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Characterizing Long COVID in Children and Adolescents

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IMPORTANCE Most research to understand postacute sequelae of SARS-CoV-2 infection (PASC), or long COVID, has focused on adults, with less known about this complex condition in children. Research is needed to characterize pediatric PASC to enable studies of underlying mechanisms that will guide future treatment.

OBJECTIVE To identify the most common prolonged symptoms experienced by children (aged 6 to 17 years) after SARS-CoV-2 infection, how these symptoms differ by age (school-age [6-11 years] vs adolescents [12-17 years]), how they cluster into distinct phenotypes, and what symptoms in combination could be used as an empirically derived index to assist researchers to study the likely presence of PASC.

DESIGN, SETTING, AND PARTICIPANTS Multicenter longitudinal observational cohort study with participants recruited from more than 60 US health care and community settings between March 2022 and December 2023, including school-age children and adolescents with and without SARS-CoV-2 infection history.

EXPOSURE SARS-CoV-2 infection.

MAIN OUTCOMES AND MEASURES PASC and 89 prolonged symptoms across 9 symptom domains.

RESULTS A total of 898 school-age children (751 with previous SARS-CoV-2 infection [referred to as *infected*] and 147 without [referred to as *uninfected*]; mean age, 8.6 years; 49% female; 11% were Black or African American, 34% were Hispanic, Latino, or Spanish, and 60% were White) and 4469 adolescents (3109 infected and 1360 uninfected; mean age, 14.8 years; 48% female; 13% were Black or African American, 21% were Hispanic, Latino, or Spanish, and 73% were White) were included. Median time between first infection and symptom survey was 506 days for school-age children and 556 days for adolescents. In models adjusted for sex and race and ethnicity, 14 symptoms in both school-age children and adolescents were more common in those with SARS-CoV-2 infection history compared with those without infection history, with 4 additional symptoms in school-age children only and 3 in adolescents only. These symptoms affected almost every organ system. Combinations of symptoms most associated with infection history were identified to form a PASC research index for each age group; these indices correlated with poorer overall health and quality of life. The index emphasizes neurocognitive, pain, and gastrointestinal symptoms in school-age children but change or loss in smell or taste, pain, and fatigue/malaise–related symptoms in adolescents. Clustering analyses identified 4 PASC symptom phenotypes in school-age children and 3 in adolescents.

CONCLUSIONS AND RELEVANCE This study developed research indices for characterizing PASC in children and adolescents. Symptom patterns were similar but distinguishable between the 2 groups, highlighting the importance of characterizing PASC separately for these age ranges.

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Long COVID, or postacute sequelae of SARS-CoV-2 infection (PASC), has been broadly defined as symptoms, signs, and conditions that develop, persist, or relapse over time after SARS-CoV-2 infection.[1,2] These symptoms can last weeks, months, or years after the acute infection resolves and can have debilitating effects. Some experts believe that worldwide, an estimated 65 million people are living with PASC,[3] with impacts on population-level health anticipated to last for decades. Most research characterizing PASC has focused on adults,[4] leading to misperception that pediatric PASC is rare or presents similarly to PASC in adults.[5,6] This may lead clinicians to miss symptoms or misdiagnose children. Consistent with the life course framework in which developmental stage influences health outcomes,[7] PASC may present in both similar and different ways compared with adults.

Studies of pediatric PASC have documented a wide range of symptoms involving every organ system.[8-11] Most pediatric research has focused on individual symptoms and either pooled data from different ages or focused on adolescents. Little is known about differences in PASC symptoms between school-age children (6-11 years) and adolescents (12-17 years).[12,13] The absence of a consistent analytic approach to objectively identify children with PASC hinders the research needed to identify underlying mechanisms of disease and treatment targets. The National Institutes of Health–funded Researching COVID to Enhance Recovery (RECOVER) Initiative aims to fill these gaps by bringing together researchers, clinicians, communities, and families in a comprehensive study of PASC in children.[14] The aims of this analysis of the RECOVER-Pediatrics cohort were to identify (1) common prolonged symptoms experienced by children (6 to 17 years old) after SARS-CoV-2 infection, (2) how these symptoms differ by age (school-age vs adolescents), (3) how symptoms cluster into phenotypes, and (4) what symptoms in combination could be used as an empirically derived index to help researchers consistently assess the likely presence of PASC. These indices, like the one previously developed for the RECOVER-Adult cohort (18 years or older),[15] were intended to be used to identify factors that distinguish children who likely have developed PASC from those who may not have and to help evaluate risk factors for developing PASC, elucidate its pathophysiology, and enable follow-up to analyze recovery and relapse.

Key Points

Question What prolonged symptoms experienced by youth are most associated with SARS-CoV-2 infection?

Findings Among 5367 participants in the RECOVER-Pediatrics cohort study, 14 symptoms in both school-age children (6-11 years) and adolescents (12-17 years) were more common in those with vs without SARS-CoV-2 infection history, with 4 additional symptoms in school-age children only and 3 in adolescents only. Empirically derived indices for PASC research and associated clustering patterns were developed.

Meaning This study developed research indices for characterizing pediatric PASC. Symptom patterns were similar but distinguishable between school-age children and adolescents, highlighting the importance of characterizing PASC separately in different age groups.

Methods

Study Design

The RECOVER Pediatric Observational Cohort Study (RECOVER-Pediatrics)[14] is a combined retrospective and prospective longitudinal study including 4 cohorts. Data presented are from 2 cohorts: the de novo RECOVER cohort, including participants from birth through 25 years with and without SARS-CoV-2 infection history newly recruited from health care and community settings, and the extant National Institutes of Health–funded Adolescent Brain Cognitive Development cohort,[16-18] the largest long-term US study of brain development in adolescence. The protocol and statistical analysis plan for RECOVER-Pediatrics were previously described[19] (see Supplements 1 and 2). Data were obtained from more than 60 sites (eTable 1 in Supplement 3). The study received institutional review board approval from NYU Grossman School of Medicine (de novo cohort) or UC San Diego Human Research Protections Program (Adolescent Brain Cognitive Development cohort), with other institutions relying on these single institutional review boards. Caregiver-child pairs provided informed consent and age-appropriate assent. Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.

RECOVER-Pediatrics Participants

Inclusion Criteria

The analytic sample included individuals aged 6 to 17 years enrolled between March 16, 2022, and December 16, 2023, with and without known SARS-CoV-2 infection history (*infected* and *uninfected*, respectively). Child age was recorded at symptom survey completion.

For these analyses, the infected group included participants who completed their survey about prolonged symptoms at least 90 days after their first infection, reported by their caregivers (eMethods in Supplement 3). SARS-CoV-2 antibodies were not required. The uninfected group was defined by caregiver report and required confirmation of negative nucleocapsid antibodies at enrollment. Those thought to be uninfected but found to be antibody-positive (Ab+) within 30 days of survey completion were analyzed separately to understand asymptomatic infection.[20] Throughout, *uninfected* refers strictly to uninfected participants who were confirmed to be nucleocapsid antibody–negative.

Exclusion Criteria

Infected participants with an unknown date for their first infection, participants with history of multisystem inflammatory syndrome in children (because this is a well-characterized entity),[21-25] uninfected participants without antibody testing, and participants with missing symptom surveys (defined as <50% of questions completed) were excluded.

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Outcomes

Caregivers completed a comprehensive symptom survey remotely (interviewer-administered if needed) assessing 89 prolonged symptoms across 9 domains, using health literacy-informed principles and plain-language descriptions (eTable 2 in Supplement 3).[19,26] Some symptoms describing a similar phenotype were combined into composites, resulting in 75 symptoms (eMethods in Supplement 3): general (12 symptoms), eyes/ears/nose/throat (15 symptoms), heart/lungs (10 symptoms), gastrointestinal (6 symptoms), dermatologic (5 symptoms), musculoskeletal (3 symptoms), neurologic (6 symptoms), behavioral/psychological (14 symptoms), and menstrual (4 symptoms). The same symptoms were assessed in both age groups (except panic attacks, which were assessed in adolescents only). Menstrual symptoms were assessed in those assigned female or intersex at birth and who started menstruating (reported only among adolescents).

The primary outcome was a prolonged symptom lasting for more than 4 weeks that started or became worse since the beginning of the pandemic and was present at the time of survey completion (at least 90 days after infection). If a symptom lasted for more than 4 weeks but was absent at survey completion, it was not counted as a prolonged symptom.

Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health Scales were assessed, measuring caregiver perception of the child's overall health, physical health, and quality of life.[27]

Covariates

The main exposure variable was SARS-CoV-2 infection. Other variables included sex, race and ethnicity, geographic origin, time since SARS-CoV-2 infection, calendar time of enrollment, and SARS-CoV-2 vaccination status (eMethods in Supplement 3). Like other variables, race and ethnicity were collected via caregiver report based on prespecified categories and measured to enhance understanding of racial and ethnic differences in PASC. Caregiver variables included relationship to child and educational attainment.

Statistical Analyses

Statistical analyses were modeled after those published for RECOVER-Adult and were age-stratified.[15] The analysis calculated the proportion of participants who reported each prolonged symptom and who reported experiencing at least 1 prolonged symptom among infected and uninfected participants separately (eTable 3 in Supplement 3). For symptoms present in at least 5% of infected participants (candidate symptoms), the risk difference, odds ratio, and relative risk for infected vs uninfected participants were estimated using linear, logistic, and Poisson regression, respectively, adjusting for sex and race and ethnicity (eMethods in Supplement 3). Second, to identify combinations of symptoms that could be used for research, a penalized logistic regression approach (least absolute shrinkage and selection operator [LASSO])[28] was used to identify what candidate symptoms (predictors) were best at differentiating participants with or without an infection history (outcome).[15] Because all sexes were combined for this analysis, menstrual symptoms were excluded. Based on the model fit, each symptom was assigned a score corresponding to the estimated log odds ratio, where a higher symptom score indicated a stronger association with infection. A total index was calculated for each participant by summing the individual scores for each symptom reported. An optimal index threshold for identifying PASC was selected based on the proportion of uninfected participants who were likely misclassified as having PASC (eMethods in Supplement 3). Participants meeting the index threshold were categorized as *PASC-probable* and others were categorized as *PASC-unspecified*. PASC rates were reported among infected and uninfected participants separately. Among infected participants, these rates were also reported by whether they were infected by December 1, 2021 (when the Omicron variant became the dominant US strain).

Third, the analysis examined correlations between PASC indices and caregiver-reported overall child health, quality of life, and physical health and symptoms selected by LASSO. Further, the frequency of all symptoms was reported in infected PASC-probable, infected PASC-unspecified, and uninfected participants separately. Fourth, symptom patterns were investigated among infected participants categorized as PASC-probable. Correlations between symptoms contributing to the PASC index among infected PASC-probable participants were calculated. K-means consensus clustering was performed based on symptoms contributing to the PASC index to identify distinct PASC symptom profiles.[29] The number of different systems affected among infected PASC-probable participants was then summarized by counting the systems in which at least 1 prolonged symptom was reported. Fifth, we summarized the characteristics and symptomatology of uninfected participants found to be Ab+.

Results

This study included 751 infected and 147 uninfected school-age children and 3109 infected and 1369 uninfected adolescents (see cohort identification details in eFigure 1 in Supplement 3). The **Table** and eTable 4 in Supplement 3 contain demographic and infection history characteristics, respectively. eTable 5 in Supplement 3 contains demographic characteristics for the adolescent cohort, stratified by recruiting cohort (Adolescent Brain Cognitive Development vs de novo).

Overall, 45% of infected (338/751) and 33% of uninfected (48/147) school-age children and 39% of infected (1219/3109) and 27% of uninfected (372/1369) adolescents reported having at least 1 prolonged symptom. Twenty-six symptoms in infected school-age children and 18 symptoms in infected adolescents were prolonged in at least 5% of participants (**Figure 1**). The lower 95% confidence bound of the adjusted odds ratio exceeded 0 for 14 symptoms in both school-age children and adolescents, with 4 additional symptoms in school-age children only and 3 in adolescents only (Figure 1). The frequency of each symptom among infected participants did not differ after stratification into quintiles based on time between first infection and symptom survey date (eFigure 2 in Supplement 3).

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Table. Demographic Characteristics of the Primary Analysis Cohort Participants Stratified by Age Group and SARS-CoV-2 Infection Status

Participant characteristic	No. (%)			
	School-age children (6-11 y)		Adolescents (12-17 y)	
	Infected (n = 751)	Uninfected (n = 147)	Infected (n = 3109)	Uninfected (n = 1369)
Age, mean (SD), y	9 (2)	8 (2)	15 (1)	15 (1)
Sex assigned at birth				
Female	362 (48)	78 (53)	1537 (49)	592 (43)
Male	389 (52)	69 (47)	1572 (51)	776 (57)
Intersex	0	0	0	1 (<0.1)
Race and ethnicity[a]	747	142	3096	1360
American Indian or Alaska Native	21 (3)	4 (3)	81 (3)	35 (3)
Asian	58 (8)	10 (7)	202 (7)	110 (8)
Black or African American	92 (12)	9 (6)	405 (13)	192 (14)
Hispanic, Latino, or Spanish	255 (34)	43 (30)	689 (22)	244 (18)
Native Hawaiian or Other Pacific Islander	2 (<0.1)	3 (2)	16 (1)	8 (1)
White	434 (58)	97 (68)	2241 (72)	1003 (74)
None of these fully describe me	6 (1)	1 (1)	29 (1)	5 (0.4)
English is primary language	659/743 (89)	133/146 (91)	2974/3092 (96)	1322/1355 (98)
Birth in the US	723/746 (97)	146 (99)	2995/3095 (97)	1331/1364 (98)
Population referral source	751	147	3109	1369
Existing non-COVID research or clinical cohort[b]	60 (8)	6 (4)	2258 (73)	1228 (90)
Community outreach	209 (28)	65 (44)	225 (7)	52 (4)
Participant tested/treated in the health system	182 (24)	11 (7)	246 (8)	25 (2)
Self-referral from RECOVER website or other unsolicited self-referral	152 (20)	44 (30)	185 (6)	34 (2)
Community health center	66 (9)	10 (7)	58 (2)	18 (1)
Public health department list	16 (2)	0	46 (1)	2 (0.1)
Long COVID clinic	15 (2)	1 (1)	41 (1)	0
Existing, prospectively followed up COVID cohort	19 (3)	2 (1)	7 (0.2)	1 (<0.1)
Other	32 (4)	8 (5)	43 (1)	9 (1)
From a medically underserved area	295 (39)	49 (33)	789 (25)	374 (27)
From a rural area	39 (5)	11 (7)	136 (4)	46 (3)
Prevalent SARS-CoV-2 strain at first infection is before Omicron (before Dec 1, 2021)	391 (52)		1636 (53)	
Vaccination status at first infection (infected) or enrollment (uninfected)[c]				
Fully vaccinated	194 (26)	99 (67)	1345 (43)	1048 (77)
Partially vaccinated	91 (12)	2 (1)	217 (7)	46 (3)
Not eligible for vaccination	337 (45)	0	1048 (34)	0
Vaccinated but missing information	23 (3)	11 (7)	90 (3)	88 (6)
Not vaccinated	106 (14)	35 (24)	409 (13)	187 (14)
Time between first infection (infected) or Mar 1, 2020 (uninfected) and symptom survey, median (IQR), d	504 (298-812)	701 (580-857)	519 (334-814)	774 (691-842)
Primary caregiver characteristics				
Relationship to child: mother	669/719 (93)	131/139 (94)	2785/3074 (91)	1220/1361 (90)
Educational attainment: college or higher	368/634 (58)	84/127 (66)	1891/2880 (66)	891/1325 (67)

[a] See eMethods in Supplement 3 for additional details on how race and ethnicity were collected (self-report); note that participants could select all race and ethnicity groups that applied.

[b] The category "Existing non-COVID research or clinical cohort" includes the Adolescent Brain Cognitive Development cohort.

[c] See eMethods in Supplement 3 for additional details on how vaccination categories were defined. Infected participants were ineligible for vaccination if their first infection date preceded when vaccines were available for children their age.

The LASSO analysis identified 10 symptoms in school-age children and 8 in adolescents that were most associated with infection history (**Figures 2**A and **3**A). Optimal index thresholds of 5.5 in school-age children and 5.0 in adolescents were identified (Figures 2B and 3B). Overall, 152 infected (20%) and 6 uninfected (4%) school-age children and 445 infected (14%) and 44 uninfected (3%) adolescents met or exceeded this index threshold (eTable 6 in Supplement 3). This percentage was higher for participants infected before vs after the emergence of Omicron (21% vs 14% for school-age

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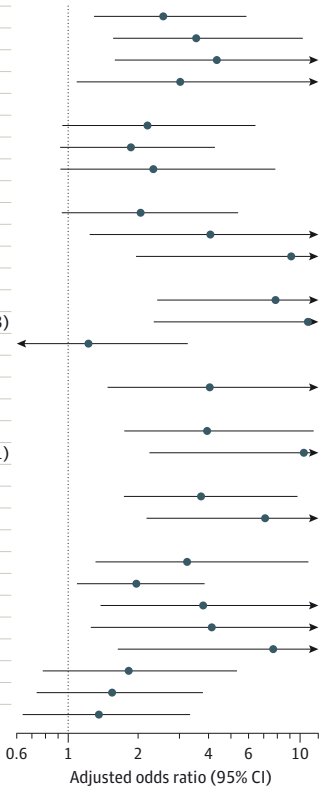
Figure 1. Participants With Each Prolonged Symptom, Adjusted Odds Ratios, and Adjusted Risk Differences Comparing Infected vs Uninfected School-Age Children and Adolescents

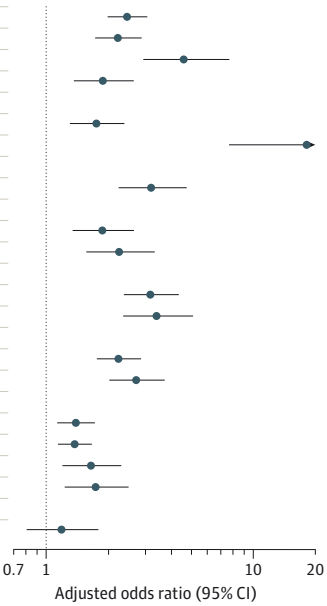
A School-age children (6-11 y)

Symptoms	No. (%) Infected (n = 751)	Uninfected (n = 147)	Adjusted risk difference (95% CI), %	Adjusted odds ratio (95% CI)
General symptoms				
Daytime tiredness, sleepiness, or low energy	96 (12.8)	8 (5.4)	7.4 (2.9 to 11.9)	2.57 (1.29 to 5.87)
Trouble sleeping	83 (11.1)	5 (3.4)	7.7 (4 to 11.4)	3.56 (1.56 to 10.28)
Tired after walking	64 (8.5)	3 (2)	6.3 (3.1 to 9.5)	4.38 (1.59 to 18.14)
Poor appetite	49 (6.5)	3 (2)	3.9 (1 to 6.8)	3.04 (1.09 to 12.68)
Eye, ear, nose, and throat				
Dark circles	51 (6.8)	5 (3.4)	3.8 (0.3 to 7.2)	2.20 (0.94 to 6.42)
Stuffy nose	81 (10.8)	8 (5.4)	4.2 (-0.1 to 8.5)	1.86 (0.92 to 4.29)
Chapped lips	51 (6.8)	4 (2.7)	3.4 (0.2 to 6.6)	2.33 (0.93 to 7.82)
Heart and lungs				
Dry cough	64 (8.5)	6 (4.1)	3.9 (0.2 to 7.7)	2.05 (0.94 to 5.41)
Palpitation during exercise	41 (5.5)	2 (1.4)	4 (1.5 to 6.5)	4.11 (1.24 to 25.43)
Feeling lightheaded or dizzy	43 (5.7)	1 (0.7)	5.2 (3 to 7.3)	9.16 (1.96 to 163.19)
Stomach				
Stomach pain	72 (9.6)	2 (1.4)	8.3 (5.4 to 11.2)	7.84 (2.42 to 48.1)
Nausea or vomiting	52 (6.9)	1 (0.7)	6.2 (3.9 to 8.5)	10.81 (2.34 to 192.13)
Constipation	38 (5.1)	6 (4.1)	0.9 (-2.7 to 4.5)	1.22 (0.54 to 3.28)
Skin, hair, and nails				
Itchy skin or skin rash	60 (8)	3 (2)	5.8 (2.8 to 8.8)	4.08 (1.48 to 16.9)
Muscles and bones				
Body, muscle, or joint pain	91 (12.2)	5 (3.4)	8.8 (5 to 12.5)	3.97 (1.75 to 11.45)
Back or neck pain	49 (6.6)	1 (0.7)	5.9 (3.6 to 8.2)	10.38 (2.24 to 184.71)
Nerves and brain				
Headache	102 (13.6)	6 (4.1)	9.5 (5.4 to 13.6)	3.74 (1.74 to 9.75)
Trouble with memory or focusing	67 (9)	2 (1.4)	7.5 (4.7 to 10.3)	7.07 (2.18 to 43.4)
Feelings and behavior				
Feeling depressed	64 (8.6)	4 (2.7)	5.6 (2.3 to 8.9)	3.26 (1.31 to 10.87)
Feeling anxious	108 (14.4)	12 (8.2)	6.6 (1.5 to 11.7)	1.97 (1.09 to 3.88)
Fear about specific things	53 (7.1)	3 (2)	5.2 (2.3 to 8.2)	3.82 (1.38 to 15.86)
Fear of crowds or enclosed spaces	39 (5.2)	2 (1.4)	4 (1.4 to 6.6)	4.16 (1.25 to 25.81)
Refusing to go to school	38 (5.1)	1 (0.7)	4.3 (2.2 to 6.3)	7.66 (1.64 to 136.69)
Nightmares	46 (6.1)	5 (3.4)	2.6 (-0.7 to 5.9)	1.82 (0.78 to 5.35)
Hyperactive	54 (7.2)	7 (4.8)	2.4 (-1.5 to 6.3)	1.55 (0.73 to 3.81)
Refusing to follow rules	48 (6.4)	7 (4.8)	1.6 (-2.3 to 5.5)	1.36 (0.64 to 3.36)



B Adolescents (12-17 y)

Symptoms	No. (%) Infected (n = 3109)	Uninfected (n = 1369)	Adjusted risk difference (95% CI), %	Adjusted odds ratio (95% CI)
General symptoms				
Daytime tiredness, sleepiness, or low energy	543 (17.5)	105 (7.7)	9.3 (7.4 to 11.3)	2.47 (1.99 to 3.09)
Trouble sleeping	360 (11.6)	75 (5.5)	5.9 (4.3 to 7.6)	2.23 (1.73 to 2.90)
Tired after walking	200 (6.4)	19 (1.4)	4.8 (3.7 to 5.8)	4.63 (2.95 to 7.69)
Poor appetite	195 (6.3)	45 (3.3)	2.7 (1.5 to 4)	1.88 (1.36 to 2.66)
Eye, ear, nose, and throat				
Stuffy nose	217 (7)	56 (4.1)	2.9 (1.5 to 4.2)	1.75 (1.31 to 2.39)
Change or loss in smell or taste	162 (5.2)	4 (0.3)	4.8 (4 to 5.6)	18.16 (7.67 to 59.11)
Heart and lungs				
Feeling lightheaded or dizzy	233 (7.5)	32 (2.3)	4.8 (3.6 to 6)	3.22 (2.24 to 4.79)
Stomach				
Stomach pain	183 (5.9)	43 (3.1)	2.6 (1.3 to 3.8)	1.87 (1.35 to 2.66)
Nausea or vomiting	173 (5.6)	33 (2.4)	2.9 (1.8 to 4)	2.26 (1.57 to 3.36)
Muscles and bones				
Body, muscle, or joint pain	342 (11.1)	50 (3.7)	7.1 (5.7 to 8.6)	3.20 (2.38 to 4.38)
Back or neck pain	231 (7.5)	30 (2.2)	4.9 (3.7 to 6.1)	3.42 (2.36 to 5.14)
Nerves and brain				
Headache	410 (13.2)	84 (6.2)	6.6 (4.9 to 8.3)	2.24 (1.76 to 2.88)
Trouble with memory or focusing	296 (9.6)	50 (3.7)	5.7 (4.3 to 7.1)	2.73 (2.02 to 3.75)
Feelings and behavior				
Feeling depressed	418 (13.6)	132 (9.7)	3.3 (1.3 to 5.3)	1.39 (1.13 to 1.72)
Feeling anxious	533 (17.2)	171 (12.6)	3.9 (1.8 to 6.1)	1.38 (1.14 to 1.67)
Fear of crowds or enclosed spaces	182 (5.9)	48 (3.5)	2.2 (0.9 to 3.4)	1.65 (1.20 to 2.31)
Panic attack	163 (5.3)	40 (2.9)	2 (0.9 to 3.2)	1.74 (1.23 to 2.51)
Menstruation				
Heavy periods	108 (7.9)	35 (6.7)	0.9 (-0.2 to 2)	1.19 (0.81 to 1.79)



A symptom was included if at least 5% of infected or uninfected participants reported experiencing that symptom. Adjusted odds ratios and risk differences were estimated from models that included infection status as the exposure and the presence of each prolonged symptom as the outcome, with adjustment for sex assigned at birth and race and ethnicity (see eMethods in Supplement 3).

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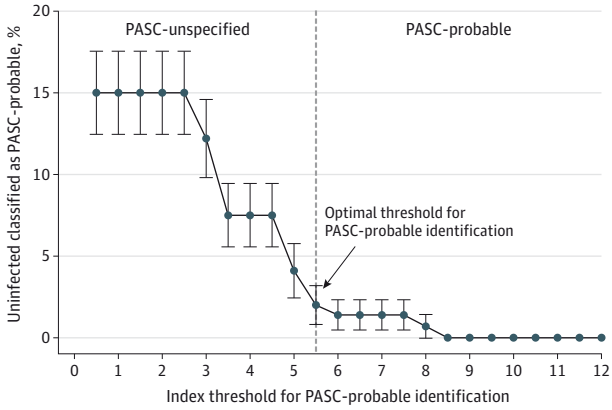
Figure 2. Development of the Postacute Sequelae of SARS-CoV-2 Infection (PASC) Research Index and Threshold for School-Age Children (6-11 Years)

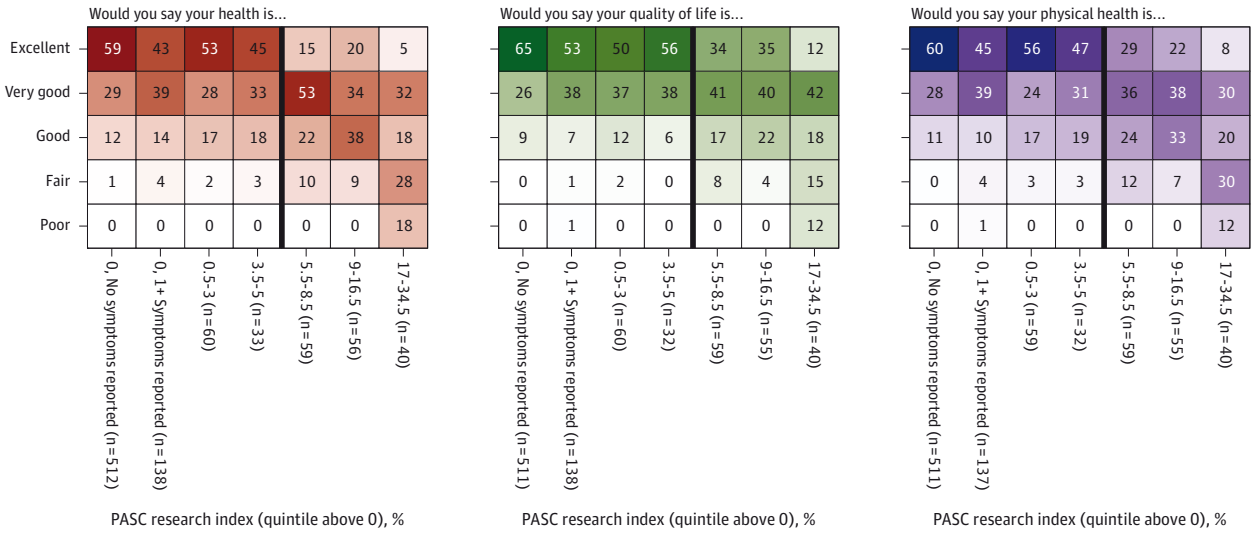
A Symptoms that contribute to the PASC research index

Symptom	Log odds ratio	Score
Trouble with memory or focusing	0.51	5.5
Back or neck pain	0.46	5.0
Stomach pain	0.45	5.0
Headache	0.41	4.5
Fear about specific things	0.27	3.0
Refusing to go to school	0.27	3.0
Itchy skin or skin rash	0.29	3.0
Trouble sleeping	0.24	2.5
Nausea or vomiting	0.23	2.5
Feeling lightheaded or dizzy	0.03	0.5

B Optimal threshold for distinguishing PASC-probable from PASC-unspecified in school-age children



C PASC research index and Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 among school-age children



A, Least absolute shrinkage and selection operator (LASSO) was used to fit a logistic regression model to identify which symptoms could be used to identify individuals likely to have PASC. Estimated log odds ratios were divided by 0.10 and rounded up to the nearest 0.5 to calculate symptom scores. An individual's PASC research index is calculated by summing the scores for each prolonged symptom a participant reported (ie, the participant experienced the symptom for 4 weeks since the beginning of the pandemic and is currently experiencing it at the time of the survey). B, The optimal index threshold for PASC was selected using bootstrapping to estimate standard error bars. An approximation of the "elbow" method was used to identify the cutoff where the number of uninfected participants misclassified as PASC-probable stabilized (eMethods in Supplement 3). The threshold (index of at least 5.5) can be used to identify school-age children with PASC for research purposes. Using this threshold, the percentage of infected PASC-probable school-age children with each symptom was as follows: headache, 55%; trouble with memory or focusing, 45%; trouble sleeping, 44%; stomach pain, 43%; nausea or vomiting, 34%; back or neck pain, 30%; itchy skin or skin rash, 29%; fear about specific things, 26%; feeling lightheaded or dizzy, 26%; and refusing to go to school, 23%. C, Participant responses to 3 questions from the Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 survey, stratified into 7 groups: participants with a zero PASC research index and no prolonged symptoms, zero PASC research index but at least 1 prolonged symptom, and participants with nonzero PASC index, divided into quintiles. The dark vertical line indicates the index threshold for PASC. Each cell is shaded according to the frequency of each response within each column, ranging from 0% to 100%.

children; 17% vs 7% for adolescents). Correlations between symptoms that contributed to the index are shown in eFigure 3 in Supplement 3. Correlations between these symptoms and those that did not contribute to the index are shown in eTable 7 in Supplement 3. Some uninfected participants may have met the index threshold due to misclassification or due to having other symptoms.

In both age groups, higher PASC research indices were correlated with worse PROMIS scores (Figures 2C and 3C). The number of systems affected among infected PASC-probable participants (eFigure 4 in Supplement 3) indicated substantial multisystem burden.

Figure 4 shows the percentage of participants in each age group experiencing each symptom after stratification

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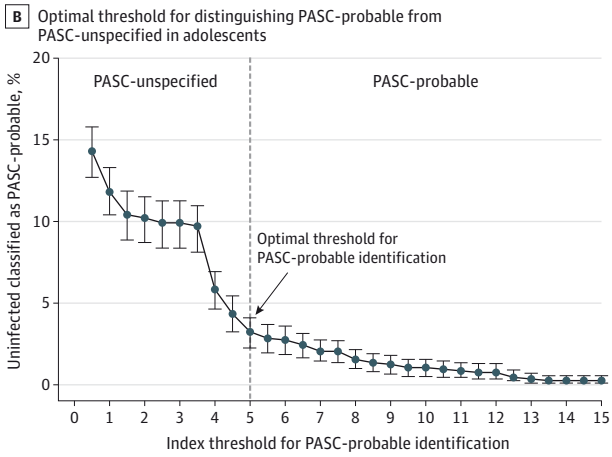
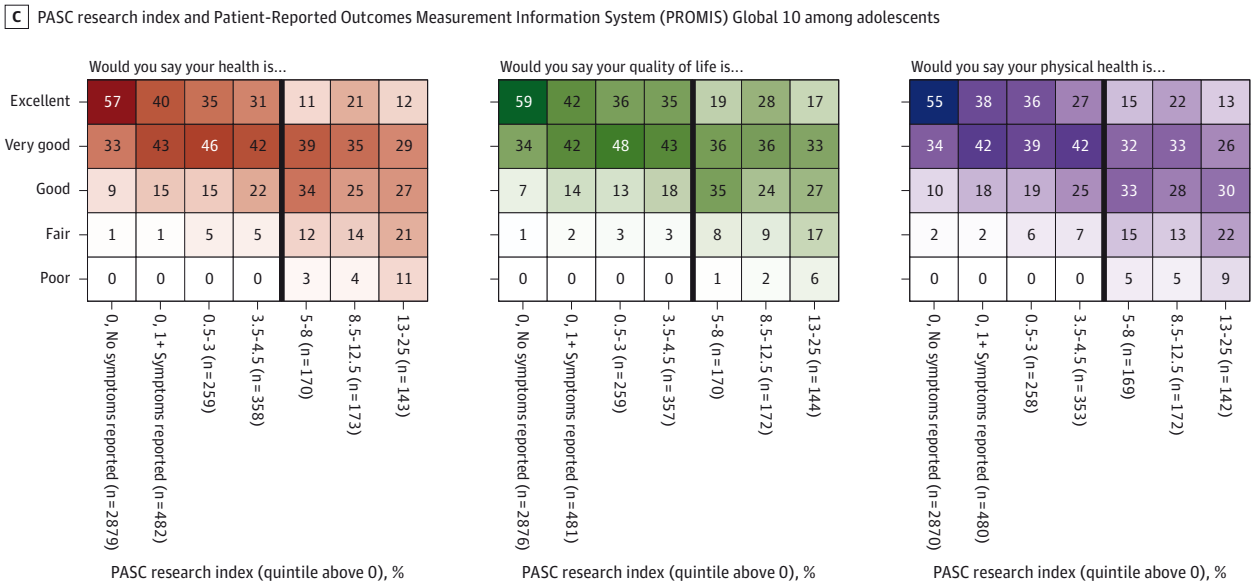
Figure 3. Development of the Postacute Sequelae of SARS-CoV-2 Infection (PASC) Research Index and Threshold for Adolescents (Ages 12 to 17 years)

A Symptoms that contribute to the PASC research index

Symptom	Log odds ratio	Score
Change or loss in smell or taste	1.15	12.0
Body, muscle, or joint pain	0.31	3.5
Daytime tiredness, sleepiness, or low energy	0.31	3.5
Tired after walking	0.27	3.0
Back or neck pain	0.09	1.0
Trouble with memory or focusing	0.09	1.0
Headache	0.05	0.5
Feeling lightheaded or dizzy	0.01	0.5





A, Least absolute shrinkage and selection operator (LASSO) was used to fit a logistic regression model to identify which symptoms could be used to identify individuals likely to have PASC. Estimated log odds ratios were divided by 0.10 and rounded up to the nearest 0.5 to calculate symptom scores. An individual's PASC research index is calculated by summing the scores for each prolonged symptom a participant reported (ie, the participant experienced the symptom for 4 weeks since the beginning of the pandemic and is currently experiencing it at the time of the survey). B, The optimal index threshold for PASC was selected using 95% CIs to estimate error bars. An approximation of the "elbow" method was used to identify the cutoff where the number of uninfected participants misclassified as PASC-probable stabilized (eMethods in Supplement 3). The threshold (index of at least 5) can be used to identify adolescents with PASC for research purposes. Using this threshold, the percentage of infected PASC-probable adolescents with each symptom was as follows: daytime tiredness/sleepiness or low energy, 80%; body, muscle, or joint pain, 61%; headache, 56%; trouble with memory or focusing, 47%; tired after walking, 42%; back or neck pain, 40%; feeling lightheaded or dizzy, 39%; and change or loss in smell or taste, 34%. C, Participant responses to 3 questions from the Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 survey, stratified into 7 groups: participants with a zero PASC research index and no prolonged symptoms, zero PASC research index but at least 1 prolonged symptoms, and participants with nonzero PASC index, divided into quintiles. The dark vertical line indicates the index threshold for PASC (to the left is PASC-unspecified, to the right is PASC-probable). Each cell is shaded according to the frequency of each response within each column, ranging from 0% to 100%.

into 3 subgroups: infected PASC-probable, infected PASC-unspecified, and uninfected. The most common prolonged symptom among PASC-probable school-age children that also contributed to the PASC research index (Figures 2B and 4) was headache (57%), followed by trouble with memory/focusing and trouble sleeping (44%) and stomach pain (43%). Among symptoms that did not contribute to the index, body/muscle/joint pain (51%), daytime tiredness/sleepiness or low energy (49%), and feeling anxious (47%) were the most common (Figure 4). The distribution of symptoms was similar between PASC-unspecified and uninfected school-age children.

Among PASC-probable adolescents, the most common prolonged symptoms contributing to the index (Figures 3B and 4) were daytime tiredness/sleepiness or low energy (80%), body/muscle/joint pain (60%), headaches (55%), and trouble

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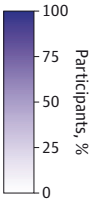
Figure 4. Frequency of Prolonged Symptoms Among School-Age Children and Adolescents Stratified by Infection and PASC Status

School-age children (6-11 y)			Symptom	Adolescents (12-17 y)		
5	4	49	Daytime tiredness, sleepiness, or low energy	80	7	8
8	6	47	Feeling anxious	47	12	12
4	3	57	Headache	55	6	6
3	2	51	Body, muscle, or joint pain	60	3	4
3	3	44	Trouble sleeping	47	6	5
1	0	44	Trouble with memory or focusing	47	3	4
3	2	35	Feeling depressed	38	9	10
2	1	38	Tired after walking	42	0	1
5	5	34	Stuffy nose	27	4	4
1	1	43	Stomach pain	27	2	3
1	0	31	Back or neck pain	41	2	2
1	1	26	Feeling lightheaded or dizzy	39	2	2
1	0	34	Nausea or vomiting	30	2	2
2	1	28	Poor appetite	30	2	3
2	3	30	Itchy skin or skin rash	15	3	4
4	5	23	Dry cough	20	2	2
1	1	17	Change or loss in smell or taste	36	0	0
3	2	24	Dark circles	19	2	2
1	1	22	Fear of crowds or enclosed spaces	22	3	4
2	2	26	Fear about specific things	17	2	2
1	2	21	Palpitation during exercise	24	1	1
3	4	20	Chapped lips	18	3	3
0	1	19	Muscle weakness	27	1	1
0	1	19	Palpitation at rest	24	1	1
0	1	18	Light hurts eyes	24	1	1
4	2	18	Constipation	17	2	2
1	1	23	Refusing to go to school	16	2	2
0	1	20	Trouble with walking, running, or stairs	20	0	1
5	3	20	Refusing to follow rules	9	2	3
3	2	23	Nightmares	11	1	2
1	1	14	Hot cold spells	24	0	1
2	1	17	Increased thirst	18	1	1
1	0	18	Chest pain	17	1	1
1	2	15	Sore throat	17	1	1
5	4	18	Hyperactive	6	1	2
1	1	15	Watery or red eyes	15	1	1
1	1	15	Diarrhea	13	1	1
3	2	14	Gained weight	10	1	2
1	2	13	Blurry vision	13	1	2
1	1	12	Excess sweat	15	1	1
1	1	15	Fear of other children/adults	11	1	2
2	2	12	Increased appetite	10	1	2
1	1	11	Tingling	15	0	1
2	2	11	Wet cough	10	1	1
			Panic attack	22	2	3
0	1	16	Repeating thoughts after traumatic event	8	0	1
1	0	11	Trouble breathing	13	0	0
1	0	9	Tremors	13	0	1
1	1	7	Lost weight	12	1	1
1	2	10	Barking cough	8	0	1
1	0	10	Ringing ears	10	0	1
0	0	11	Problems with talking	8	0	0
0	1	9	Fever	9	0	0
1	0	9	Breathing pain	9	0	0
2	1	7	Serious behavior problems	4	1	1
0	0	9	Problem with teeth/gums	4	0	1
0	1	6	Dry mouth	6	0	0
0	0	5	Hair problems	8	0	1
0	1	8	Frequent urination	4	0	0
0	0	5	Problems with swallowing	6	0	0
1	0	6	Hallucinations	5	0	0
1	1	3	Dry eyes	6	1	1
0	0	9	Hearing changed	2	0	0
0	0	7	Skin color change	4	1	0
1	0	6	Rocking back and forth	3	0	0
0	0	3	Loss of voice	5	0	1
0	0	4	Color change in fingers/toes	4	0	0
0	0	3	Nail problems	3	0	0
0	0	5	Urination pain	2	0	0
1	0	1	Lost height	3	0	0
0	0	3	Unable to move body	2	0	0
Uninfected (n = 147)	Infected, PASC-unspecified (n = 599)	Infected, PASC-probable (n = 152)		Infected, PASC-probable (n = 445)	Infected, PASC-unspecified (n = 2664)	Uninfected (n = 1369)



Symptoms, sorted from most to least common in the study population overall, are in the center column. Left columns correspond to school-age children in 3 groups: uninfected, infected and not meeting the PASC research index threshold (infected, PASC-unspecified), and infected and meeting the PASC research index threshold (infected, PASC-probable). The columns on the right correspond to adolescents with columns in the reverse order. Note that school-age children were not asked about panic attacks. Frequency of each prolonged symptom is indicated by shading, from 0% to 100%.

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with memory/focusing (47%). Among symptoms that did not contribute to the index, trouble sleeping (47%), feeling anxious (47%), and feeling sad/depressed (38%) were the most common (Figure 4). The distribution of symptoms was similar between PASC-unspecified and uninfected adolescent participants.

Among school-age children, 4 symptom clusters were identified (**Figure 5**). Cluster 1 had high rates of many symptoms and the highest symptom burden. Cluster 2 was characterized by high rates of headache (95%), body/muscle/joint pain (60%), and daytime tiredness/sleepiness or low energy (52%). Cluster 3 was characterized by higher rates of trouble sleeping (64%) and trouble with memory/focusing (62%). Cluster 4 was characterized predominantly by stomach pain (100%) and nausea/vomiting (61%). Among adolescents, 3 clusters were identified (Figure 5). Cluster 1 had high rates of many symptoms, similar to the first school-age cluster. Cluster 2 was characterized by high rates of daytime tiredness/sleepiness or low energy (89%) and body/muscle/joint pain (87%). Cluster 3 was characterized by having change/loss in smell or taste (100%), with relatively low rates of all other symptoms. The clusters with the most symptoms in both school-age children and adolescents (cluster 1) had the highest mean number of systems affected (eTable 8 in Supplement 3) and were correlated with poorer overall health and quality of life (eFigure 5 in Supplement 3).

Overall, 64 school-age children and 781 adolescents enrolled as uninfected but were Ab+ (ie, asymptomatically infected; eFigure 1 and eTable 9 in Supplement 3). Among school-age children, 6 (9%) met the index threshold whereas 18 (28%) reported experiencing at least 1 prolonged symptom. Among adolescents, 29 (4%) met the index threshold and 175 (22%) reported at least 1 prolonged symptom.

Symptom frequencies for all groups (infected, uninfected, and uninfected Ab+), including estimated risk ratios and odds ratios, are shown in eTable 10 in Supplement 3.

Discussion

In this large-scale study, children with probable PASC experienced prolonged symptoms in almost every organ system, with the majority having multisystem involvement. A clear pattern of symptom differences was identified between school-age children and adolescents, underscoring the importance of characterizing PASC separately in these 2 age groups.

This study developed an empirically derived index that can be used to help researchers identify children likely to have PASC, which was associated with overall health, physical health, and quality of life. This PASC research index, distinct for each age group, used combinations of 10 symptoms in school-age children and 8 symptoms in adolescents to indicate the likelihood of PASC. Although many other symptoms were more common in infected compared with uninfected participants, symptoms selected for the index were those that were most associated with infection history. Because these other symptoms were highly associated with the symptoms selected for the index (eTable 7 in Supplement 3), it was rare for participants not meeting the index threshold to have these other symptoms (Figure 4). In this cohort, 20% of infected school-age children exceeded the PASC symptom threshold, while 14% of adolescents exceeded the threshold. PASC symptoms clustered into 4 distinct clusters in school-age children and 3 in adolescents.

The PASC research index presents a framework for future studies and can be used as a continuous or binary outcome variable (based on derived thresholds) to determine risk factors for developing PASC and the trajectory of PASC and its resolution (or relapse). Although this provisional index may be used for research, it is not intended for clinical practice, and 1 symptom may be sufficient to indicate PASC in any given child.

This study makes a substantial contribution to the understanding of pediatric PASC. Most research to understand PASC symptoms has focused on adults, potentially due to the misperception that children were not severely affected by COVID-19, leaving childhood symptoms less understood. Most prior pediatric studies have relied on electronic health records.[30,31] The current study had the advantage of comprehensively assessing caregiver-reported symptoms across every organ system, examining them in combination, and comparing them directly to an uninfected seronegative control group. The symptoms identified as being related to PASC were associated with infection, not only symptoms that became more common during the pandemic.

This study identified separate PASC research indices for school-age children and adolescents based on symptoms most likely to differentiate between those with and without an infection history. Higher indices were correlated with worse functional outcomes, and those with indices meeting the PASC threshold reported many prolonged symptoms, not just those selected by LASSO.[28] The strongest differentiators of infection history in adults (RECOVER-Adult study)[15] and adolescents overlapped considerably. There was less overlap between adults and school-age children. These findings underscore the need for separate assessments in different age groups. This may be one reason that younger children with PASC are being undercounted in studies and/or undiagnosed clinically, although undercounting may also be due to younger children being less able to recognize and report symptoms. The pathophysiology behind these age-related differences warrants future study, given substantial changes in growth, development, immunological factors, and pubertal hormones that occur across the life course.[11]

Among infected participants, there was a wide range of time elapsed between infection and survey completion (median [IQR] time was 501 [297-801] days for school-age children and 518 [333-810] days for adolescents). However, symptom frequency did not change meaningfully when comparing different times between infection and survey completion, underscoring the usefulness of the PASC index for any child in the postacute phase of SARS-CoV-2 infection.

Four symptom clusters in school-age children and 3 in adolescents were identified. In both age groups, there was a single cluster with high symptom burden (as in adults) and a cluster predominated by fatigue and pain symptoms. Other clusters differed by age. School-age children had a cluster

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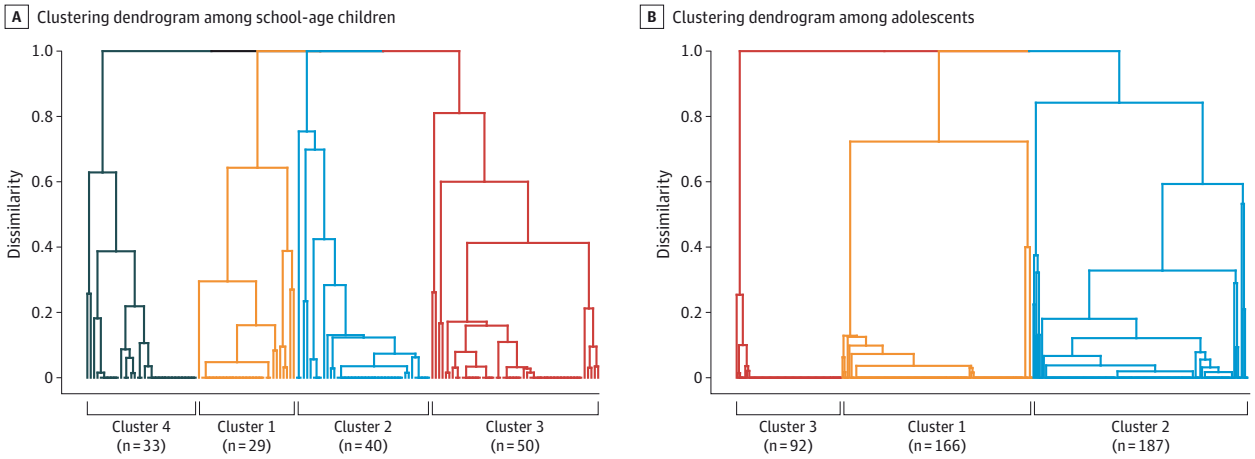
Figure 5. Defining Subgroups of Postacute Sequelae of SARS-CoV-2 Infection (PASC)–Probable Participants



C Frequency of symptoms among school-age children

	Participants, %			
	Cluster 1 (n = 29)	Cluster 2 (n = 40)	Cluster 3 (n = 50)	Cluster 4 (n = 33)
Trouble with memory or focusing	79	25	62	9
Back or neck pain	59	42	22	6
Stomach pain	76	5	16	100
Headache	100	95	0	58
Fear about specific things	28	10	48	12
Refusing to go to school	45	15	22	15
Itchy skin or skin rash	48	25	24	27
Trouble sleeping	62	20	64	27
Nausea or vomiting	66	15	12	61
Feeling lightheaded or dizzy	86	22	6	9
Body, muscle, or joint pain	83	60	30	42
Daytime tiredness, sleepiness, or low energy	79	52	36	36
Feeling anxious	69	32	50	42
Tired after walking	69	42	26	24
Feeling depressed	69	28	30	21
Stuffy nose	45	38	36	18
Poor appetite	24	28	28	30
Dark circles	38	25	22	15
Dry cough	34	25	18	18
Palpitation during exercise	55	22	8	9
Nightmares	38	18	24	15
Trouble with walking, running, or stairs	52	15	14	9
Fear of crowds or enclosed spaces	31	12	30	12
Muscle weakness	48	12	14	9
Palpitation at rest	41	20	10	12
Chest pain	48	15	4	15
Chapped lips	31	15	22	12
Constipation	28	10	10	30
Light hurts eyes	38	20	12	6
Refusing to follow rules	21	10	30	15
Increased thirst	24	15	14	18
Sore throat	41	12	2	15
Change or loss in smell or taste	28	15	16	12
Hyperactive	14	10	30	15
Diarrhea	34	8	10	15
Hot cold spells	41	12	2	9
Repeating thoughts after traumatic event	31	2	24	6
Watery or red eyes	24	20	10	9
Fear of other children/adults	21	8	18	15
Gained weight	24	5	20	6
Blurry vision	21	22	8	3
Trouble breathing	38	8	2	6
Excess sweat	21	12	8	12
Increased appetite	21	5	10	15
Wet cough	21	5	6	18
Tingling	28	12	6	3
Problems with talking	24	5	14	3
Ringing ears	28	8	4	6
Tremors	34	8	2	0
Barking cough	17	5	8	12
Breathing pain	31	10	0	0
Fever	21	5	2	12
Hearing changed	17	8	8	6
Problem with teeth/gums	17	5	10	3
Color change in fingers/toes	17	0	2	0

D Frequency of symptoms among adolescents

	Participants, %		
	Cluster 1 (n = 166)	Cluster 2 (n = 187)	Cluster 3 (n = 92)
Change or loss in smell or taste	30	11	100
Body, muscle, or joint pain	78	67	14
Daytime tiredness, sleepiness, or low energy	97	89	28
Tired after walking	65	41	3
Back or neck pain	61	39	9
Trouble with memory or focusing	72	40	13
Headache	86	44	22
Feeling lightheaded or dizzy	94	6	5
Feeling anxious	64	43	24
Trouble sleeping	60	49	21
Feeling depressed	47	39	21
Poor appetite	48	22	15
Nausea or vomiting	55	17	10
Stuffy nose	29	29	21
Stomach pain	45	22	4
Muscle weakness	49	21	1
Palpitation during exercise	51	10	5
Palpitation at rest	48	10	8
Light hurts eyes	42	18	3
Hot cold spells	45	17	1
Fear of crowds or enclosed spaces	34	19	9
Panic attack	36	17	8
Dry cough	24	18	16
Trouble with walking, running, or stairs	40	12	2
Chapped lips	25	15	12
Dark circles	31	14	5
Sore throat	23	14	13
Increased thirst	25	15	10
Chest pain	34	9	3
Fear about specific things	26	14	5
Constipation	27	14	4
Refusing to go to school	21	17	5
Watery or red eyes	21	12	9
Excess sweat	30	9	3
Tingling	34	5	1
Itchy skin or skin rash	22	12	7
Trouble breathing	29	4	4
Diarrhea	23	9	5
Tremors	30	4	1
Blurry vision	23	9	2
Lost weight	20	9	5
Wet cough	16	6	8
Nightmares	20	8	1
Fear of other children/adults	19	8	2
Ringing ears	22	5	1
Breathing pain	18	4	2

A and B, Subgroups formed using consensus clustering to group participants with similar symptom profiles (based on prolonged symptoms contributing to the PASC research index only). Four clusters were identified in PASC-probable school-age children and 3 clusters among adolescents. C and D, Frequencies of each prolonged symptom are shown for each cluster, where shading indicates frequency from 0%-100%. Symptoms that contribute to the PASC research index are above the dark horizontal line, and those below do not contribute to the PASC research index, sorted in decreasing frequency among all PASC-probable participants. Symptoms present in <5% of participants in every cluster were omitted. The full set of symptoms is in eFigure 6 in Supplement 3.

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with neuropsychological and sleep impacts and another with gastrointestinal predominance. Adolescents had a cluster that was primarily loss of taste and smell,[32] similar to that found in adults, which was not noted in the school-age clusters. Clusters predominated by respiratory symptoms were not identified, possibly related to community recruitment or few participants with severe acute illness. Future research should evaluate whether these pediatric clusters are associated with different pathophysiology from adults,[33-35] which will be critical for identifying the treatment targets needed for clinical trials.[36-40]

Limitations

This study has limitations. First, the research index is not intended for use in clinical practice to diagnose PASC. Rather it must be considered with clinical judgement because children may have PASC without meeting the index threshold. There are many prolonged symptoms that differ between those previously infected and uninfected with SARS-CoV-2 that are not part of this index. It remains unknown how many children with other diagnoses would have similar prolonged symptoms. This index may evolve over time with changing variants and population immunity. Although children with higher PASC indices report worse quality of life, the cross-sectional analyses preclude causal inference. If a symptom lasted more than 4 weeks but was absent at survey completion, it was not included as a prolonged symptom because this index was not meant to describe incidence. However, it can be used for longitudinal follow-up of recovery and relapse, which would not be possible if resolved symptoms were used in the calculations.

Second, the population prevalence of pediatric PASC cannot be determined with the current design because participants with more prolonged symptoms may have been more inclined to enroll. To mitigate differences that may have resulted from having an extant adolescent cohort, community outreach within the school-age group was encouraged.

Third, some participants in the infected and uninfected groups could have been misclassified. Infected participants were not required to have evidence of SARS-CoV-2 infection; this study relied on caregiver-reported COVID-19 infection history, given variable access to testing. Uninfected children were confirmed to not have SARS-CoV-2 antibodies, but it is possible that some may have been unknowingly infected without developing antibodies or their immunity waned.[41] Uninfected participants may have another postviral syndrome or other conditions that may have symptoms and even pathophysiology that overlaps with PASC.[42] Despite this uncertainty, important differences between infected and uninfected groups were detected.

Fourth, given that symptoms were caregiver-reported, recall bias is possible. In addition, caregiver perceptions of their adolescents' symptoms may differ from those of the adolescents themselves. However, to enable valid comparisons across age groups, data collection methods were standardized. Future analyses will combine caregiver-reported surveys with objective measures collected during the in-person longitudinal study phase.[19]

Fifth, this empirically derived index is a framework that identified commonalities for research purposes. Iterative adaptation of how PASC is assessed may occur as more RECOVER data are collected and as children are followed up. Future analyses will examine PASC symptoms in early childhood (birth to 5 years) and the effects of SARS-CoV-2 on worsening underlying conditions and increasing new conditions,[43-45] such as diabetes,[46] autoimmune diseases,[47] neurocognitive disorders, and postinfectious syndromes.[11]

Conclusions

In this large-scale study, symptoms that characterized pediatric PASC differed by age group, and several distinct phenotypic PASC presentations were described. The research indices developed here will help researchers identify children and adolescents with high likelihood of PASC. Although these indices will require further research and validation, this work provides an important step toward a clinically useful tool for diagnosis with the ultimate goal of supporting optimal care for youth with PASC.

ARTICLE INFORMATION

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