Tiredness >4 weeks: 6% seropositive, 4% seronegative Sleep disturbances >12 weeks: 2% seropositive, 0% seronegative Sleep disturbances >4 weeks: 3% seropositive, 1% seronegative
Roge et al., (2021) [62]	Ambidirectional cohort study (Latvia)	236 with confirmed COVID-19	142 with other respiratory infections	0–18	Children <18 treated in outpatient or inpatient settings	PCR or retrospective seroconversion	Interviews covering four domains: physical and mental health, social, and psycho-emotional wellbeing	−16.9% impaired attention −10.2% impaired memory −16.9% headache −12.3% loss of taste or smell −25.2% fatigue −8.9% dizziness −23.3% mood changes Symptoms such as fatigue, headache, loss of taste/smell and cognitive/mood symptoms were significantly associated with COVID-19 group as compared to controls
Savino et al., (2022) [63]	Case series (Italy)	5	0	2–15	Children <18 admitted due to new onset of neuropsychiatric symptoms (1 week to few months post-infection)	PCR	Clinical assessment plus blood tests, MRI, EEG	−2/5 anxiety − 4/5 tics/involuntary movements − 1/5 food restriction − 1/5 psychosis

(*Continued*)

Table 1. (Continued).

Study	Study design (country)	N long COVID	N Controls	Age mean (SD) or range	Sample source	COVID infection confirmation	Symptom assessment method	Prevalence
Smane et al., (2020) [64]	Retrospective cohort study (Latvia)	30 (including 9 with persistent symptoms)	0	9.2 (5.2)	Children <18 treated in outpatient or inpatient settings for COVID-19	PCR	Comprehensive medical assessment with physical examination and detailed history	Symptoms at follow-up (average 101 days post-infection): −3.3% headache −3.3% anosmia −3.3% ageusia
Sterky et al., (2021) [65]	Prospective cohort study (Sweden)	147 (of whom 12 had persistent symptoms)	0	0–18	Children admitted to two pediatric hospitals with confirmed COVID-19	PCR	Structured telephone interviews with parents and children on any persisting health issues following hospitalization. Symptoms reviewed by pediatricians	Symptoms at follow-up (>4 months post-admission): −16.6% cognitive difficulties −30% headache −16.6% reduced smell/taste −66.6% fatigue −25% depression
Taquet et al (2022) [66]	Analysis of 2-year retrospective cohort studies (US, Australia, UK, Spain, Bulgaria, India, Malaysia, Taiwan)	1,487,712 (of whom 185,748 children) with confirmed COVID-19	1,487,712 (of whom 185,748 children) with other respiratory infection	42.5 (21.9) [with subgroup analysis in children < 18]	Any individual with confirmed COVID-19 recorded on TriNetX electronic health records network	NI	Clinical diagnosis based on ICD-10	Epilepsy or seizure hazard ratio (95% CI) – 1.14 (1.09–1.19)
Taskeen et al., (2023) [67]	Prospective cohort study (Turkey)	200 (100 hospitalized and 100 treated at home)	0	8–18	Children <18 with positive PCR attending university pediatric services	PCR	Posttraumatic stress reaction index (CPTS-RI), child depression inventory (CDI), and screen for child anxiety-related disorders (SCARED)	10% depression 17% panic/somatization symptoms 34% separation anxiety 19.5% social phobia 6% school phobia 44% high PTSD scores 4% very high PTSD scores
Westman & Zelano (2022) [68]	National register-based matched study (Sweden)	1,221,801 (of whom 240,230 aged < 20) with COVID-19	1,223,312 without COVID-19	0–100+	Any individual with confirmed COVID-19 recorded on the system for communicable disease surveillance in Sweden (SmiNet) and linked to data from the National Patient Register (NPR) and Cause of Death register in Sweden	PCR or antigen test	Review of ICD-10 codes and dates of out- or inpatient hospital-based care via the health register	Epilepsy: .05% of seropositive; 0.10% of seronegative
Werner et al., (2022) [79]	Prospective cohort study (Germany)	45	0	0–18	Children <18 presenting to long COVID clinic	NI	Children's Sleep Habits Questionnaire (CSHQ-DE)	At a median of 20 weeks post-infection: −44% concentration/learning difficulties −36% headache −62% fatigue −42% sleep disorders

Abbreviations: CI=confidence interval; CSF=cerebrospinal fluid; EEG=electroencephalogram; MIS-C= Multisystem inflammatory syndrome-children; MRI=magnetic resonance imaging; NI=no information; PCR=polymerase chain reaction; US=United States; UK=United Kingdom.

3. Neurological conditions associated with long COVID

In this section, we describe the most common neurological symptoms associated with long COVID in the pediatric population (Table 1). These include 'brain fog' and memory/attention deficits (2–81%), headache (3–80%), impairment of smell or taste (12–70%), and dizziness (3–20%) [16]. We have also included fatigue (3–87%) [16], as it has been associated with hypothalamic dysfunction, although multiple physiological and psychological factors are likely at play in its pathogenesis, as discussed. Finally, for completeness, we included rarer and more severe COVID-related neurological manifestations, such as seizures and encephalitis/encephalopathy. Seizures typically present as acute SARS-CoV-2 sequelae [69,70]; however, a large cohort study reported that the two-year cumulative risk of seizures/epilepsy was significantly higher in children (but not in adults) after COVID infection as compared to other respiratory infections [66]. Similarly, encephalitis/encephalopathy typically develop during the acute phase of disease or in the context of MIS-C [10,71], but delayed immunomediated onset has also been described [71]. Further, cognitive and neurological deficits may persist in those who survive [55,72].

3.1. Cognitive deficits

Cognitive symptoms have been commonly reported among children with long COVID [62,65,74], encompassing concentration difficulties, memory problems, and 'brain fog.' The latter refers to a lack of mental clarity with poor concentration and fatigue [80]. A meta-analysis reported an overall prevalence of 6.3% [19]. However, great variability has been observed even among studies with similar sample size. For instance, concentration difficulties were reported in either 8.9% or 45% of children with long COVID by two similar studies, whilst another report indicated a prevalence of 19% [73,74,81]. Memory problems have been reported more consistently, with estimates ranging from 10.1% to 18% [17,73,74,81]. Brain fog was reported with a prevalence of only 2% [74] over 12 weeks after infection [74]. Studies have also shown a great variability in time to recovery, ranging from 2 weeks to 6 months [20,82]. Overall, cognitive impairment was mainly observed in older children [82]. The pathophysiological mechanisms underlying cognitive symptoms have not been fully elucidated. It has been suggested that they may be an epiphenomenon of other systems involvement, or a result of systemic inflammation, with consequent BBB disruption and/or brain microglia activation and mitochondrial disfunction [46,80]. However, despite these symptoms being commonly identified in children with long COVID, a case-control study reported higher rates of concentration difficulties in controls [83]. This suggests that pandemic-related contextual factors may also play a role.

In sum, there is great variability in reported prevalence rates of persistent cognitive symptom, ranging from 2% to 81% [16], with older children being more affected. Biological changes related to inflammation and systemic involvement have been suggested among underlying pathophysiological mechanisms [46,80]. However, pandemic-related stressors may also contribute [16,83].

3.2. Headaches

Headaches have been frequently reported as one of the most common persisting symptoms following COVID-19 infection [17,20,62,64,65,73,74,76]. According to the International Classification of Headache Disorders, 3rd edition [84], headaches commonly manifest during the acute phase of infection with a bilateral and pressing quality [83]. However, the clinical phenotype of headaches is much more heterogenous and less specific in youths with long COVID [85]. Prevalence estimates in Long COVID range from 3% to 80% [16,76]. A meta-analysis reported an overall prevalence of 35%; however, upon inclusion of only controlled studies, this reduced to 5% [86]. Similarly, another meta-analysis indicated a pooled prevalence of 7.8% [19]. Variability has also been observed in duration of symptoms. For instance, Guido et al. [76] reported that estimates reduced over time, decreasing from 33.5% to 7.5% after 3–5 months from infection. Buonsenso et al. [17] reported an average duration of 8 months in children with confirmed COVID-19 infection. Considering risk factors, increasing age has been associated with increased risk. Although headaches can manifest in children of any age, various reports have identified that they were more frequent in older children [73,76], i.e. either above the age of 11 [76] or between 6 and 17 years of age [73,87]. In addition to age, a genetic predisposition to migraine [85], or a personal history of migraine [88], may also increase the risk [85,88]. Finally, the pathophysiological mechanisms underlying the persistence of headache are not fully understood, but have been related to a protracted immuno-mediated release of cytokine and interleukins in the peripheral blood [85]. However, previous studies have reported inconsistent findings, with both increased and decreased levels of cytokine and interleukins in patients with post-COVID headaches [85].

In sum, headaches are a common symptom both during the acute infection phase and in long-COVID. They mainly affect adolescents and, although have been observed even after 8 months from infection, they tend to improve over time. Persistence of headache may be related to a protracted release of pro-inflammatory cytokines, but this has not been confirmed.

3.3. Anosmia and Ageusia

Both anosmia (loss of smell) and ageusia (loss of taste) have been reported as characteristic symptoms of COVID-19 in both children and adults. Prevalence estimates of anosmia are highly variable, depending on sample size and study design. For instance, several studies reported anosmia in 12–33% of children and young people [54,59,76,86], especially in those above the age of 6 [54,76,89]. A meta-analysis including an overall sample of 3986 children/adolescents indicated a prevalence of 18% [86], whereas a larger meta-analysis including over 80.000 youths reported a pooled prevalence of 5.6% [19]. The onset of anosmia has been observed prior [59,86] or concurrent with COVID-19 general

symptoms [54]. It has also been reported after the onset of general symptoms, with varying estimates, ranging from 43% [54] to 5% [59]. There are limited and inconsistent data regarding the duration of anosmia. For instance, Buonsenso et al. [53] reported a median duration of 120 days in a sample of 129 children/adolescents, whilst Elvan-Tuz et al. [54], observed a median duration of 7 days in a multicenter study including 10,157 adolescents. Persistence after a month has been reported in 8.4% of cases [54], and after 3–5 months in 2.2% of cases [76]. Ageusia has been reported with similar prevalence estimates, ranging from 18% to 27.8% [59,76]. It has been estimated that it persists between 6.6% and 3% of cases after a month [54,76] and in about 6.5% of affected youths after 3–5 months [76]. Age was not reported as a risk factor but ageusia was more commonly identified in females [54,90]. Given that anosmia and ageusia are often co-occurring [54], many studies have combined them in a single symptom category. For instance, Ashkenazi-Hoffnung et al. [73] identified a prevalence of 25.6% for anosmia-ageusia in a prospective study of 90 children attending a specialist long COVID clinic. However, meta-analytical evidence suggests a much lower combined prevalence of 0.5%, with anosmia being more common [91]. Of note, greater prevalence was reported in young people over the age of 11, when the two symptoms were combined [73]. Similarly, a review reported higher rates of persistence when they were considered together, with 27% of youths still experiencing anosmia-ageusia at 6 months [81] Regarding the underlying pathophysiological mechanisms, research has shown that these symptoms may be linked to the infection of olfactory and oral epithelial cells. For instance, ACE2 and TMPRSS2 are abundantly expressed by the olfactory epithelium, and may mediate SARS-CoV-2 entry into the host cells, often resulting in temporary loss of smell despite the olfactory nerve being intact [92]. SARS-CoV-2 can also infect sustentacular cells, which are supporting epithelial cells, and this may cause further damage to the olfactory epithelium and loss of olfactory cilia [92]. However, cilia may begin to regrow within 7–10 days from infection [93]. Interestingly, imaging studies have shown that persistent anosmia was associated with atrophy of the olfactory bulb and nerve, and additional primary olfactory cortical abnormalities in one-fifth of cases [46,94,95]. Although these studies were in adults and in small samples, they suggest that COVID-related injury to olfactory pathways may contribute to the persistence of hypo/anosmia. Considering ageusia, oral epithelial cells also express ACE2 and, when SARS-CoV-2 binds to this surface protein, it may interfere with glycoproteins-mediated transport of tastants and thus contribute to the loss of taste [96]. Inflammation associated with COVID-19 infection has also been thought to increase epithelial cell exfoliation [97,98]. This, alongside reduced stem cell turnover, could contribute to taste dysfunction.

In sum, anosmia and ageusia are considered characteristic symptoms of COVID-19 infection, although they may be less frequent in children than in adults. Persistence has been noted between 12% and 70% [16,20,62,64,65] of cases, with pooled estimates of less than 6% [19]. The rich expression of ACE2 on olfactory and oral epithelial cells may play a major role in the development of these symptoms, whereas inflammation and injury of neuronal pathways may contribute to their persistence.

3.4. Fatigue

Fatigue has been identified as one of the most common symptoms of long COVID across the literature, although rates range between 3% and 87% [16,20,62,65]. Initial meta-analytic evidence indicated a prevalence of 47%, making it the most reported long COVID symptom included in the analysis [86]. However, after the exclusion of uncontrolled studies, the prevalence reduced to only 5%. Similarly, a more recent meta-analysis identified a prevalence rate of 9.7% [19]. Of note, between 6.8% and 30% [76,81] of children continued to experience fatigue after 5-6 months following infection. However, the lack of longer follow-ups prevents to draw conclusion on the duration of such symptom. Age has been identified as a risk factor. For instance, a study of 322 COVID-positive children and young people, reported that those between 6 and 17 years of age experienced fatigue more commonly than younger children [76]. A challenging aspect in the study of fatigue is its variable and often subjective definition. The term 'fatigue' refers to both a common experience of daily living ('physiological fatigue') and the result of a disease, such as an infection ('pathological fatigue') [99]. Further it is challenging to measure, as it may be objectifiable, as a reduced physical force, or a purely subjective sensation [99]. Due to the subjective nature of fatigue, its pathogenesis is also poorly understood. It is likely that multiple factors may contribute to this symptom, including systemic inflammation, sleep alterations, and reduced activity [100]. Psychological factors (including pre-infection characteristics and response to the infection and pandemic related restrictions) may also play a role [99]. Finally, physiological changes may contribute to fatigue. It has been suggested that, similarly to Chronic Fatigue Syndrome (CFS), inflammatory mediators released at the site of viral infection may trigger the hypothalamic paraventricular nucleus (PVN), which physiologically acts as a stress-integrator. In genetically susceptible people, however, excessive stimulation of this center can cause it to become dysfunctional and hyper-sensitive to a wide range of psychological and physiological stressors [101].

In sum, fatigue has been reported as one of the most common symptoms of long COVID in children and young people. Reported estimates range between 3% and 87% of cases [16], according to the study, with a pooled prevalence of 9.6% [19]. The pathophysiological mechanisms underlying fatigue have not been fully elucidated, also because of its subjective nature. However, systemic inflammation, sleep problems, physiological changes, and psychological responses to the infection and pandemic-related restrictions have been identified as contributing factors [76].

3.5. Dizziness

Dizziness ranges from fleeting light-headedness to a more severe and impairing balance disorder [102]. It has been reported in 3–20% of children and young people with long COVID [16,20], but meta-analytic evidence suggested that

only about 4% experience persistent dizziness [19]. Studies are also inconsistent regarding its duration. For instance, a prospective cohort study including 1734 school-aged children reported a median duration of 2 days [57]; and a study following up 322 children in a specialist post-COVID clinic could not identify any case at the one-month follow-up [76]. However, other studies reported persistence up to 8 months post-infection [17,103]. For instance, Buonsenso et al. [53] surveyed 510 children with long COVID, and dizziness was self-reported in 47.2% of cases at 8 months. Female sex [17] and older age [17,57] have been identified as risk factors. The pathogenetic mechanisms are not completely understood, but infection-related neuronal dysfunction, hypoxia, hypercoagulopathy, as well as immune-mediated injury are among the suggested mechanisms [104].

In sum, dizziness is not a very common symptom of long COVID and may be of short duration. However, most studies have used self-reported, as compared to objective, measures of assessment [17,57,104], and this may affect the reliability of prevalence estimates and our understanding of the underlying pathophysiological mechanisms.

3.6 Seizures

Seizures are typically acute SARS-CoV-2 sequelae rather than long COVID manifestations, especially in the pediatric population. For instance, a recent two-year population-wide study in Sweden showed that SARS-CoV-2 infection was not associated with an increased risk of epilepsy diagnosis [68]. Similarly, a large prospective UK study including about 260.000 children/young people (not all with confirmed infection) did not observe increased risk of seizures in long COVID [57]. However, a large two-year retrospective cohort study including over 180.000 pediatric confirmed cases of COVID-19 across several countries reported that, although the overall risk of epilepsy and seizures was low at 6 months (hazard ratio = 1.14), children and young people had a significant higher two-year cumulative risk as compared to other respiratory infections, which was not observed in adults [66]. Thus, future studies are needed to clarify age-related differences in the potential risk of epilepsy in the post-COVID period. Further, it is possible that different COVID variants may be associated with varying risk of neurological symptoms, including seizures. For instance, a small case series study reported a surge of pediatric emergency presentations with provoked seizures in the context of Omicron infections in the U.S.A. [105]. Thus, the potential differential effect of distinct COVID variants warrants further investigation [66,106,107]. Different pathogenetic mechanisms have been proposed to explain COVID-related seizures. These include the release of proinflammatory cytokines, such as IL-lβ and TNF-α, which has been previously associated with seizures [108]. COVID-19 may also disrupt the BBB, and cause the passage of blood cells and proteins into the CNS, altering its osmotic balance [108]. Finally, activation of the coagulation cascade may increase the risk of seizures [108].

In sum, seizures appear to be a rare complication of acute COVID-19 infection and may be associated with preexisting risk factors (e.g. positive personal history). However, some studies suggest that specific COVID-19 variants or younger age may be risk factors for provoked seizures or post-COVID epilepsy, and these warrant further investigation.

3.7. Encephalitis and encephalopathy

More severe neurological conditions, such as encephalitis, an inflammatory condition of the brain, and encephalopathy, a brain disorder typically characterized by altered consciousness, are rare and often fatal [71,80]. For instance, a study including 3707 children, reported that only 1% developed encephalopathy [109], but this was associated with increased mortality [110]. Thus, encephalitis/encephalopathy have been less commonly reported by studies on the long-term effects of COVID. However, they can result in long-term neurological and cognitive impairment in those who survive [55,72]. For instance, a study of 1,695 hospitalized children/young people with documented COVID-19 reported that 15 had possible/confirmed encephalitis, of whom 13% were discharged with new neurological deficits [55]. Unfortunately, still little is known on other possible sequelae, from neurocognitive impairments to behavioral and personality changes, which can be observed in nearly half survivors of pediatric encephalitis [72]. Encephalitis/encephalopathy may develop due to different mechanisms, including the direct effects of the infection, systemic inflammation with cytokine storm, and autoimmunity [80,111]. The latter may play a major role in delayed-onset presentations. For instance, there have been increasing reports of young people with post-COVID acute disseminated encephalomyelitis (ADEM), a post-infectious demyelinating encephalitis, which develop 2–30 days following infection [71,112,113].

In sum, encephalitis and encephalopathy are rare and often fatal complications of COVID-19. However, delayed onset immune-mediated presentations have been described even in young people. Further, longitudinal studies are needed to clarify cognitive and behavioral outcomes in those who survive.

4. Neuropsychiatric conditions associated with long COVID

Long COVID has also been associated with neuropsychiatric symptoms in children and young people, most commonly sleep problems (2–63%), and mood symptoms (5–24%) [16] (Table 1). Notably, a meta-analysis identified mood and anxiety symptoms as the most prevalent overall in long COVID (16.5%) [19]. Other mental health presentations may include obsessive compulsive disorder (OCD), tics, eating disorders and, more rarely, psychosis and mania. Some of these have been related to the direct effect of the infection or the immune response, although the psychosocial effects of the pandemic (both direct, e.g. concerns around infection; and indirect, e.g. pandemic related restrictions) are likely to play a role. In fact, several studies in both the general and the psychiatric population have reported a surge of new and/or worsening mental health symptoms

in children and young people, independently of infection [114–116].

4.1. Sleep problems

Sleep problems, such as insomnia and hypersomnia, have been frequently reported in children and young people with long COVID [79]. Meta-analytical evidence indicates a prevalence of 8.4% [19], with smaller studies reporting higher estimates [17,76,79]. Estimates also vary among age groups, with higher prevalence in adolescents [79]. A study using the Children's Sleep Habits Questionnaire (CSHQ-DE) reported the greatest effect on daytime sleepiness [79]. In most cases, symptoms decreased over time, although differences were still significant at 3 months. Similarly, Buonsenso et al. [17], reported that disordered sleep symptoms persisted over 60 days.

In sum, sleep problems have been reported as one of the most prevalent clinical manifestations of long COVID [19], especially in adolescents. They have been linked to the effects of proinflammatory cytokines, infection-related involvement of other systems (e.g. respiratory), reduced exercise, as well as psychosocial factors [46].

4.2. Mood and anxiety symptoms

Mood symptoms (such as sadness or anger) and mood or anxiety disorders have been commonly reported following COVID-19. A meta-analysis indicated an overall prevalence of 16.5% of children and young people with long COVID [19]. However, prevalence may vary with age and type of symptom/disorder considered. A study of 322 children and young people reported that internalizing symptoms were more common in both under 5s and 6–17-year-olds, however anxiety was observed in 8% and 28% of cases respectively [76]. Conversely, 19% of older participants suffered from low mood [76]. Thus, anxiety appeared to be more frequent than depression, especially social and separation anxiety, and both were more common in the older group [76]. Conversely, a study of 200 COVID-19 positive children and adolescents showed that 41% had anxiety and 10% had depression but did not identify age differences [67]. Of note, a two-year retrospective study reported that the post-infection increased incidence of mood and anxiety was transient, and risks of both disorders returned to baseline within two months [66]. It is well known that inflammation plays a role in the development of mood disorders, thus this may also be a contributing factor in the context of COVID-19 [117]. However, anxiety and depressive symptoms were also experienced by non-infected individuals during the pandemic [118]. For instance, a study of 1365 students observed no difference in mood symptoms between seropositive and seronegative participants, apart from reported sadness [52]. Overall, these findings suggest that pandemic-related factors, such as restrictions and social isolation, may have a prominent role in the development of these symptoms.

In sum, anxiety and mood symptoms are among the most common symptoms associated with pediatric long COVID. They appear to be more common in adolescents, despite some inconsistencies in the literature, and tend to remit over time. Inflammation may play a role in mood symptom development, however, as non-infected individuals experience similar symptoms, pandemic-related stressors are likely to play a major role. Pre-existing mental health conditions may also be a potential risk factor [114,119].

4.3. Obsessive Compulsive Disorder (OCD)

OCD is characterized by the presence of obsessions (i.e. recurring, unwanted thoughts or images) and/or compulsions (i.e. repeated behaviors or mental acts) [120]. A study including 226 children and young people reported that 23% developed new onset symptoms of OCD post COVID-19 infection [76]. Similarly, case reports identified new-onset OCD in male adolescents, mainly presenting with fear of infection and compulsive hand-washing [60,121,122]. Symptoms were still present at the two-month follow-up in one case [60,121,122]. The association between low-grade inflammation and OCD is well-documented, and may represent the pathogenetic mechanism underlying COVID-related OCD cases [123]. However, research is needed to demonstrate this link. Further, new-onset OCD symptoms have been reported in adolescents during the COVID-19 pandemic independently from documented infection, and have been related to fear of infection and psychosocial changes [56,58,121,122].

In sum, there are reports of new onset OCD symptoms in children after COVID-19 infection; suggesting that this may be a relatively common manifestation [76]. Most cases are associated with good outcome. Immuno-mediated mechanisms have been implicated, due to the known association between bacterial infections and OCD [124]. However, pandemic-related psychosocial changes and fear of infection may play a major role [123].

4.4. Tics

Tics are sudden repeated twitches, movements, or sounds. Several cases of tics have been reported in children following COVID-19 infection. For instance, a survey of 510 children with long COVID identified tics in 9.2% of cases, with no differences among age groups [53]. Persistence was reported in 10.6% of them after 7 months [53]. Motor and ocular tics have been observed more frequently than vocal tics [51,63]. Largely, individuals with new onset tics experienced full recovery, however, both motor and ocular tics persisted after three months in several cases [60,63]. Considering the pathogenetic mechanisms, tics have been associated with fronto-striatal dopaminergic abnormalities [125]. ACE2 is co-expressed and co-regulated with Dopa Decarboxylase (DDC), an enzyme involved in the biosynthesis of dopamine [126]. As ACE2 is highly expressed on dopaminergic neurons, it has been suggested that SARS-CoV-2 may induce a defective expression of ACE2, which may be paralleled by a DDC dysfunction, resulting in altered dopamine levels [126]. Nevertheless, pandemic-related psychosocial stressors may also play a role, as an increase in new onset tics has also been identified in children and adolescents in the general population [127].

In sum, tics appear to affect about 9% of children with long COVID regardless of age and, in a minority of cases, they can persist several months [53]. It has been suggested that tics

may result from COVID-induced changes in ACE2 pathways and consequent altered dopamine signaling, however, psychosocial stressors may also play an important role.

4.5. Eating disorders

Changes in eating behaviors, including either reduction or increase in oral intake, have been identified in children with long COVID [76]. For example, a study of 322 children and young people reported that 10.6% experienced changes in their eating pattern. Restrictive eating was more common (6.6% of cases) [25] and especially in 6–17-year-olds [76]. Interestingly, a study including a small sample of 84 children and young people identified an association between anosmia-ageusia and restrictive eating. Among the 24 participants with smell and taste dysfunction, five subsequently received a diagnosis of Anorexia Nervosa. Of these, three improved between 32 to 84 days, which was attributed to the beneficial effects of psychotherapy [75]. In addition to the effects of anosmia and ageusia, other factors may contribute to changes in eating behaviors. For instance, the immune response to the infection has been associated to inflammation and gut problems [128]. Imbalances in gut bacteria can disrupt hunger cues, as well as contribute to mood changes and disordered eating [129,130]. Stomach discomfort has also been reported in infected individuals and may affect their eating patterns [131]. Finally, psychosocial factors may contribute to the development of disordered eating. For instance, a large population study using health care records identified an increased incidence of eating disorders during the pandemic, and especially that of anorexia nervosa in adolescents [132].

In sum, many children with long COVID demonstrate changes in their eating, even if they do not necessarily meet the diagnostic threshold for an eating disorder [19]. This has been considered the consequence of other symptoms, such as anosmia, ageusia, and stomach discomfort; an effect of inflammation and microbiota changes; and/or linked to pandemic-related psychosocial stressors.

4.6. Psychosis and mania

Several case reviews have reported psychotic symptoms (e.g. associated with mania) in young people with COVID-19 [51,56,58,133,134]. However, this has not yet been studied on a larger scale, thus estimating their prevalence and persistence remains challenging. Further, the presentation may vary. Delusions have been frequently reported in case reports [51,56,77,133], alongside visual, auditory, and olfactory hallucinations [56,58,121,122]. Mania has not been reported frequently in the literature, with only three adolescents identified [51,56]. All cases presenting with psychosis/mania appeared to respond well to treatment and improved in a relatively short period of time [51,56,77,133]. This appears similar to what has been previously reported in adult cases, with psychotic symptoms lasting up to 90 days [135]. However, compared to adults, adolescents have been identified to be at a greater risk of experiencing psychotic symptoms in the 6 months following infection [66]. Due to the limited number of studies, it is difficult to identify potential risk factors. Further, although these symptoms appeared after COVID-19 infection, causation cannot be definitively proved, and other factors may be at play. It has been suggested that the inflammatory response can precipitate symptoms. However, neuropsychological stresses associated with the diagnosis of COVID-19, as well as treatment with steroids, can also precipitate/contribute to psychotic episodes [136].

In sum, case reports have highlighted that psychosis/mania can develop in the context of COVID-19. Unfortunately, estimating prevalence and persistence is challenging due to the limited number and nature of these studies. However, a large retrospective cohort study reported that adolescents have an increased risk of psychosis as compared to adults in the 6 months following infection [66]. Pathogenetic mechanisms may include inflammatory response, corticosteroid treatment, as well as psychosocial stressors.

4.7. Meta-analytic evidence on the impact of COVID-19 on mental health in children and adolescents

Whilst several meta-analyses on the mental health in children and adolescents have been published [143], a recent systematic review and meta-analysis [144], including 51 studies, stands out for its methodological rigor, as it included only longitudinal cohort studies and cross-sectional studies with follow-up, reporting changes from pre-pandemic to intra-pandemic periods on a validated scale, or studies comparing samples from different cohorts or cross-sectional studies from pre-pandemic to intra-pandemic periods, when the populations were comparable. The authors found that i) anxiety (self-reported items), internalizing symptoms (parent-reported items), and hyperactivity and inattention symptoms (self-reported) did not change significantly; ii) internalizing symptoms (self-report) deteriorated slightly during the pandemic; iii) conduct problem symptoms (self-reported) decreased in severity; iv) prosocial behaviors and peer relationships slightly deteriorated; v) depressive (self-reported) symptom changes were mixed. However, when considering only studies judged by the authors to be of high quality, the findings showed indeed an increase in the severity of the depressive symptoms. The results of this meta-analysis should be considered alongside those of a recent Bayesian nonlinear dose – response meta-analysis [145] of studies in children and adults showing a U shape relationship, with anxiety and depressive symptoms worsening during the first 60 days, and then a flatter slope after 2 months. It also found a linear association between severity of depression and anxiety symptoms and stringency index, a measure indicating the stringency of policy-related containment restrictions.

5. Conclusions

Overall, headache, cognitive deficits, anosmia, ageusia, and dizziness appear to be common neurological symptoms associated with long COVID in the pediatric population. Prevalence estimates are highly variable in the literature due to study heterogeneity in terms of design, sample size, inclusion of children with confirmed and non-confirmed infection, severity of primary COVID infection (mild vs severe symptoms requiring hospitalization), and method of case identification (e.g. general population vs specialized long COVID clinics). Pooled

prevalence estimates range between 9.7% (fatigue) to 4.4% (dizziness) [19]. Similarly, symptom duration varies across studies and, although symptoms generally improve over time, they have been reported even after several months following initial infection. Increasing age has been identified as a risk factor, as well as female sex for some symptoms (ageusia and dizziness). Seizures typically present as acute SARS-CoV-2 sequela, but long-term risk warrants further investigation. Finally, encephalitis/encephalopathy are rare and often fatal acute complications but may be associated with long-term cognitive/neurological symptoms in survivors.

Apart from mood/anxiety symptoms and sleep problems, neuropsychiatric conditions have received less attention in the literature and some have been reported mostly by small studies or case reports (e.g. psychosis and mania). It is therefore more challenging to estimate their prevalence and persistence. Increasing age has been identified as a risk factor. For instance, sleep disorders were more prevalent in older children, and many of the case reports (e.g. on psychosis) described adolescents. Pre-existing mental health conditions may also increase the risk [114].

Although their pathogenesis is not fully understood, studies suggest that neurological and neuropsychiatric symptoms may differ in the underlying mechanisms. For instance, infection-related mechanisms, as discussed in section 2, may have a more prominent role in the development of neurological symptoms [42,87]. Conversely, pandemic-related restrictions and social isolation may play a more prominent role in neuropsychiatric manifestations, such as anxiety and sleep problems [130,146–148]. Future research is needed to better understand the prevalence of neuropsychiatric symptoms associated with long COVID, and to disentangle the direct effects of COVID-19 infection from pandemic-related factors. Further, as children's clinical presentations may differ as compared to those in adults, more in depth comparison is required to fully understand the differences and the underlying pathogenetic mechanisms. Future research is also warranted to understand not only the risk, but also protective/resilience factors in the context of neuropsychiatric symptoms. In this regard, the large-scale study Collaborative Outcomes study on Health and Functioning during Infection Times (COH-FIT) [149], an anonymous online survey ongoing since 26 April 2020, targeting adults and children in the general population and involving over 220 researchers from 49 different countries, may provide unvaluable insights.

Overall, understanding the underlying pathophysiology, alongside risk and protective factors for the development of neurological and neuropsychiatric symptoms in children and young people, is crucial to develop new interventions strategies and to support clinical practice and policies during the current and, possibly, future pandemics.

6. Expert opinion

Reviewed evidence suggest that children and adolescents may develop persistent neurological and neuropsychiatric symptoms following acute SARS-CoV-2 infection. This is an important area of research due to the potential debilitating effects of these conditions on daily functioning, school attainment, and well-being. Studies to date have provided inconsistent data on prevalence and symptom duration; as many were limited by the small sample size, lack of comparative data, and short follow-up. Several studies have investigated potential biological underpinnings, especially for neurological conditions, and suggested that multiple mechanisms may be involved, including systemic inflammatory response and immune-mediated processes. The pathogenesis of neuropsychiatric symptoms is less clear. During the pandemic, there has been a world-wide increase in rates of depression, anxiety, problematic eating and alcohol and cannabis use among previously healthy children and young people [115,116,132,150]. Although the presented case reports suggest that SARS-CoV-2 infection may directly contribute to some of these manifestations, e.g. by causing inflammation, disentangling the effects of social restrictions and isolation remains challenging.

Overall, studies in larger samples with longer follow-ups are needed to clarify prevalence and symptom duration. Most studies have considered age and sex among risk factors, but other associated factors need to be investigated, such as genetic predisposition, ethnicity, and comorbidities. Finally, the inclusion of control (seronegative) samples would be important to separate the direct effects of the infection from those of pandemic-related psychosocial stressors. We recommend that future research prioritizes the investigation of risk factors, as this is pivotal to guide prevention strategies and early intervention. Screening programs and psychoeducation may also enhance the early recognition of these symptoms. In addition to risk factors, it is also crucial to understand protective/resilience factors vis-a-vis the development of neuropsychiatric symptoms. Overall, clarifying pathogenetic mechanisms is paramount to develop more targeted and effective treatment.

In line with this, there are increasing efforts to identify putative biomarkers that can aid recognition and guide treatment. For instance, a study in adults has shown that individuals with COVID-related acute respiratory distress syndrome (ARDS) maintained high plasma levels of neurofilament light chain (NfL), a marker of neuro-axonal damage, up to three months post-discharge [151]. Similarly, another study reported that one-third of adults hospitalized due to COVID had persistent elevated d-dimer post-discharge [152]. Although these studies have been conducted in adults, and their applicability to youths is not known, they promote the identification of biomarkers to assess severity and inform the need for further investigations or rehabilitation.

Medical societies in different countries have developed guidelines to aid recognition and treatment of long COVID [14,153,154], including in the pediatric population. For instance, the NICE [14] guidelines recommend not to underestimate symptoms such as fatigue, lack of concentration and poor memory, especially in the context of worse performance or school absences. They advise to conduct a holistic and preferably face-to-face assessment of youths with suspected long COVID, carry out blood tests/investigations to exclude alternative diagnoses, and refer appropriately and early to specialist services if needed. They also flag up the uncertain evidence base for children and young people, due to the limited number of robust studies, small sample sizes, and risk of bias. Similarly, a tailored and multidisciplinary approach has been recommended by an Italian inter-society consensus [153], with scheduled pediatric reviews at four

and 12 weeks post-infection and further investigations if needed. Differential diagnosis with neuropsychiatric manifestations secondary to other underlying disorders (e.g. respiratory) or in the context of intensive care sequelae have been also recommended [46]. Finally, there is a growing body of research into interventions to promote mental health in the context of long COVID, including psychological and pharmacological interventions. However, as highlighted by a systematic review, many are feasibility trials and do not specifically include pediatric samples [155].

Considering mental health needs, it is important to mention the increased prevalence of Post-traumatic stress disorder (PTSD) across the population [137,138,139]. Although PTSD is not classically considered in the context of long COVID, a small survey study following up 38 children at three months post-hospitalization reported that one-third had PTSD symptoms [140]. Similarly, a study in adults reported that 35% of those discharged from intensive care post COVID infection had significant PTSD symptoms, even 2 years after their care [141]. These results suggest that hospitalization may be a risk factor for developing PTSD, and that symptoms may persist long term. Data on children with long COVID without hospitalization are inconsistent, either reporting increased symptoms [76] or no difference from controls [142]. Nevertheless, it is important that clinicians are aware that children may also experience PTSD symptoms, especially those previously hospitalized; with pre-existing poor mental health; or higher levels of parental concerns [140,142].

In conclusion, more research is needed to tackle the gap in management recommendations for pediatric neuropsychiatric symptoms of long COVID, and a pragmatic and tailored approach is recommended, considering both the physical and psychological needs of the child [46,153].

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