Postacute Sequelae of SARS-CoV-2 in Children

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The coronavirus disease 2019 (COVID-19) pandemic has caused significant medical, social, and economic impacts globally, both in the short and long term. Although most individuals recover within a few days or weeks from an acute infection, some experience longer lasting effects. Data regarding the postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) in children, or long COVID, are only just emerging in the literature. These symptoms and conditions may reflect persistent symptoms from acute infection (eg, cough, headaches, fatigue, and loss of taste and smell), new symptoms like dizziness, or exacerbation of underlying conditions. Children may develop conditions de novo, including postural orthostatic tachycardia syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, autoimmune conditions and multisystem inflammatory syndrome in children. This state-of-the-art narrative review provides a summary of our current knowledge about PASC in children, including prevalence, epidemiology, risk factors, clinical characteristics, underlying mechanisms, and functional outcomes, as well as a conceptual framework for PASC based on the current National Institutes of Health definition. We highlight the pediatric components of the National Institutes of Health-funded Researching COVID to Enhance Recovery Initiative, which seeks to characterize the natural history, mechanisms, and long-term health effects of PASC in children and young adults to inform future treatment and prevention efforts. These initiatives include electronic health record cohorts, which offer rapid assessments at scale with geographical and demographic diversity, as well as longitudinal prospective observational cohorts, to estimate disease burden, illness trajectory, pathobiology, and clinical manifestations and outcomes.

The coronavirus disease 2019 (COVID-19) pandemic has caused unprecedented devastating medical, social, and economic impacts globally, both in the short and long term.[1–4] COVID-19 disproportionately affects Black, Indigenous, and people of color communities,[5] families living in rural communities, and/or communities facing economic hardships. Although most individuals recover within a few days or weeks after an acute severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2) infection, some experience longer lasting effects. Given that ~20% of COVID cases in the United States are in children,[6] and that current pediatric postacute sequelae of SARS CoV-2 (PASC) prevalence estimates are 10% to 20%, PASC is estimated to affect up to 5.8 million children, representing a significant community impact. The scientific community has acknowledged an urgent need to understand more about PASC in children.[7] Although PASC can affect any individual, populations deserving specific focus include children with intellectual and developmental disabilities, children with

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medical complexity, and those with prolonged debilitating symptoms.[8,9] Critical to this work is the effective use of both electronic health record (EHR) cohorts to offer rapid assessments at scale with geographical and demographic diversity, and longitudinal prospective cohorts to estimate disease burden, clinical manifestations, and evaluate effects of treatment and vaccination. This state-of-the-art narrative review provides a summary of our current knowledge about PASC in children, including prevalence, epidemiology, risk factors, clinical characteristics, underlying mechanisms, and functional outcomes, as well as a conceptual framework for PASC based on the current National Institutes of Health (NIH) definition. Subject matter experts (spanning general pediatrics, neurology, infectious diseases, pulmonology, rheumatology, immunology, cardiology, gastroenterology, rhinology, psychology, rehabilitation medicine, and patient and parent advocates) reviewed the literature for relevant pediatric studies and summarized the findings, with a focus on higher-quality pediatric data (Supplemental Table 1). We also highlight the pediatric efforts of the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative, which seek to characterize the natural history of PASC in children and young adults and its underlying mechanisms and long-term health effects, with the aim to fill critical research gaps and inform future treatment and prevention.[10]

DEFINITIONS

Several terms and definitions exist for the symptoms and conditions after SARS-CoV-2 infection. The term PASC has been adopted for more widespread use in the scientific community. The NIH definition of PASC refers to ongoing, relapsing, or new symptoms, or other health effects occurring after the acute phase of SARS-CoV-2 infection that is present 4 or more weeks after the acute infection.[10] The World Health Organization definition of post–COVID-19 condition is the continuation or development of new symptoms 3 months after the initial infection, with symptoms lasting for at least 2 months with no other explanation.[11] Another group of experts has recently characterized post–COVID-19 condition in children as at least 1 physical symptom persisting for a minimum of 12 weeks after initial confirmed infection that may continue or develop after infection, cannot be explained by an alternative diagnosis, has an effect on everyday functioning, and may fluctuate or relapse over time.[12]

EPIDEMIOLOGY

The incidence of PASC in children is less well-characterized than in adults and varies widely, ranging from 4% to 62% across existing large studies, with more studies reporting estimates closer to 10% to 20% within the first 6 months after acute infection.[9,13–21] Overall, the wide range of estimates of PASC incidence relates to differences in study design, setting, population, follow-up period, variable ascertainment methods, and variable diagnostic criteria. To date, the majority of studies of PASC in children can be characterized as small, case-based, cross-sectional, retrospective, clinic-based, or convenience samples. PASC can also be difficult to diagnose because associated signs and symptoms are broad, affecting numerous organ systems, and can overlap with underlying comorbidities.

Less is known about the trajectory of PASC. In 1 study, PASC symptoms resolved in the majority of children over the course of several months,[22] with one-third of children having ongoing symptoms at 12 months.[23] However, few studies have examined outcomes beyond 12 months after infection or examined the full range of symptomatology. In terms of PASC symptoms from initial versus subsequent infections, 1 study did not show a significant difference in PASC symptoms between those with a first episode of infection or reinfection during the o era.[24]

Some risk factors for PASC in children have begun to be elucidated. Although PASC can develop in those with asymptomatic infection,[14,20,25] in one study assessing pooled prevalence, the incidence was smaller after asymptomatic (15%) versus symptomatic (45%) infections.[26] Other risk factors include pre omicron variant periods,[23] increasing child age, higher severity of illness and number of organ systems involved during acute infection, underlying chronic medical conditions, and increased weight status.[9,13,27] Furthermore, there are bio–psycho–social and environmental factors that contribute to PASC manifestations. The specific effect of adverse social drivers of health (SDoH) on the development of PASC have not been well studied; however, many SDoH have greatly increased during the pandemic, including housing and food insecurity, reduced family income, and disrupted access to health care and educational resources. Adverse SDoH have been associated with increased rates of physical and mental health problems in children, and can contribute to the development or exacerbation of illnesses via decreased immunologic functioning secondary to the effects of chronic stress and poor nutrition.[28–30]

A CONCEPTUAL MODEL FOR PASC

On the basis of our current understanding and utilizing of aforementioned definitions, PASC encompasses a heterogeneous collection of symptoms and conditions after SARS-CoV-2 infection. These symptoms and conditions may reflect persistent symptoms from acute COVID-19 infection, such as cough, shortness of breath, headaches, fatigue, chronic pain, and loss of taste and smell. They may further reflect exacerbation of underlying conditions, such as persistent cough in children with asthma and chronic lung disease, diabetic ketoacidosis in children with diabetes, exacerbation of mental health and neurodevelopmental conditions, and other disease flares.

For this reason, special considerations are required for the study of PASC in children with medical complexity, who may be more at risk for SARS-CoV-2 infection.[31–34] Some postacute conditions may arise de novo, including new-onset autoimmune conditions,[35] such as the development of type 1 diabetes.[36] These conditions may follow mild or even asymptomatic infection. One example of a serious complication after infection that was identified early in the pandemic is multisystem inflammatory syndrome in children (MIS-C), which results from a hyperinflammatory response to SARS-CoV-2, observed 2 to 6 weeks after initial infection (Fig 1).

PERSISTENT SYMPTOMS AND COMPLICATIONS OF COVID-19 INFECTION

PASC comprises a heterogeneous collection of symptoms and conditions that can affect any organ system. Conditions and symptoms that have been reported in children are summarized in Fig 2. A summary of some of the more common presentations is outlined below.

Constitutional Symptoms/Syndromes

Fatigue and malaise are common manifestations of PASC in children,[13] and may be accompanied by weakness, shortness of breath, difficulties in concentration/brain fog, somnolence, or depressed mood. These are commonly triggered after physical and/or cognitive activities, which is referred to as postexertional malaise (PEM). PEM is "the worsening of a patient's symptoms and function after exposure to physical, cognitive, emotional, or orthostatic stressors that were normally tolerated before disease onset. PEM is an exacerbation or relapse of symptoms that occurs as a consequence of exertional activity."[37] When these symptoms persist, and present as a disabling symptom, a diagnosis of post-COVID fatigue may be considered.[38] Children with persistent fatigue and PEM meet official criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with profound fatigue occurring for at least 6 months with significant impairment in day-to-day functioning including physical functioning, school performance, and extracurricular activities.[39] Common concurrent symptoms include musculoskeletal pain (myalgias or arthralgias), cognitive difficulties/brain fog, and persistent headaches.

Respiratory Manifestations

Respiratory symptoms including cough,[40] chest tightness, and shortness of breath constitute some of the commonest PASC symptoms.[41,42] Persistent respiratory symptoms may occur independently of preexisting or measurable abnormalities in lung structure or function.[43–45] There is histologic evidence of proinflammatory and procoagulant factors that contribute to parenchymal damage during the acute infection phase, with inflammatory, autoimmunity, and profibrotic changes developing during the chronic phase associated with fibrosis.[46] In a study of children presenting with persistent pulmonary symptoms ≥4 weeks after acute infection managed in a pediatric post-COVID clinic with 2 to 3 month follow-up, common respiratory presentations included cough, chest pain, dyspnea at rest, and exertional dyspnea. Most children (77%) had normal spirometry; however, 15% demonstrated obstructive deficits and 31% demonstrated a positive bronchodilator response. Additional phenotypes observed included paradoxical vocal cord motion dysfunction and exertional fatigue with functional limitations.[47]

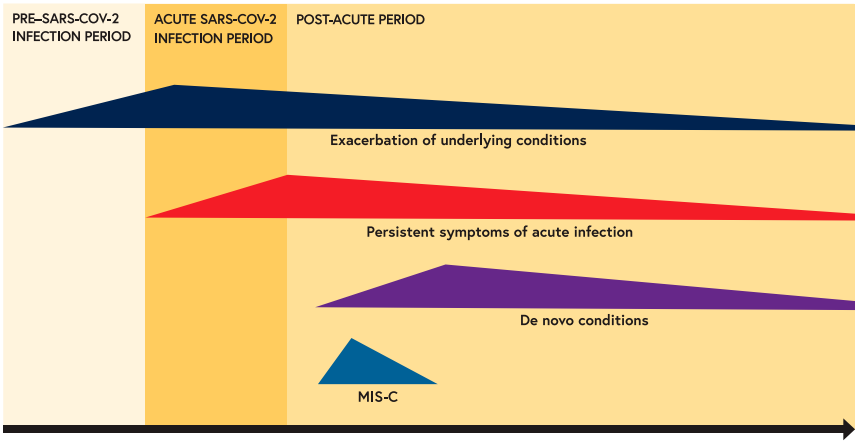

FIGURE 1

Conceptual model of the PASC. Legend: The NIH defines the PASC as symptoms or conditions which may reflect exacerbation of underlying conditions, persistent symptoms of acute infection, or may be new symptoms or conditions arising de novo, distinct from the acute SARS-CoV-2 infection period.

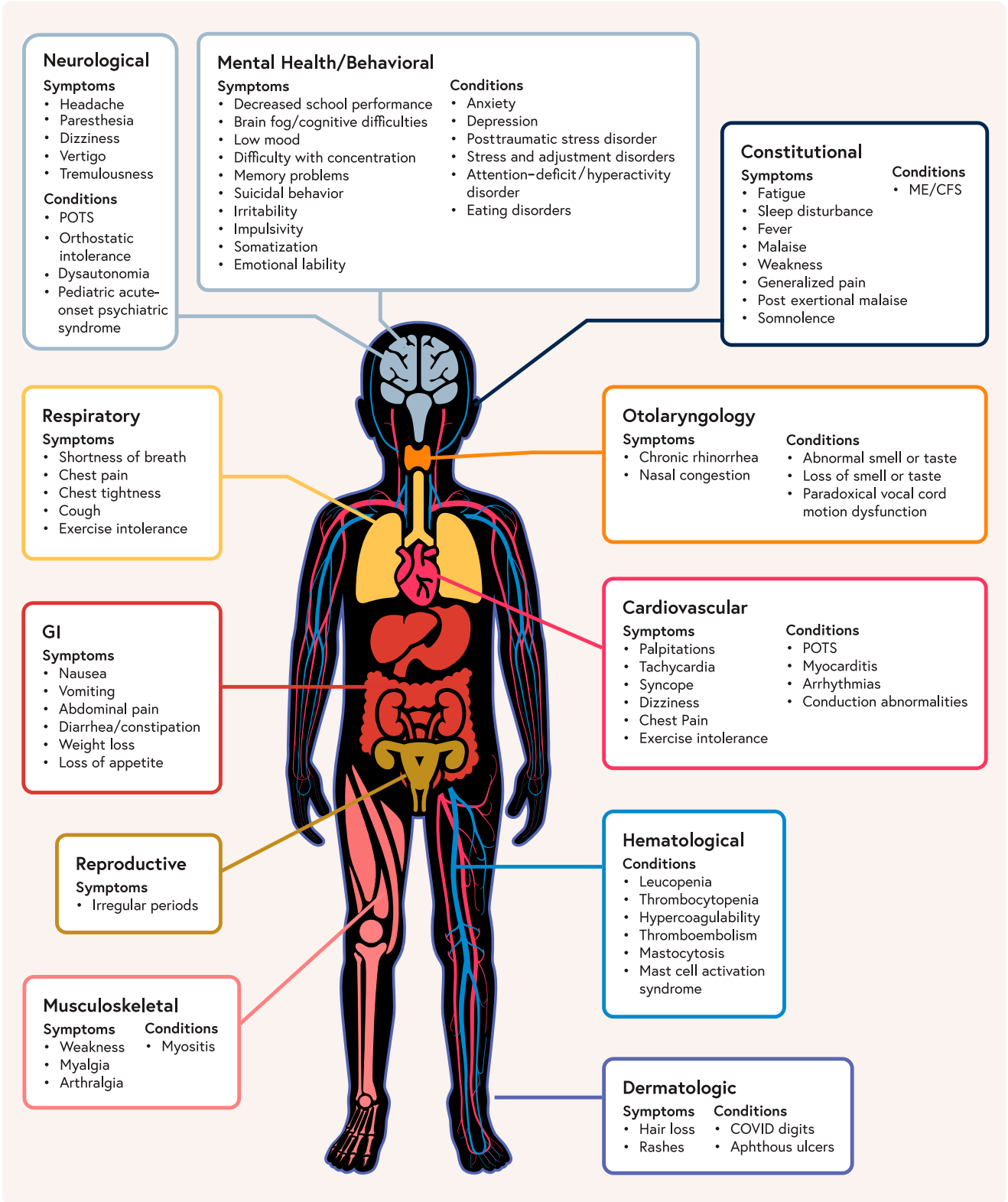

FIGURE 2

Organ system involvement of PASC in children. Legend: The figure outlines symptoms and conditions, grouped by body system, which have been associated with the PASC. Some symptoms may be transient and rare in children, and a description of more common manifestations is provided in the main text.

Cardiac Manifestations

Cardiac complications of COVID-19 include myocarditis, MIS-C (with or without coronary artery dilation),[48–50] arrhythmias,[51] electrocardiographic,[52] and conduction abnormalities.[53] Inappropriate activation of the inflammatory cascade is thought to underly the myocardial damage.[54] Despite the gravity of the initial MIS-C presentation, the majority of children are asymptomatic by 6 months,[55] with only mild abnormalities detected by imaging.[56,57] However, persistent cardiovascular symptoms do occur in a minority of children/adolescents with and without MIS-C, notably unexplained exercise intolerance, fatigue, resting sinus tachycardia, orthostatic intolerance, orthostatic hypotension, and postural orthostatic tachycardia syndromes (POTS).[58–60] There is a growing recognition of POTS as an important presentation of PASC. POTS is defined in children as a sustained heart rate increase of at least 40 beats per minute or maximum heart rate >130 beats per minute or >125 beats per minute for adolescents aged 13 to 18 years within 10 minutes of standing, with an absence of orthostatic hypotension, frequent orthostatic symptoms with duration for at least 3 months, and the absence of other conditions.[61] PASC-related tachycardias can occur in isolation or as part of the ME/CFS spectrum. There appears to be both phenotypic and treatment overlap of PASC-mediated POTS with POTS diagnosed prepandemic,[62] although the underlying mechanism of orthostatic intolerance may differ.[63]

Otolaryngologic Manifestations

Persistent olfactory dysfunction is 1 of the hallmarks of PASC, and lasting abnormalities in smell and taste may adversely affect dietary and behavioral choices.[64] In the largest retrospective cohort study to date, smell and taste disturbances and loss of smell had the highest adjusted hazard ratios (1.96, 1.85, respectively)[9] among all features of PASC. Challenges remain in appropriately characterizing olfactory function across pediatric cohorts because of the wide age range and associated difficulty in reliably reporting olfaction through subjective and objective measures. Although likely reflecting underlying neurologic changes, children with PASC report increased rates of persistent dizziness,[15] along with nasal congestion and rhinorrhea.[18] The incidence of persistent sore throat and other ear conditions was not higher in children with COVID-19 versus children with other upper respiratory infections.[18] Sudden sensorineural hearing loss, often accompanied by tinnitus, is rare but well documented in adults.[65] To date, however, there is little clear evidence of similar effects in children.[66]

Mental Health Conditions

Numerous mental health conditions have been identified in children as a result of the COVID-19 pandemic, including anxiety, stress, depression, panic, irritability, impulsivity, sleep problems, emotional lability, posttraumatic stress disorder, eating disorders, and suicidal behavior.[67–69] However, mechanistic studies exploring the specific pathobiology and carefully conducted studies with adequate control subjects are required to explore effects from SARS-CoV-2 infection versus the situational context of the pandemic (such as social distancing, school closures, canceled extracurriculars, loss of loved ones). Large EHR cohort studies have demonstrated increased incidence of a neurologic or psychiatric diagnosis in the 6 months after SARS-CoV-2,[44,70] compared with those without confirmed infection. In children, a COVID-19 diagnosis has been shown to be associated with experiencing a new mental health condition (within a median of 33 days after infection) compared with negative controls. The most common mental health-associated PASC conditions observed among children and adolescents were anxiety, attention-deficit/hyperactivity disorder, and disorders related to trauma or stressors.[71] There have also been case reports of pediatric acute-onset neuropsychiatric syndrome in children after SARS-CoV-2 infection.[72,73]

Neurologic Manifestations

Common neurologic symptoms include headaches, dizziness, and loss of taste and smell. Dysautonomia including POTS and orthostatic intolerance are commonly reported sequela of SARS-CoV-2, described above. Many children and adolescents with PASC complain of cognitive impairment, commonly referred to as brain fog, and the prevalence has been determined to be between 2% and 44% in pediatric studies and case series.[74–76] Abnormal brain findings on fluorodeoxyglucose positron emission tomography scans of patients reporting brain fog include localized hypometabolic regions in the anterior and posterior cingulate cortex, precuneus, and pons.[77] Other neurologic manifestations reported include neuropathy, tics, chronic migraines, and sensory issues.

Gastrointestinal (GI) Manifestations

The most common GI symptoms of acute COVID-19 infection and MIS-C in children include diarrhea, abdominal pain, vomiting, and anorexia.[78,79] The prevalence of these symptoms and others (ie, constipation, loss of appetite, weight loss) generally decrease over time.[80] However, some persist or even develop at least 4 weeks after acute infection.[18] The reported prevalence ranges widely (ie, abdominal pain 1%[81]–72.2%),[82] which may be influenced by data collection methodology (self-report versus EHR review) and severity of acute infection. Some PASC studies describe coexistent neuropsychological and GI symptoms.[19,25,82–84] Other studies among individuals with COVID-19 demonstrated prolonged fecal shedding of SARS-CoV-2 RNA associated with persistent GI symptoms.[61,85–87]

Dermatological Manifestations

Skin lesions, a known complication of COVID-19, are reported in children and adults, and may persist beyond the acute infection. Skin rashes may include maculopapular eruptions, erythema, vesicles, pustules, erythema multiforme, desquamation, and urticarial lesions.[88] Most lesions are localized to the trunk and extremities. A complication described early in the pandemic was "COVID toes," representing chilblain-like erythematous, edematous, and painful pruritic lesions on the extremities.[89]

Musculoskeletal Manifestations

Musculoskeletal involvement secondary to the hyperinflammatory state includes myalgia, muscle weakness, and myositis. Elevated cytokine and chemokine expression can be associated with muscle inflammation, and resulting loss of muscle tissue, decreased muscle contractility, and fibrosis.[90] Joint pathology in the form of self-limited postinfectious reactive arthritis has been reported in children[91,92] after SARS-CoV-2 infection. Patients with MIS-C also occasionally develop inflammatory arthritis, although reports are rare.

Hematologic/Inflammatory Presentations

Mast cell disorders such as mastocytosis and idiopathic mast cell activation syndrome can be associated with many symptoms observed in PASC, including neuropsychiatric, fatigue and cognitive impairment, chronic pain, GI symptoms, food intolerance, skin rash, and itch. Autonomic symptoms can also be present, such as palpitations, orthostatic intolerance, skin flushing, and heat intolerance. There is evidence that mast cells and mast cell mediators are present in severe COVID-19, and that these mediators persist in PASC compared with SARS-CoV-2–infected individuals who do not develop PASC.[93–96] Mast cell activation may be overexpressed in atopic individuals, which has been suggested as a possible reason for increased incidence of PASC among individuals with asthma and allergies.[17] There have been scattered reports of the clinical efficacy of mast cell mediator blockade in PASC, such as H1 or H2 antagonists.[97–99] A placebo-controlled trial for SARS-CoV-2–infected outpatients demonstrated reductions in symptom length in individuals treated with famotidine, an H2 antagonist,[100] though the precise effect remains to be clarified.[101]

EXACERBATION OF UNDERLYING CONDITIONS

PASC may represent the exacerbation of underlying comorbidities; for example, chronic cough among children with asthma, and pain exacerbations among children with connective tissue diseases and fibromyalgia.

Asthma

Similar to other respiratory pathogens,[102–105] SARS-CoV-2 can exacerbate chronic pulmonary conditions such as asthma and cystic fibrosis. Several studies have found that children with asthma did not experience increased severity during an acute infection.[106] Although some studies, limited by sample size or lack of an adequate comparison group, have not found an association between SARS-CoV-2 infection and subsequent poor asthma control,[107,108] a larger study comprising data from 108 health systems across the United States showed a worsening of asthma outcomes in children during the 6 months after polymerase chain rection-confirmed infection.[109]

Connective Tissue Disorders and Fibromyalgia

COVID-19 may exacerbate conditions like fibromyalgia and connective tissue diseases such as Ehlers Danlos syndrome, Marfan, and other hypermobility syndromes, which can trigger pain and are often nonremitting. These conditions are known to be associated with other manifestations including ME/CFS, mast cell activation syndrome, and dysautonomia.[110,111]

POSTINFECTIOUS CONDITIONS

Multiinflammatory Syndrome in Children (MIS-C):

MIS-C is the most serious postacute sequelae of SARS CoV-2 infection, usually developing 2 to 6 weeks after SARS CoV-2 infection. The current Centers for Disease Control and Prevention definition of MIS-C is an individual $\leq$21 years old presenting with fever, laboratory evidence of inflammation, involvement of $\geq$2 organ systems, absence of an alternative diagnosis, evidence of clinically severe illness requiring hospitalization, and evidence of infection or exposure to a SARS-CoV-2 case within 4 weeks of symptom onset.[112] The presentation includes fever, respiratory (shortness of breath), cardiac (chest pain), GI (nausea, abdominal pain, vomiting), and/or dermatologic (rash, mucosal changes) system involvement.[113] A higher proportion of children with MIS-C are male, African American or Hispanic, and have comorbid obesity.[114] The highest rates appear to be among those 6 to 12 years old, although more recently, MIS-C has been increasingly recognized in neonates, associated with maternal SARS-CoV-2 in the prenatal period.[115–117] Hypotension, shock, cardiac dysfunction (most commonly left ventricular dysfunction), arrhythmia, and myocarditis remain the most serious MIS-C complications.[118] A recent systematic review and meta-analysis identified the combined prevalence of myocarditis/pericarditis to be 34.3% and coronary artery abnormalities to be 15.2%.[119] Cardiac MRI has demonstrated global myocardial inflammation and edema, in contrast with regional inflammation and edema in COVID-19 myocarditis.[120] Although serologic testing was an important component of diagnosis during the earlier phase of the pandemic, increasing natural immunity and vaccination in pediatric populations has rendered this testing to be less useful clinically during the

present time.[121] MIS-C likely represents an illness spectrum, with milder cases having been described,[122] with the incidence[123] and severity decreasing over the course of the pandemic.[124] Although data on long-term outcomes are accruing, most cases show resolution of inflammation and related symptoms within 1 to 4 weeks after illness onset. One-year follow-up of critically ill children after MIS-C demonstrates favorable outcomes including resolution of cardiac abnormalities on echocardiogram,[125] with no significant medium- or long-term sequelae.[126]

De Novo Conditions

There have been reports in adult and pediatric studies of new health conditions arising after COVID-19, distinct from symptoms arising during the acute infection phase. These conditions include diabetes, neurologic conditions, and other autoimmune conditions.

Type 1 and Type 2 Diabetes

Multicenter studies have reported an increase in the incidence of type 1 and type 2 diabetes and increased frequency and severity of diabetic ketoacidosis in children and adolescents at least 30 days after SARS-CoV-2 infection,[127–131] including compared with uninfected controls.[128] Several large multicenter studies have demonstrated an association between type 1 diabetes after SARS-CoV-2 infection, including a US study demonstrating a 72% increased risk of developing type 1 diabetes in the first 6 months after infection,[36] with similar findings from a study from Norway.[132] A Scottish study found an increased risk of type 1 diabetes during the first few months of the pandemic, a trend which did not continue over time.[133] A study using EHR-extracted data from 24 diabetes clinics in the United States demonstrated a 77% increase in children diagnosed with new-onset type 2 diabetes during the pandemic versus the prepandemic year. These findings mirror similar findings in adults.[6,44,134,135] The reasons for this association warrant further evaluation, but potential mechanisms include increased underlying stress contributing to the pathophysiology of diabetes, as well as increased rates of obesity in children. In vitro studies have demonstrated that SARS-CoV-2 attenuates pancreatic insulin levels and secretion and induces apoptosis of pancreatic β cells, which express the angiotensin-converting enzyme 2 receptors to which SARS-CoV-2 binds.[136] Other hypotheses include stress hyperglycemia secondary to the hyperinflammatory state during infection, as well as perturbations in glucose metabolism resulting from infection, which may precipitate an individuals' predisposition to type 2 diabetes.

Autoimmunity

There have been reports of new autoimmune conditions developing in the weeks to months after acute SARS-CoV-2 infection, including immune thrombocytopenic purpura, Graves' disease, systemic lupus erythematosus, antiphospholipid antibody syndrome, vasculitis, myocarditis, uveitis, and Sjogren's syndrome.[35] New-onset autoantibodies have been detected after acute infections,[137] and a broad autoantibody response can occur even in the absence of severe clinical disease.[138] Although the immune mechanisms are still being elucidated, and may be conflated by other infectious triggers (eg, viral copathogens, secondary bacterial pathogens, pathogens from previous or subsequent infections), factors may include proinflammatory cytokines and chemokines, damage-associated molecular patterns, molecular mimicry, cross-reactive antibodies, and auto-antibodies.[139] Despite the high frequency of autoantibodies in studies of patients with acute infection (with some studies demonstrating up to 50% of people hospitalized with severe COVID-19 having at least 1 type of autoantibody versus 15% of healthy controls[137] and another study showing up to 52% of hospitalized COVID-19 patients with antiphospholipid antibodies[140]), only a relative few patients develop autoimmune disease during the follow-up period, suggesting other factors contributing to the pathogenesis of disease, as well as the need for longer-term follow-up spanning several years.

Neurologic Conditions

Although neurologic manifestations during acute infection are relatively common, including headache, dizziness, and loss of taste and smell, postacute manifestations including meningoencephalitis, demyelinating syndromes including optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, anti-N-methyl-D-aspartate receptor encephalitis, Guillain-Barre syndrome, polyneuropathy, and multiple sclerosis have also been described[141–143] in the weeks after acute infection. These presentations are much rarer in children compared with adults, and are limited to case reports and case series.[144,145] The presentations of children with encephalitis include altered sensorium/delirium, seizures/status epilepticus, and focal neurologic deficits. More fulminant presentations have been described, including acute hemorrhagic necrotizing encephalitis, limbic encephalitis, and rhombencephalitis resulting in more serious neurologic deficits.[141] Demyelinating conditions resulting from postinfectious, immune-mediated mechanisms appear to share features observed with other infections including other respiratory pathogens such as influenza.[145–150] There have been several reports of COVID-19–related cases of Guillain-Barre syndrome, with up to 10% presenting with the Miller-Fisher variant.[151] Cerebrovascular events including ischemic and hemorrhagic stroke, cortical venous sinus thrombosis, and intracranial vasculitis-induced microvascular occlusive disorder have been reported less frequently in children versus adults, and are generally limited to the acute phase.

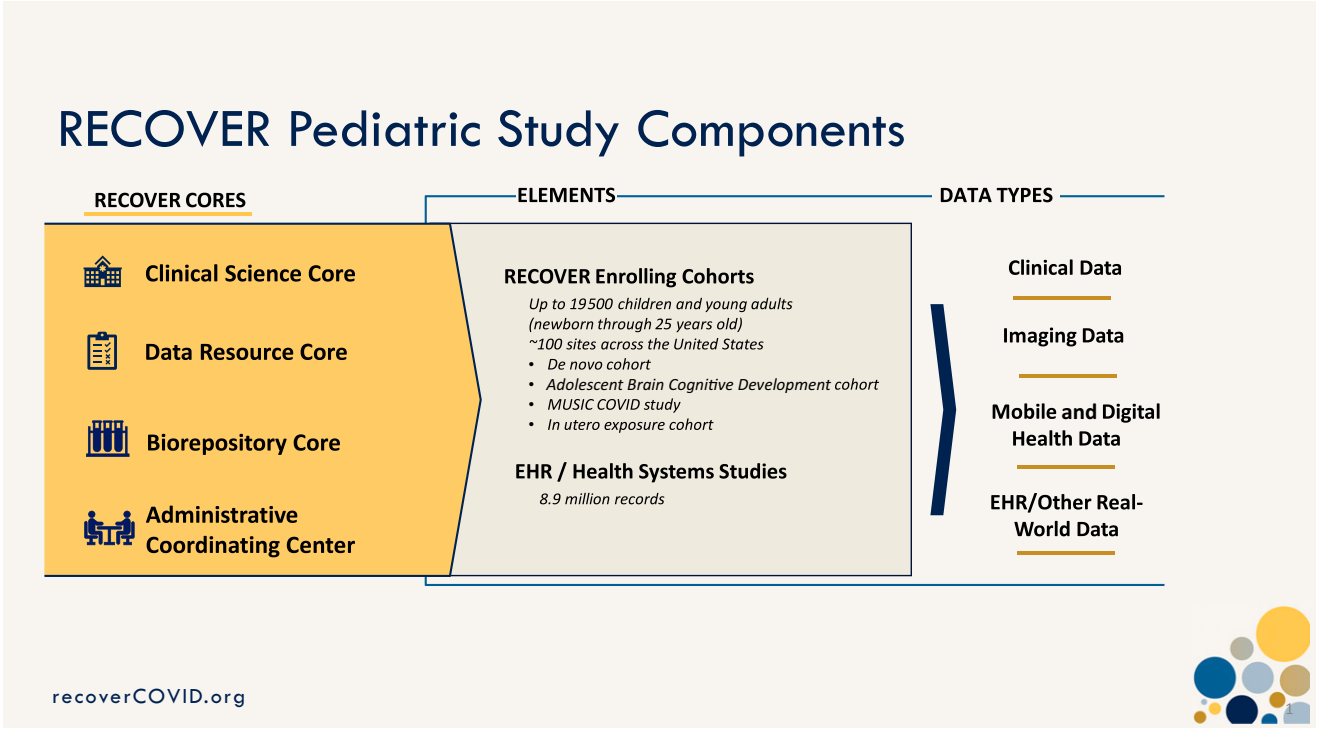

FIGURE 3

Outline of the pediatric-specific components of the RECOVER Initiative. Legend: The RECOVER Initiative includes 4 cores: (1) clinical science core, which leads study implementation and provides scientific leadership in collaboration with hub and site principal investigators; (2) data resource core, which conducts statistical leadership and data management; (3) biorepository core, which manages biospecimens; and (4) administrative coordinating center, which provides administrative support. The enrolling cohorts form the basis of the observational studies. Up to 19 500 participants will be enrolled in these studies in a combined retrospective and prospective, longitudinal observational meta-cohort. The RECOVER enrolling cohorts include the de novo cohort (prospective cohort including children and young adults ages birth through 25 years, with or without a known history of infection, and their caregivers), Adolescent Brain Cognitive Development Cohort, COVID MUSIC study, evaluating the long-term outcomes of MIS-C in children, and in utero exposure cohort (including children <3 years old born to individuals with and without a SAR-CoV-2 infection during pregnancy). The EHR/Health Systems Studies utilizes 8.9 million inpatient and outpatient records from PEDSnet and PCORnet sites (for more information about these cohorts, go to https://pedsnet.org/ and https://pcornet.org/data/). From these elements, RECOVER will encompass diverse data types, including clinical, imaging, mobile and digital health, and EHR data.

NEURODEVELOPMENTAL CONDITIONS

The impacts of COVID-19 infection on neurodevelopment are still to be fully understood. Perinatally, many viruses can affect the developing fetus and placenta because of direct effects from the virus or immune activation.[152,153] Neurodevelopment-related genes have been found to be dysregulated when exposed to peptides and spike protein from SARS-CoV-2 in human in vitro neuronal/glial models.[154] Although SARS-CoV-2 infection does not seem to cause gross neurodevelopmental abnormalities in neonates of infected versus uninfected mothers,[155,156] long-term effects may not be evident for years and therefore require continued longitudinal follow-up. Although the effects of SARS-CoV-2 infection on the nervous system of older children have been described in cases series and reports,[157] few studies have evaluated the long-term consequences on the cognitive, behavioral, motor, and academic domains of affected children. It is also important, though challenging, to differentiate neurodevelopmental sequelae because of SARS-CoV-2 infection versus those related to pandemic stressors.

FUNCTIONAL OUTCOMES OF PASC IN CHILDREN

When evaluating PASC in children and adolescents, it is necessary to consider functional outcomes (ie, behaviors or skills that are meaningful to a child's everyday life or overall well-being, and that facilitate achieving daily goals). Short-term functional outcome domains include mental health, sensory functioning, communication, motor functioning, feeding ability, and respiratory status; longer-term domains include cognition, school performance, ability to perform daily routines, relationships, and sleep/mood status. Studies exploring the functional outcomes of children with PASC are lacking. A retrospective cohort study looking

at outcomes of pediatric patients after MIS-C found that at 6 months, although few organ-specific sequelae were observed, physical reconditioning and mental health support needs persisted.[158] In another descriptive study of patients with PASC with normal pulmonary function testing, many reported persistent exertional dyspnea, cough, impaired 6-minute walk test, and exercise intolerance, suggesting ongoing functional limitations.[42] Standardized assessment tools or validated measures should be developed in children to appropriately track or monitor functional status after acute SARS-CoV-2 infection to help monitor illness trajectories and response to therapeutic strategies.

FUTURE DIRECTIONS AND THE RECOVER INITIATIVE

Three years after the start of the pandemic, we are developing an enhanced understanding of the varied presentations of PASC in children, as well as risk factors and trajectory. However, much remains yet to be discovered. It is important to characterize distinct subphenotypes and patterns of symptom clustering of PASC and to understand why some children develop PASC but not others.[159] Further, it is essential to learn how symptoms reemerge over time during periods of physiologic and/or psychological stress and reinfection, as well as how to prevent latent physiologic injury from developing into chronic health conditions in adulthood. Long-term studies are needed to evaluate the effectiveness of COVID-19 vaccination on the prevention of PASC.[160–166] Studies of effective therapies are also lacking. Although clinical trials are needed to identify and test therapeutic targets, delays in their execution exist in pediatrics, therefore other study designs, such as clinical trial emulation and comparative effectiveness studies to discover therapeutic agents and understand the potential size of their treatment effect, are important.

The NIH has responded to these research gaps by funding the RECOVER Initiative, which has brought together researchers, communities, patient and parent partners, and other key stakeholders to develop a comprehensive national multisite study seeking to characterize the natural history of PASC in children and young adults, its underlying mechanisms, and long-term health effects, using both prospective clinical and EHR cohorts (Fig 3).[10,167] The aims of RECOVER–Pediatrics include:

1. characterizing the prevalence and incidence of new-onset or worsening PASC symptoms;
2. describing the clinical symptoms of PASC, including distinct phenotypes, and describing the clinical course and recovery;
3. identifying risk and resiliency factors for developing and recovering from PASC; and
4. defining the pathophysiology and underlying mechanism of PASC.

RECOVER–Pediatrics consists of clinical cohorts from >100 study sites throughout the United States, which are prospectively following children and young adults from birth through 25 years of age for up to 4 years.[168] As of August 2023, >11 000 children have been enrolled into the pediatric clinical cohort of RECOVER, and EHR cohorts comprise data from >8.9 million records. Overall, RECOVER–Pediatrics includes children and young adults with and without SARS-CoV-2 infection, as well as those who have and have not developed PASC, to differentiate effects of the SARS-CoV-2 infection from the societal impacts of the pandemic. Medical, social, biological, and immunologic data are being collected to characterize symptoms associated with PASC across the early life spectrum, and evaluate how PASC exacerbates preexisting conditions and de novo conditions that arise, providing a more comprehensive approach than other existing global initiatives whose focus is solely patient-reported outcomes. These studies will help the pediatric community in the recognition and management of PASC using a multidisciplinary approach,[169] and will lay the groundwork for needed pediatric treatments and preventative strategies for PASC.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
EHR: electronic health record
GI: gastrointestinal
ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome
MIS-C: multisystem inflammatory syndrome in children
NIH: National Institutes of Health
PASC: postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection
PEM: postexertional malaise
POTS: postural orthostatic tachycardia syndromes
RECOVER: Researching COVID to Enhance Recovery
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2 infection
SDoH: social drivers of health

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REFERENCES

1. US Census Bureau. The coronavirus pandemic's economic impact. Available at: https://www.census.gov/library/publications/2022/econ/coronavirus-pandemics-economic-impact.html. Accessed June 20, 2023
2. Munblit D, Simpson F, Mabbitt J, Dunn-Galvin A, Semple C, Warner JO. Legacy of COVID-19 infection in children: long COVID will have a lifelong health/economic impact. *Arch Dis Child.* 2022;107(3):e2
3. The World Bank. The economic impacts of the COVID-19 crisis. Available at: https://www.worldbank.org/en/publication/wdr2022/brief/chapter-1-introduction-the-economic-impacts-of-the-covid-19-crisis. Accessed June 20, 2023
4. Center on Budget and Policy Priorities. Tracking the COVID-19 economy's effects on food, housing, and employment hardships. Available at: https://www.cbpp.org/research/poverty-and-inequality/tracking-the-covid-19-economys-effects-on-food-housing-and#:~:text=The%20majority%20of%20jobs%20lost,to%20Labor%20Department%20employment%20data. Accessed June 20, 2023
5. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by race/ethnicity. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed March 21, 2023
6. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* 2022;10(5):311–321
7. Long COVID and kids: more research is urgently needed. *Nature.* 2022;602(7896):183
8. Stephenson T, Pinto Pereira SM, Shafran R, et al. CLoCk Consortium. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. *Lancet Child Adolesc Health.* 2022;6(4):230–239
9. Rao S, Lee GM, Razzaghi H, et al. Clinical features and burden of postacute sequelae of SARS-CoV-2 infection in children and adolescents. *JAMA Pediatr.* 2022;176(10):1000–1009
10. RECOVER. RECOVER: Researching COVID to Enhance Recovery. Available at: https://recovercovid.org/. Accessed March 21, 2023
11. World Health Organization. Post–COVID-19 condition (long COVID). Available at: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition#:~:text=Definition,months%20with%20no%20other%20explanation. Accessed March 21, 2023
12. Stephenson T, Allin B, Nugawela MD, et al. CLoCk Consortium. Long COVID (post–COVID-19 condition) in children: a modified Delphi process. *Arch Dis Child.* 2022;107(7):674–680
13. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep.* 2022;12(1):9950
14. Kikkenborg Berg S, Dam Nielsen S, Nygaard U, et al. Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKidsDK): a national, cross-sectional study. *Lancet Child Adolesc Health.* 2022;6(4):240–248
15. Borch L, Holm M, Knudsen M, Ellermann-Eriksen S, Hagstroem S. Long COVID symptoms and duration in SARS-CoV-2 positive children: a nationwide cohort study. *Eur J Pediatr.* 2022;181(4):1597–1607
16. Trapani G, Verlato G, Bertino E, et al. Long COVID-19 in children: an Italian cohort study. *Ital J Pediatr.* 2022;48(1):83
17. Osmanov IM, Spiridonova E, Bobkova P, et al. Sechenov StopCOVID Research Team. Risk factors for post–COVID-19 condition in previously hospitalized children using the ISARIC Global follow-up protocol: a prospective cohort study. *Eur Respir J.* 2022;59(2):2101341
18. Funk AL, Kuppermann N, Florin TA, et al. Pediatric Emergency Research Network–COVID-19 Study Team. Post–COVID-19 conditions among children 90 days after SARS-CoV-2 infection. *JAMA Netw Open.* 2022;5(7):e2223253
19. Guido CA, Lucidi F, Midulla F, et al. Long-Covid Group of Department of Maternal Sciences. Neurological and psychological effects of long COVID in a young population: a cross-sectional study. *Front Neurol.* 2022;13:925144
20. Adler L, Israel M, Yehoshua I, et al. Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study. *BMJ Open.* 2023;13(2):e064155
21. Baptista de Lima J, Salazar L, Fernandes A, Teixeira C, Marques L, Afonso C. Long COVID in children and adolescents: a retrospective study in a pediatric cohort. *Pediatr Infect Dis J.* 2023;42(4):e109–e111
22. Wulf Hanson S, Abbafati C, Aerts JG, et al. Global Burden of Disease Long COVID Collaborators. Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA.* 2022;328(16):1604–1615
23. Morello R, Mariani F, Mastrantoni L, et al. Risk factors for post–COVID-19 condition (long COVID) in children: a prospective cohort study. *EClinicalMedicine.* 2023;59:101961
24. Pinto Pereira SM, Mensah A, Nugawela MD, et al. CLoCk Consortium. Long COVID in children and young after infection or reinfection with the omicron variant: a prospective observational study. *J Pediatr.* 2023;259:113463
25. Al-Rahamneh H, Arafa L, Al Orani A, Baqleh R. Long-term psychological effects of COVID-19 pandemic on children in Jordan. *Int J Environ Res Public Health.* 2021;18(15):7795
26. Ma Y, Deng J, Liu Q, Du M, Liu M, Liu J. Long-term consequences of asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis. *Int J Environ Res Public Health.* 2023;20(2):1613
27. Maddux AB, Berbert L, Young CC, et al. Overcoming COVID-19 Investigators. Health impairments in children and adolescents after hospitalization for acute COVID-19 or MIS-C. *Pediatrics.* 2022;150(3):e2022057798
28. Gray NA, Dhana A, Van Der Vyver L, Van Wyk J, Khumalo NP, Stein DJ. Determinants of hair cortisol concentration in children: a systematic review. *Psychoneuroendocrinology.* 2018;87:204–214
29. Vliegenthart J, Noppe G, van Rossum EF, Koper JW, Raat H, van den Akker EL. Socioeconomic status in children is associated

with hair cortisol levels as a biological measure of chronic stress. *Psychoneuroendocrinology.* 2016;65:9–14

30. McEniry M. Early-life conditions and older adult health in low- and middle-income countries: a review. *J Dev Orig Health Dis.* 2013;4(1):10–29
31. Diskin C, Buchanan F, Cohen E, et al. The impact of the COVID-19 pandemic on children with medical complexity. *BMC Pediatr.* 2022;22(1):496
32. Wanga V, Gerdes ME, Shi DS, et al. Characteristics and clinical outcomes of children and adolescents aged <18 years hospitalized with COVID-19—6 hospitals, United States, July–August 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(5152):1766–1772
33. Woodruff RC, Campbell AP, Taylor CA, et al. Risk factors for severe COVID-19 in children. *Pediatrics.* 2022;149(1):e2021053418
34. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open.* 2021;4(6):e2111182
35. Machhi J, Herskovitz J, Senan AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. *J Neuroimmune Pharmacol.* 2020;15(3):359–386
36. Kendall EK, Olaker VR, Kaelber DC, Xu R, Davis PB. Association of SARS-CoV-2 infection with new-onset type 1 diabetes among pediatric patients from 2020 to 2021. *JAMA Netw Open.* 2022;5(9):e2233014
37. Bateman Horne Center. ME/CFS: diagnosing and managing. Available at: https://batemanhornecenter.org/providers/mecfs/diagnosing-managing/#symptoms-supporting-diagnosis. Accessed August 28, 2023
38. Sandler CX, Wyller VBB, Moss-Morris R, et al. Long COVID and postinfective fatigue syndrome: a review. *Open Forum Infect Dis.* 2021;8(10):ofab440
39. Jason LA, Brown A, Clyne E, Bartgis L, Evans M, Brown M. Contrasting case definitions for chronic fatigue syndrome, Myalgic Encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. *Eval Health Prof.* 2012;35(3):280–304
40. Roessler M, Tesch F, Batram M, et al. Post–COVID-19-associated morbidity in children, adolescents, and adults: a matched cohort study including more than 157 000 individuals with COVID-19 in Germany. *PLoS Med.* 2022;19(11):e1004122
41. Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. *J Infect.* 2022;84(2):158–170
42. Leftin Dobkin SC, Collaco JM, McGrath-Morrow SA. Protracted respiratory findings in children post-SARS-CoV-2 infection. *Pediatr Pulmonol.* 2021;56(12):3682–3687
43. Nalbandian A, Sehgal K, Gupta A, et al. Postacute COVID-19 syndrome. *Nat Med.* 2021;27(4):601–615
44. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of postacute sequelae of COVID-19. *Nature.* 2021;594(7862):259–264
45. Morin L, Savale L, Pham T, et al. Writing Committee for the COMEBAC Study Group. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA.* 2021;325(15):1525–1534
46. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol.* 2020;2(7):e437–e445
47. Palacios S, Krivchenia K, Eisner M, et al. Long-term pulmonary sequelae in adolescents post–SARS-CoV-2 infection. *Pediatr Pulmonol.* 2022;57(10):2455–2463
48. Feldstein LR, Rose EB, Horwitz SM, et al. Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem inflammatory syndrome in us children and adolescents. *N Engl J Med.* 2020;383(4):334–346
49. Dufort EM, Koumans EH, Chow EJ, et al. New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York state. *N Engl J Med.* 2020;383(4):347–358
50. Cem E, Böncüoğlu E, Kõymet E, et al. Which findings make multisystem inflammatory syndrome in children different from the prepandemic Kawasaki disease? *Pediatr Cardiol.* 2023;44(2):424–432
51. Samuel S, Friedman RA, Sharma C, et al. Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR-positive SARS-CoV-2 infection, including drug-induced changes in the corrected QT interval. *Heart Rhythm.* 2020;17(11):1960–1966
52. Regan W, O'Byrne L, Stewart K, et al. Electrocardiographic changes in children with multisystem inflammation associated with COVID-19: associated with coronavirus disease 2019. *J Pediatr.* 2021;234:27–32.e2
53. Dionne A, Mah DY, Son MBF, et al. Atrioventricular block in children with multisystem inflammatory syndrome. *Pediatrics.* 2020;146(5):e2020009704
54. Truong DT, Dionne A, Muniz JC, et al. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults: suspected myocarditis after COVID-19 vaccination. *Circulation.* 2022;145(5):345–356
55. Capone CA, Misra N, Ganigara M, et al. Six-month follow-up of patients with multisystem inflammatory syndrome in children. *Pediatrics.* 2021;148(4):e2021050973
56. Yasuhara J, Masuda K, Watanabe K, et al. Longitudinal cardiac outcomes of multisystem inflammatory syndrome in children: a systematic review and meta-analysis. *Pediatr Cardiol.* 2023;44(4):892–907
57. Arslan SY, Bal ZS, Bayraktaroglu S, et al. Cardiac assessment in children with MIS-C: late magnetic resonance imaging features. *Pediatr Cardiol.* 2023;44(1):44–53
58. Drogalis-Kim D, Kramer C, Duran S. Ongoing dizziness following acute COVID-19 infection: a single center pediatric case series. *Pediatrics.* 2022;150(2):e2022056860
59. Buchhorn R. Dysautonomia in children with postacute sequelae of coronavirus 2019 disease and/or vaccination. *Vaccines (Basel).* 2022;10(10):1686
60. Petracek LS, Suskauer SJ, Vickers RF, et al. Adolescent and young adult ME/CFS after confirmed or probable COVID-19. *Front Med (Lausanne).* 2021;8:668944

61. Chiappini E, Licari A, Motisi MA, et al. Gastrointestinal involvement in children with SARS-COV-2 infection: an overview for the pediatrician. *Pediatr Allergy Immunol*. 2020;31(Suppl 26):92–95

62. Buchhorn R. Therapeutic approaches to dysautonomia in childhood, with a special focus on long COVID. *Children (Basel)*. 2023;10(2):316

63. Novak P, Mukerji SS, Alabsi HS, et al. Multisystem involvement in postacute sequelae of coronavirus disease 19. *Ann Neurol*. 2022; 91(3):367–379

64. Brasseler M, Schönecker A, Steindor M, et al. Development of restrictive eating disorders in children and adolescents with long COVID-associated smell and taste dysfunction. *Front Pediatr*. 2022; 10:1022669

65. Meng X, Wang J, Sun J, Zhu K. COVID-19 and sudden sensorineural hearing loss: a systematic review. *Front Neurol*. 2022;13:883749

66. Malesci R, Rizzo D, Del Vecchio V, et al. The absence of permanent sensorineural hearing loss in a cohort of children with SARS-CoV-2 infection and the importance of performing the audiological "workup." *Children (Basel)*. 2022;9(11):1681

67. Hamatani S, Hiraoka D, Makita K, Tomoda A, Mizuno Y. Longitudinal impact of COVID-19 pandemic on mental health of children in the ABCD study cohort. *Sci Rep*. 2022;12(1):19601

68. Hossain MM, Tasnim S, Sultana A, et al. Epidemiology of mental health problems in COVID-19: a review. *F1000 Res*. 2020;9:636

69. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*. 2020;395(10227):912–920

70. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. Six-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416–427

71. Ali MM, Schreier A, West KD, Plourde E. Mental health conditions among children and adolescents with a COVID-19 diagnosis. *Psychiatr Serv*. 2022;73(12):1412–1413

72. Pavone P, Ceccarelli M, Marino S, et al. SARS-CoV-2 related pediatric acute-onset neuropsychiatric syndrome. *Lancet Child Adolesc Health*. 2021;5(6):e19–e21

73. Efe A. SARS-CoV-2/COVID-19 associated pediatric acute-onset neuropsychiatric syndrome a case report of female twin adolescents. *Psychiatry Res Case Rep*. 2022;1(2):100074

74. Morrow AK, Ng R, Vargas G, et al. Postacute/long COVID in pediatrics: development of a multidisciplinary rehabilitation clinic and preliminary case series. *Am J Phys Med Rehabil*. 2021;100(12):1140–1147

75. Brackel CLH, Lap CR, Buddingh EP, et al. Pediatric long COVID: an overlooked phenomenon? *Pediatr Pulmonol*. 2021;56(8):2495–2502

76. Tarantino S, Graziano S, Carducci C, Giampaolo R, Grimaldi Capitello T. Cognitive difficulties, psychological symptoms, and long-lasting somatic complaints in adolescents with previous SARS-CoV-2 infection: a telehealth cross-sectional pilot study. *Brain Sci*. 2022;12(8):969

77. Hugon J, Msika EF, Queneau M, Farid K, Paquet C. Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. *J Neurol*. 2022;269(1):44–46

78. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017–1032

79. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal symptoms as a major presentation component of a novel multisystem inflammatory syndrome in children that is related to coronavirus disease 2019: a single-center experience of 44 cases. *Gastroenterology*. 2020;159(4):1571–1574.e2

80. Roge I, Smane L, Kivite-Urtane A, et al. Comparison of persistent symptoms after COVID-19 and other non–SARS-CoV-2 infections in children. *Front Pediatr*. 2021;9:752385

81. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. *JAMA*. 2021;326(9):869–871

82. Buonsenso D, Pujol FE, Munblit D, Pata D, McFarland S, Simpson FK. Clinical characteristics, activity levels and mental health problems in children with long coronavirus disease: a survey of 510 children. *Future Microbiol*. 2022;17(8):577–588

83. Werner S, Doerfel C, Biedermann R, et al. The CSHQ-DE Questionnaire Uncovers relevant sleep disorders in children and adolescents with long COVID. *Children (Basel)*. 2022;9(9):1419

84. Mayer EA, Nance K, Chen S. The gut–brain axis. *Annu Rev Med*. 2022;73:439–453

85. Natarajan A, Zlitni S, Brooks EF, et al. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. *Med*. 2022;3(6):371–387.e9

86. Du W, Yu J, Liu X, Chen H, Lin L, Li Q. Persistence of SARS-CoV-2 virus RNA in feces: a case series of children. *J Infect Public Health*. 2020;13(7):926–931

87. Xu CLH, Raval M, Schnall JA, Kwong JC, Holmes NE. Duration of respiratory and gastrointestinal viral shedding in children with SARS-CoV-2: a systematic review and synthesis of data. *Pediatr Infect Dis J*. 2020;39(9):e249–e256

88. Kaya G, Kaya A, Saurat JH. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19: review of the literature. *Dermatopathology (Basel)*. 2020;7(1):3–16

89. Baeck M, Herman A. COVID toes: where do we stand with the current evidence? *Int J Infect Dis*. 2021;102:53–55

90. Silva CC, Bichara CNC, Carneiro FRO, et al. Muscle dysfunction in the long coronavirus disease 2019 syndrome: pathogenesis and clinical approach. *Rev Med Virol*. 2022;32(6):e2355

91. López-González MD, Peral-Garrido ML, Calabuig I, et al. Case series of acute arthritis during COVID-19 admission. *Ann Rheum Dis*. 2021;80(4):e58

92. Sinaei R, Pezeshki S, Parvaresh S, et al. Post–SARS-CoV-2 infection reactive arthritis: a brief report of two pediatric cases. *Pediatr Rheumatol Online J*. 2021;19(1):89

93. Wechsler JB, Butuci M, Wong A, Kamboj AP, Youngblood BA. Mast cell activation is associated with post-acute COVID-19 syndrome. *Allergy*. 2022;77(4):1288–1291

94. Gebremeskel S, Schanin J, Coyle KM, et al. Mast Cell and eosinophil activation are associated with COVID-19 and TLR-mediated viral inflammation: implications for an anti-siglec-8 antibody. *Front Immunol*. 2021;12:650331

95. Schaller T, Märkl B, Claus R, et al. Mast cells in lung damage of COVID-19 autopsies: a descriptive study. *Allergy*. 2022;77(7):2237–2239

96. Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: famotidine, histamine, mast cells, and mechanisms. *Front Pharmacol*. 2021; 12:633680

97. Pinto MD, Lambert N, Downs CA, et al. Antihistamines for postacute sequelae of SARS-CoV-2 infection. *J Nurse Pract*. 2022;18(3):335–338

98. Nurek M, Rayner C, Freyer A, et al. Delphi panelists. Recommendations for the recognition, diagnosis, and management of long COVID: a Delphi study. *Br J Gen Pract*. 2021;71(712):e815–e825

99. May BC, Gallivan KH. Levocetirizine and montelukast in the COVID-19 treatment paradigm. *Int Immunopharmacol*. 2022; 103:108412

100. Brennan CM, Nadella S, Zhao X, et al. Oral famotidine versus placebo in nonhospitalized patients with COVID-19: a randomized, double-blind, data-intense, phase 2 clinical trial. *Gut*. 2022;71(5):879–888

101. Cheema HA, Shafiee A, Athar MMT, et al. No evidence of clinical efficacy of famotidine for the treatment of COVID-19: a systematic review and meta-analysis. *J Infect*. 2023;86(2):154–225

102. Rohde G, Wiethege A, Borg I, et al. Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalization: a case-control study. *Thorax*. 2003;58(1):37–42

103. Gibson PG, Grootendor DC, Henry RL, et al. Sputum induction in children. *Eur Respir J Suppl*. 2002;37:44s–46s

104. Peltola V, Jartti T, Putto-Laurila A, et al. Rhinovirus infections in children: a retrospective and prospective hospital-based study. *J Med Virol*. 2009;81(10):1831–1838

105. Johnston SL, Pattemore PK, Sanderson G, et al. Community study of role of viral infections in exacerbations of asthma in 9- to 11-year-old children. *BMJ*. 1995;310(6989):1225–1229

106. Wu T, Yu P, Li Y, et al. Asthma does not influence the severity of COVID-19: a meta-analysis. *J Asthma*. 2022;59(6):1188–1194

107. Ruano FJ, Somoza Álvarez ML, Haroun-Díaz E, et al. Impact of the COVID-19 pandemic in children with allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(9):3172–3174.e1

108. Amat F, Delaisi B, Labbé JP, Leonardi J, Houdouin V. Asthma may not be a risk factor for severe COVID-19 in children. *J Allergy Clin Immunol Pract*. 2021;9(6):2478–2479

109. Chou CC, Morphew T, Ehwerhemuepha L, Galant SP. COVID-19 infection may trigger poor asthma control in children. *J Allergy Clin Immunol Pract*. 2022;10(7):1913–1915

110. Gavrilova N, Soprun L, Lukashenko M, et al. New clinical phenotype of the post–COVID syndrome: fibromyalgia and joint hypermobility condition. *Pathophysiology*. 2022;29(1):24–29

111. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms, and recommendations. *Nat Rev Microbiol*. 2023;21(3):133–146

112. Centers for Disease Control and Prevention. Information for health care providers about multisystem inflammatory syndrome in children (MIS-C). Available at: https://www.cdc.gov/mis/mis-c/hcp/index.html. Accessed March 21, 2023

113. Kalyanaraman M, Anderson MR. COVID-19 in children. *Pediatr Clin North Am*. 2022;69(3):547–571

114. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. *Eur J Pediatr*. 2021;180(7):2019–2034

115. Pawar R, Gavade V, Patil N, et al. Neonatal multisystem inflammatory syndrome (mis-n) associated with prenatal maternal SARS-CoV-2: a case series. *Children (Basel)*. 2021;8(7):572

116. Divekar AA, Patamasucon P, Benjamin JS. Presumptive neonatal multisystem inflammatory syndrome in children associated with coronavirus disease 2019. *Am J Perinatol*. 2021; 38(6):632–636

117. More K, Aiyer S, Goti A, et al. Multisystem inflammatory syndrome in neonates (MIS-N) associated with SARS-CoV2 infection: a case series. *Eur J Pediatr*. 2022;181(5):1883–1898

118. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. *JAMA Pediatr*. 2021;175(8):837–845

119. Arantes MAF Jr, Conegundes AF, Branco Miranda BC, et al. Cardiac manifestations in children with the multisystem inflammatory syndrome (MIS-C) associated with SARS-CoV-2 infection: systematic review and meta-analysis. *Rev Med Virol*. 2023;33(3):e2432

120. Li DL, Davogustto G, Soslow JH, et al. Characteristics of COVID-19 myocarditis with and without multisystem inflammatory syndrome. *Am J Cardiol*. 2022;168:135–141

121. Mejias A, Schuchard J, Rao S, et al. Leveraging serologic testing to identify children at risk for post-acute sequelae of SARS-CoV-2 infection: an EHR-based cohort study from the RECOVER program. *J Pediatr*. 2023:257:113358

122. Jhaveri R, Webb R, Razzaghi H, et al. RECOVER consortium. Can multisystem inflammatory syndrome in children be managed in the outpatient setting? An EHR-based cohort study from the RECOVER program. *J Pediatric Infect Dis Soc*. 2023;12(3):159–162

123. Centers for Disease Control and Prevention. COVID data tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance. Accessed March 21, 2023

124. Rao S, Jing N, Liu X, et al. Spectrum of severity of multisystem inflammatory syndrome in children: an EHR-based cohort study from the RECOVER program. *Sci Rep*. 2023;13(1):21005

125. You SD, Kim JH, You J. Clinical characteristics and short-term outcomes of multisystem inflammatory syndrome in a country with a high prevalence of KD. *Front Pediatr*. 2023;11:1088529

126. Davies P, du Pré P, Lillie J, Kanthimathinathan HK. One-year outcomes of critical care patients post–COVID-19 multisystem inflammatory syndrome in children. *JAMA Pediatr*. 2021;175(12):1281–1283

127. Magge SN, Wolf RM, Pyle L, et al. COVID-19 and Type 2 Diabetes Consortium. The coronavirus disease 2019 pandemic is associated with a substantial rise in frequency and severity of presentation of youth-onset type 2 diabetes. *J Pediatr*. 2022;251:51–59.e2

128. Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years–United States, March 1, 2020–June 28, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(2):59–65

129. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children During COVID-19: multicenter regional findings in the United Kingdom. *Diabetes Care*. 2020;43(11):e170–e171

130. Vlad A, Serban V, Timar R, et al. Increased incidence of type 1 diabetes during the COVID-19 pandemic in Romanian children. *Medicina (Kaunas)*. 2021;57(9):973

131. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *JAMA*. 2020;324(8):801–804

132. American Association for the Advancement of Science. COVID-19 infection may increase risk of type 1 diabetes, suggests nationwide study of 1.2 million children. Available at: https://www.eurekalert.org/news-releases/965465. Accessed March 21, 2023

133. McKeigue PM, McGurnaghan S, Blackbourn L, et al. Relation of incident type 1 diabetes to recent COVID-19 infection: cohort study using e-health record linkage in Scotland. *Diabetes Care*. 2023;46(5):921–928

134. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post–COVID syndrome in individuals admitted to hospital with COVID-19: retrospective cohort study. *BMJ*. 2021;372:n693

135. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2021;23(3):870–874

136. Wu CT, Lidsky PV, Xiao Y, et al. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metab*. 2021;33(8):1565–1576.e5

137. Chang SE, Feng A, Meng W, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;12(1):5417

138. Liu Y, Ebinger JE, Mostafa R, et al. Paradoxical sex-specific patterns of autoantibody response to SARS-CoV-2 infection. *J Transl Med*. 2021;19(1):524

139. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. *Curr Opin Rheumatol*. 2021;33(2):155–162

140. Zuo Y, Estes SK, Ali RA, et al. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. *Sci Transl Med*. 2020;12(570):eabd3876

141. Desai I, Manchanda R, Kumar N, Tiwari A, Kumar M. Neurological manifestations of coronavirus disease 2019: exploring past to understand present. *Neurol Sci*. 2021;42(3):773–785

142. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683–690

143. Ahmad I, Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci*. 2020;77:8–12

144. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol*. 2020;77(11):1440–1445

145. Ray STJ, Abdel-Mannan O, Sa M, et al. CoroNerve study group. Neurological manifestations of SARS-CoV-2 infection in hospitalized children and adolescents in the United Kingdom: a prospective national cohort study. *Lancet Child Adolesc Health*. 2021;5(9):631–641

146. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler*. 2013;19(10):1261–1267

147. Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e663

148. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. *Neurology*. 2017;89(3):269–278

149. Wells E, Hacohen Y, Waldman A, et al. Attendees of the International Neuroimmune Meeting. Neuroimmune disorders of the central nervous system in children in the molecular era. *Nat Rev Neurol*. 2018;14(7):433–445

150. Höftberger R, Lassmann H. Inflammatory demyelinating diseases of the central nervous system. *Handb Clin Neurol*. 2017;145:263–283

151. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. *J Neurol*. 2021;268(4):1133–1170

152. Rad HS, Röhl J, Stylianou N, et al. The effects of COVID-19 on the placenta during pregnancy. *Front Immunol*. 2021;12:743022

153. Cribiù FM, Erra R, Pugni L, et al. Severe SARS-CoV-2 placenta infection can impact neonatal outcome in the absence of vertical transmission. *J Clin Invest*. 2021;131(6):e145427

154. Pistollato F, Petrillo M, Clerbaux LA, et al. Effects of spike protein and toxin-like peptides found in COVID-19 patients on human 3D neuronal/glial model undergoing differentiation: possible implications for SARS-CoV-2 impact on brain development. *Reprod Toxicol*. 2022;111:34–48

155. Ayed M, Embaireeg A, Kartam M, et al. Neurodevelopmental outcomes of infants born to mothers with SARS-CoV-2 infections during pregnancy: a national prospective study in Kuwait. *BMC Pediatr*. 2022;22(1):319

156. Munian D, Das R, Hazra A, Ray S. Outcome of neonates born to COVID-positive women at 6 months of age. *Indian Pediatr*. 2021;58(9):853–856

157. Singer TG, Evankovich KD, Fisher K, Demmler-Harrison GJ, Risen SR. Coronavirus infections in the nervous system of children: a scoping review making the case for long-term neurodevelopmental surveillance. *Pediatr Neurol*. 2021;117:47–63

158. Penner J, Abdel-Mannan O, Grant K, et al. GOSH PIMS-TS MDT Group. Six-month multidisciplinary follow-up and outcomes of patients with pediatric inflammatory multisystem syndrome (PIMS-TS) at a United Kingdom tertiary pediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health*. 2021;5(7):473–482

159. Schleiss MR, Permar SR, John CC. What are the key pediatric public policy priorities as the COVID-19 pandemic persists? *Pediatr Res*. 2023;93(6):1451–1455

160. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of COVID-19 vaccination on long covid: systematic review. *BMJ Med*. 2023;2(1):e000385

161. Ayoubkhani D, Bosworth ML, King S, et al. Risk of long COVID in people infected with severe acute respiratory syndrome coronavirus 2 after 2 doses of a coronavirus disease 2019 vaccine: community-based, matched cohort study. *Open Forum Infect Dis*. 2022;9(9):ofac464

162. Azzolini E, Levi R, Sarti R, et al. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA*. 2022;328(7):676–678

163. Zisis SN, Durieux JC, Mouchati C, Perez JA, McComsey GA. The protective effect of coronavirus disease 2019 (COVID-19) vaccination on postacute sequelae of COVID-19: a multicenter study from a large national health research network. *Open Forum Infect Dis*. 2022;9(7):ofac228

164. Ayoubkhani D, Bermingham C, Pouwels KB, et al. Trajectory of long COVID symptoms after COVID-19 vaccination: community-based cohort study. *BMJ*. 2022;377:e069676

165. Wisnivesky JP, Govindarajulu U, Bagiella E, et al. Association of vaccination with the persistence of post-COVID symptoms. *J Gen Intern Med*. 2022;37(7):1748–1753

166. Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long COVID and on existing long COVID symptoms: a systematic review. *EClinicalMedicine*. 2022; 53:101624

167. Thaweethai T, Jolley SE, Karlson EW, et al. RECOVER Consortium. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA*. 2023;329(22):1934–1946

168. Gross R, Thaweethai T, Rosenzweig EB, et al. Researching COVID to Enhance Recovery (RECOVER) pediatric study protocol: rationale, objectives and design. [Preprint] *medRxiv*. 2023;2023.04.27.23289228

169. Malone LA, Morrow A, Chen Y, et al. Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of postacute sequelae of SARS-CoV-2 infection (PASC) in children and adolescents. *PM R*. 2022;14(10):1241–1269