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Characterizing Long COVID in Children and Adolescents

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### Publication Date

2024-08-01

### DOI

10.1001/jama.2024.12747

Peer reviewed

# 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.<sup>1-4</sup> COVID-19 disproportionately affects Black, Indigenous, and people of color communities,<sup>5</sup> 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,<sup>6</sup> 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.<sup>7</sup> Although PASC can affect any individual, populations deserving specific focus include children with intellectual and developmental disabilities, children with

## abstract



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**DOI:** <https://doi.org/10.1542/peds.2023-062570>

Accepted for publication Nov 1, 2023

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**To cite:** Rao S, Gross RS, Mohandas S, et al. Postacute Sequelae of SARS-CoV-2 in Children. *Pediatrics*. 2024;153(3):e2023062570

medical complexity, and those with prolonged debilitating symptoms.<sup>8,9</sup> 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.<sup>10</sup>

## 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup>

## 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.<sup>9,13–21</sup> 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,<sup>22</sup> with one-third of children having ongoing symptoms at 12 months.<sup>23</sup> 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*.<sup>24</sup>

Some risk factors for PASC in children have begun to be elucidated. Although PASC can develop in those with asymptomatic infection,<sup>14,20,25</sup> in one study assessing pooled prevalence, the incidence was smaller after asymptomatic (15%) versus symptomatic (45%) infections.<sup>26</sup> Other risk factors include pre omicron variant periods,<sup>23</sup> increasing child age, higher severity of illness and number of organ systems involved during acute infection, underlying chronic medical conditions, and increased weight status.<sup>9,13,27</sup> 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.<sup>28–30</sup>

## 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.<sup>31-34</sup> Some postacute conditions may arise de novo, including new-onset autoimmune conditions,<sup>35</sup> such as the development of type 1 diabetes.<sup>36</sup> 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.

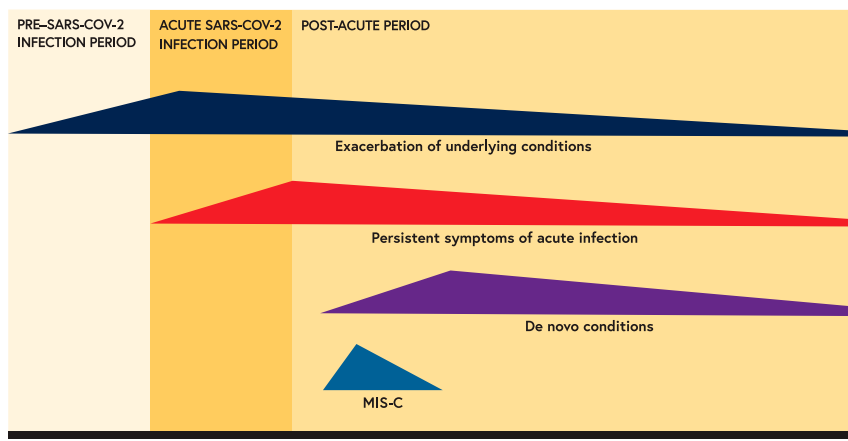
#### Constitutional Symptoms/Syndromes

Fatigue and malaise are common manifestations of PASC in children,<sup>13</sup> 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.”<sup>37</sup> When these symptoms persist, and present as a disabling

symptom, a diagnosis of post-COVID fatigue may be considered.<sup>38</sup> 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.<sup>39</sup> Common concurrent symptoms include musculoskeletal pain (myalgias or arthralgias), cognitive difficulties/brain fog, and persistent headaches.

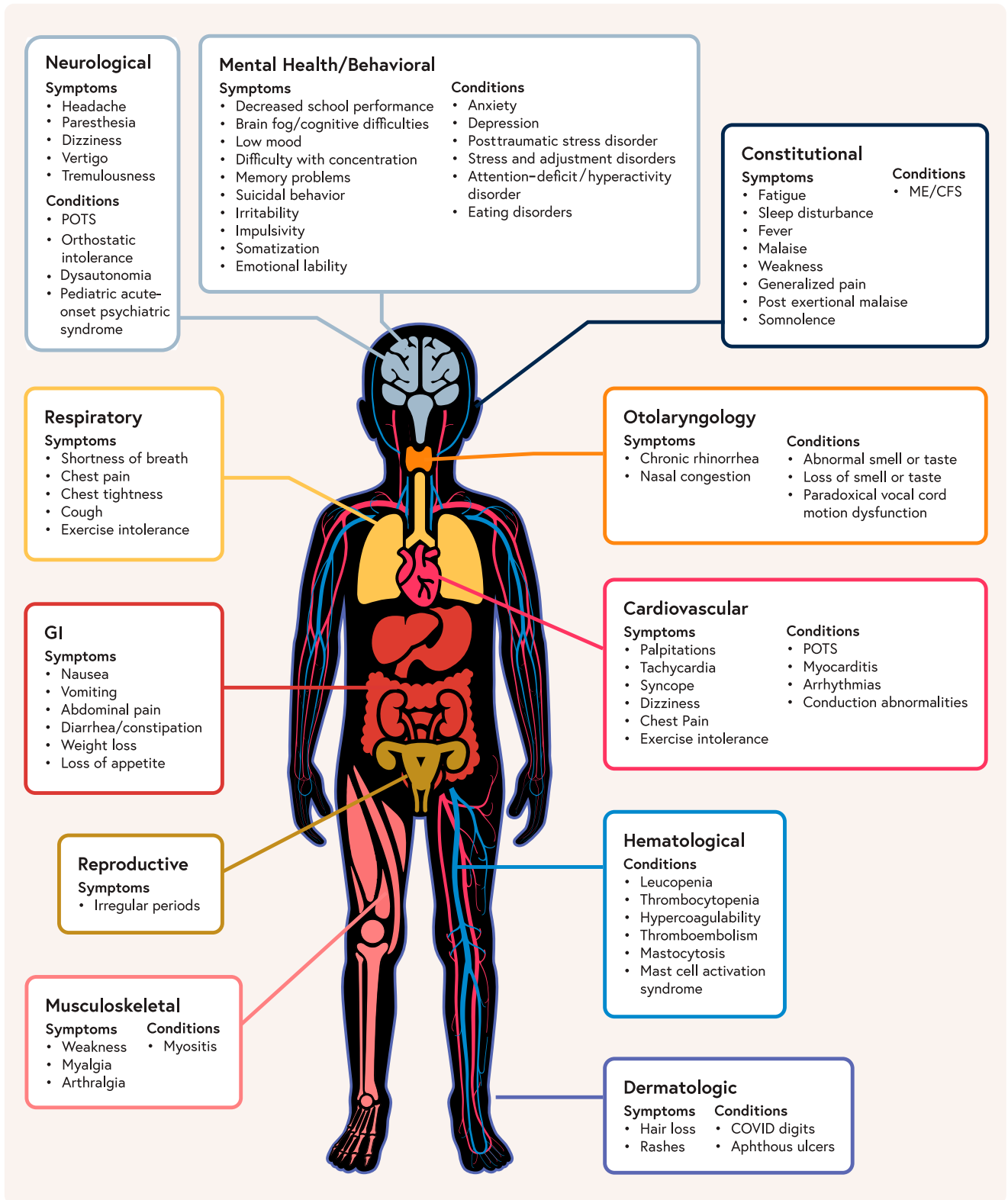
#### Respiratory Manifestations

Respiratory symptoms including cough,<sup>40</sup> chest tightness, and shortness of breath constitute some of the commonest PASC symptoms.<sup>41,42</sup> Persistent respiratory symptoms may occur independently of preexisting or measurable abnormalities in lung structure or function.<sup>43-45</sup> 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.<sup>46</sup> In a study of children presenting with persistent pulmonary symptoms  $\geq 4$  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.<sup>47</sup>



**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),<sup>48-50</sup> arrhythmias,<sup>51</sup> electrocardiographic,<sup>52</sup> and conduction abnormalities.<sup>53</sup> Inappropriate activation of the inflammatory cascade is thought to underly the myocardial damage.<sup>54</sup> Despite the gravity of the initial MIS-C presentation, the majority of children are asymptomatic by 6 months,<sup>55</sup> with only mild abnormalities detected by imaging.<sup>56,57</sup> 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).<sup>58-60</sup> 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.<sup>61</sup> 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,<sup>62</sup> although the underlying mechanism of orthostatic intolerance may differ.<sup>63</sup>

## 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.<sup>64</sup> 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)<sup>9</sup> 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,<sup>15</sup> along with nasal congestion and rhinorrhea.<sup>18</sup> 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.<sup>18</sup> Sudden sensorineural hearing loss, often accompanied by tinnitus, is rare but well documented in adults.<sup>65</sup> To date, however, there is little clear evidence of similar effects in children.<sup>66</sup>

## 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.<sup>67-69</sup> 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,<sup>44,70</sup> 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.<sup>71</sup> There have also been case reports of pediatric acute-onset neuropsychiatric syndrome in children after SARS-CoV-2 infection.<sup>72,73</sup>

## 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.<sup>74-76</sup> 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.<sup>77</sup> 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.<sup>78,79</sup> The prevalence of these symptoms and others (ie, constipation, loss of appetite, weight loss) generally decrease over time.<sup>80</sup> However, some persist or even develop at least 4 weeks after acute infection.<sup>18</sup> The reported prevalence ranges widely (ie, abdominal pain 1%<sup>81</sup>-72.2%),<sup>82</sup> 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.<sup>19,25,82-84</sup> Other studies among individuals with COVID-19 demonstrated prolonged fecal shedding of SARS-CoV-2 RNA associated with persistent GI symptoms.<sup>61,85-87</sup>

## 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.<sup>88</sup> 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.<sup>89</sup>

## 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.<sup>90</sup> Joint pathology in the form of self-limited postinfectious reactive arthritis has been reported in children<sup>91,92</sup> 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.<sup>93–96</sup> 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.<sup>17</sup> There have been scattered reports of the clinical efficacy of mast cell mediator blockade in PASC, such as H1 or H2 antagonists.<sup>97–99</sup> A placebo-controlled trial for SARS-CoV-2-infected outpatients demonstrated reductions in symptom length in individuals treated with famotidine, an H2 antagonist,<sup>100</sup> though the precise effect remains to be clarified.<sup>101</sup>

## 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,<sup>102–105</sup> 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.<sup>106</sup> 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,<sup>107,108</sup> 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 reaction-confirmed infection.<sup>109</sup>

## 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.<sup>110,111</sup>

## 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.<sup>112</sup> The presentation includes fever, respiratory (shortness of breath), cardiac (chest pain), GI (nausea, abdominal pain, vomiting), and/or dermatologic (rash, mucosal changes) system involvement.<sup>113</sup> A higher proportion of children with MIS-C are male, African American or Hispanic, and have comorbid obesity.<sup>114</sup> 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.<sup>115–117</sup> Hypotension, shock, cardiac dysfunction (most commonly left ventricular dysfunction), arrhythmia, and myocarditis remain the most serious MIS-C complications.<sup>118</sup> 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%.<sup>119</sup> Cardiac MRI has demonstrated global myocardial inflammation and edema, in contrast with regional inflammation and edema in COVID-19 myocarditis.<sup>120</sup> 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.<sup>121</sup> MIS-C likely represents an illness spectrum, with milder cases having been described,<sup>122</sup> with the incidence<sup>123</sup> and severity decreasing over the course of the pandemic.<sup>124</sup> 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,<sup>125</sup> with no significant medium- or long-term sequelae.<sup>126</sup>

### 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,<sup>127-131</sup> including compared with uninfected controls.<sup>128</sup> 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,<sup>36</sup> with similar findings from a study from Norway.<sup>132</sup> 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.<sup>133</sup> 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.<sup>6,44,134,135</sup> 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  $\beta$  cells, which express the angiotensin-converting enzyme 2 receptors to which SARS-CoV-2 binds.<sup>136</sup> 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,

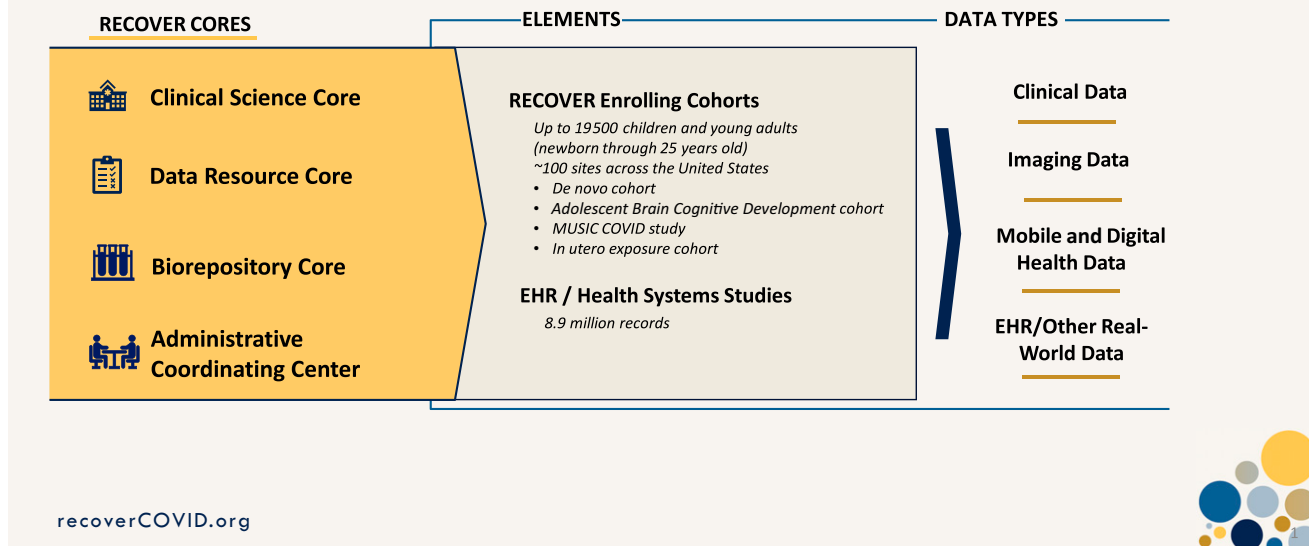
Graves' disease, systemic lupus erythematosus, antiphospholipid antibody syndrome, vasculitis, myocarditis, uveitis, and Sjogren's syndrome.<sup>35</sup> New-onset autoantibodies have been detected after acute infections,<sup>137</sup> and a broad autoantibody response can occur even in the absence of severe clinical disease.<sup>138</sup> 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.<sup>139</sup> 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<sup>137</sup> and another study showing up to 52% of hospitalized COVID-19 patients with antiphospholipid antibodies<sup>140</sup>), 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<sup>141-143</sup> 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.<sup>144,145</sup> 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.<sup>141</sup> Demyelinating conditions resulting from post-infectious, immune-mediated mechanisms appear to share features observed with other infections including other respiratory pathogens such as influenza.<sup>145-150</sup> There have been several reports of COVID-19-related cases of Guillain-Barre syndrome, with up to 10% presenting with the Miller-Fisher variant.<sup>151</sup> 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.



# RECOVER Pediatric Study Components



**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 SARS-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://pcorner.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.<sup>152,153</sup>

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.<sup>154</sup> Although SARS-CoV-2 infection does not seem to cause gross neurodevelopmental abnormalities in neonates of infected versus uninfected mothers,<sup>155,156</sup> 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,<sup>157</sup> 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.<sup>158</sup> 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.<sup>42</sup> 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.<sup>159</sup> 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.<sup>160–166</sup> 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).<sup>10,167</sup> 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.<sup>168</sup> 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,<sup>169</sup> 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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**FUNDING:** Funded by the National Institutes of Health Agreement OTA OT2HL161847-01 as part of the Researching COVID to Enhance Recovery program of research. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the National Institutes of Health.

**CONFLICT OF INTEREST DISCLOSURES:** Dr Rao reports previous grant support from GSK and Biofire, and was a former consultant for Sequiris. Dr Jhaveri is a consultant for AstraZeneca, Seqirus, and Dynavax, and receives an editorial stipend from Elsevier. All other authors have indicated they have no conflicts of interest relevant to this article to

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