How Common is Long COVID in Children and Adolescents?

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Abstract: In children, the risk of coronavirus disease (COVID) being severe is low. However, the risk of persistent symptoms following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is uncertain in this age group, and the features of "long COVID" are poorly characterized. We reviewed the 14 studies to date that have reported persistent symptoms following COVID in children and adolescents. Almost all the studies have major limitations, including the lack of a clear case definition, variable follow-up times, inclusion of children without confirmation of SARS-CoV-2 infection, reliance on self- or parent-reported symptoms without clinical assessment, nonresponse and other biases, and the absence of a control group. Of the 5 studies which included children and adolescents without SARS-CoV-2 infection as controls, 2 did not find persistent symptoms to be more prevalent in children and adolescents with evidence of SARS-CoV-2 infection. This highlights that long-term SARS-CoV-2 infection–associated symptoms are difficult to distinguish from pandemic-associated symptoms.

Key Words: SARS-CoV-2, symptoms, persistent, outcome, severity, neurologic, mental health, chronic fatigue, headache

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Children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are usually asymptomatic or have mild coronavirus disease (COVID) with low rates of hospitalization (<2%) or death (<0.03%).¹⁻⁹ Reported hospitalization rates might overestimate severity as many studies do not specify whether children are hospitalized with COVID or because of COVID.¹⁰ The disease burden is higher in adolescents, who are more frequently infected and hospitalized than younger children.⁹

Despite the low-risk that acute COVID poses in children in the short term, 2 longer term consequences of SARS-CoV-2 infection are of more concern. The first is "pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)" or "multisystem inflammatory syndrome in children (MIS-C)," an immune-mediated disease that occurs in a small proportion (<0.1%) of children 2 to 6 weeks after being infected with SARS-CoV-2.^{11–20}

The second is "long COVID," also called "post-COVID syndrome" or "post-acute sequelae of SARS-CoV-2 (PASC)." These terms describe the persisting symptoms following COVID,

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described mainly in adults, affecting the sensory, neurologic, and cardiorespiratory systems, as well as mental health.^{21–23} To date, there is no clear definition for this syndrome and no agreement on the duration of symptoms that justify the diagnosis, which ranges from 4 to 12 weeks after the acute infection. Over 200 symptoms have been attributed to long COVID, many of them nonspecific and highly prevalent in the general population, such as fatigue, sleep disturbance, concentration difficulties, loss of appetite, and muscle or joint pain.^{24–26} In adults, reported risk factors for long COVID include female sex, middle age, white ethnicity and comorbidities, especially asthma.^{27–29} There is much less data on long COVID in children and adolescents.

The low-risk posed by the acute disease means that 1 of the key benefits of COVID vaccination of children and adolescents might be to protect them from long COVID. An accurate determination of the risk of long COVID is therefore crucial in the debate about the risks and benefits of vaccination in this age group. Here, we review and summarize studies that have reported long COVID symptoms in children and adolescents.

STUDIES OF LONG COVID IN CHILDREN AND ADOLESCENTS

We identified 14 studies (4 cross-sectional studies,^{26,30-32} 9 prospective cohort studies,³³⁻⁴¹ 1 retrospective cohort study⁴²) investigating long COVID symptoms in a total of 19,426 children and adolescents (Table 1 and Fig. 1; Table, Supplementary Digital Content 1, http://links.lww.com/INF/E531). The number of children and adolescents in each study varied from 16 to 6804 (median 330, interquartile range 89–1533). All of the studies were done in high-income countries. Case reports, studies which followed children after a SARS-CoV-2 infection but did not evaluate symptoms of long COVID or studies which did not address predominantly children and adolescents were not included.^{43–50}

There is marked heterogeneity between studies, including differences in design, inclusion criteria, outcomes, and follow-up times (Table 2). Children were evaluated for persistent symptoms for varying durations: more than 4 weeks (2 studies),^{31,36} more than 4 and 8 weeks (1 study),³⁵ more than 4 and 12 weeks (2 studies),^{34,41} more than 12 weeks (1 study),³⁷ more than 5 months (2 studies),^{33,40} and at arbitrary timepoints (6 studies).^{26,30,32,38,39,42} In 7 studies, evaluation of symptoms was done only through online questionnaires or phone interviews,^{26,31,32,34–36,40} while 5 studies included study visits.^{30,33,39,41,42}

RESULTS OF STUDIES OF LONG COVID IN CHILDREN AND ADOLESCENTS

The prevalence of long COVID symptoms varied considerably between studies from 4 to 66%.^{26,33–38,40–42} There was also a large variation in the reported frequency of persistent symptoms. The most common reported symptoms were headache (3 to 80%), fatigue (3 to 87%), sleep disturbance (2 to 63%), concentration difficulties (2 to 81%), abdominal pain (1 to 76%), myalgia or arthralgia (1 to 61%), congested or runny nose (1 to 12%), cough (1 to 30%), chest tightness or pain (1 to 31%), loss of appetite or weight (2 to 50%), disturbed smell or anosmia (3 to 26%), and rash (2 to 52%) (Fig. 2; Table, Supplementary Digital Content 1,

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First author	Country	Study	Age (y) ^a	Timing	g Cases	Controls	Prevalence of patients with persisting symptoms							
Blankenburg	Germany	CS	median 15 (14-16)	nr	nr	nr	nr Studies with controls							
Miller	UK	PCS	nr, ≤17	4w	8/174	72/4504	5% <i>p</i> =0.009 □ 2%							
Molteni	UK	PCS	median 13 (10-15)	4w	77/1734	15/1734	4% <i>p</i> =0.0001							
				8w	25/1734	nr	2%							
Radtke	Switzerland	PCS	median 11 (nr)	4w	10/109	121/1246	9% p=0.9 10%							
				12w	4/109	28/1246	₽ 4% p=0.3 2% p<0.0001							
Stephenson	UK	PCS	range 11-17	12w	2038/3065	1993/3739								
Ashkenazi-Hoffnung	Israel	PCS	mean 12 (5)	b	90	-	nr Studies without controls							
Blomberg	Norway	PCS	median 8 (6-12)	5m	2/16	-	13%							
Brackel	Netherlands	CS	median 13 (9-15)	nr	89	-	nr							
Buonsenso	UK, USA	CS	mean 10 (3.8)	4w	510	-	nr							
Buonsenso	Italy	CS	mean 11 (4.4)	с	75/129	-	58%							
Osmanov	Russia	PCS	median 10 (3-15)	5m	126/518	-	24%							
Say	Australia	PCS	mean 3.7 (3.5)	4w	12/151	-	8%							
				12w	0/151	-	0%							
Smane	Latvia	RCS	mean 9.2 (5.2)	d	9/30	-	30%							
Sterky	Sweden	PCS	nr, ≤18	16w	12/55	-	22%							

° mean 163d after infection, SD 114d

d mean 101d after infection, SD 17d

CS, cross-sectional study; d, days; m, month; nr, not reported; PCS, prospective cohort study; RCS, retrospective cohort study; SD, standard deviation; w, weeks; y, years

FIGURE 1. Proportion of children and adolescents with persistent symptoms after SARS-CoV-2 infection.

http://links.lww.com/INF/E531).^{26,30-42} Four studies reported a much higher prevalence of symptoms compared with the other studies.^{26,30-32} Of these studies, 3 were done at arbitrary timepoints after a SARS-CoV-2 infection.^{26,30,32} Six studies reported a positive correlation between increasing age,^{30,35-37,39,40} 3 between female sex^{30,36,37} and 1 each between allergic diseases⁴⁰ or worse pre-infection physical and mental health³⁷ and the prevalence of persisting symptoms.⁴⁰ Furthermore, one study found an association between longer hospitalization and more severe persistent symptoms, and between PIMS-TS and a higher prevalence of persistent symptoms.³⁸

A control group was included in only 5 of the 14 studies. These 5 studies reported symptoms in children and adolescents without evidence of SARS-CoV-2 infection as a comparison group.^{30,34–37} Three of these studies found persistent symptoms to be more prevalent in children and adolescents with evidence of a SARS-CoV-2 infection.^{35–37}

STRENGTHS AND LIMITATIONS OF STUDIES

The strengths and limitations of the studies are summarized in Table 2. Almost all the studies to date on long COVID in children and adolescents have major limitations.

The first major limitation is the lack of a clear case definition meaning studies have used variable inclusion criteria and follow-up times. Some studies included children with self-reported SARS-CoV-2 infection without laboratory confirmation.^{31,32} In addition to the heterogeneity in inclusion criteria, studies followed up children

at arbitrary time points and the method of assessment varied. Most studies relied on self- or parent-reported symptoms from questionnaires without clinical assessment and objective parameters, such as lung function testing or imaging.^{26,30–32,34–38,40} Using apps or online questionnaires is likely to select participants from higher socio-economic background, who have a lower risk of poor outcomes following SARS-CoV-2 infection.⁵¹

A second major limitation is the lack of a control group in the majority of studies. In the absence of a control group, it is impossible to distinguish symptoms of long COVID from symptoms attributable to the pandemic, such as lockdown measures (school closures, deprivation of seeing friends or being unable to do sports and other activities) or seeing family and friends suffering or even dying from COVID. The results from the studies to date suggest that infection-associated symptoms are not necessarily more common or severe than pandemic-associated symptoms.^{30,34} The prevalence of symptoms consistent with long COVID, including psychosomatic symptoms, have been considerably higher in children and adolescents since the start of the pandemic, and lockdown measures have been shown to have negative effects on the well-being and mental health of children and adolescents.52,53 While lockdown measures, including school closures decrease SARS-CoV-2 transmission and prevent late manifestations of COVID, these actions restrict social contact, self-determination and education, and therefore amplify pandemic-associated symptoms.

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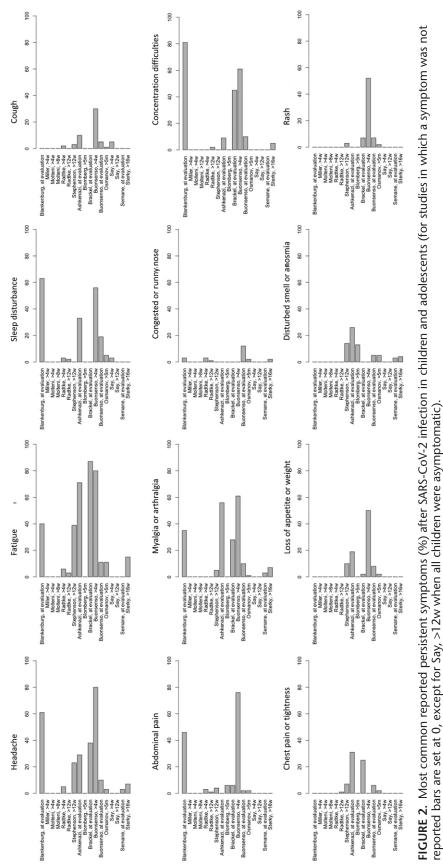
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Which Investigated Persistent Symptoms After SARS-CoV-2 Infection in Children and Adolescents	1 and Adolescents	anoitstimi.I rədturf		Includes participants up to 38y of age		Participants who did not answer every week were excluded (73%)		More female and adolescent participants			Fatigue, concentration difficulties, memory problems assessed only in adults				Only includes hospitalized children	Low median age		Only includes hospitalized children		
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agths		Control Group Without SARS- CoV-2 Infection	Studies with controls		>	>	>	>	>	ntrols										ng.
TABLE 1. Strer		ζbuż ²		Blankenburg et al ³⁰	Miller et al ³⁶	Molteni et al 35	Radtke et al ³⁴	Stephenson et al ³⁷	Studies without controls	Ashkenazi-Hoffnung et al ³⁹	Blomberg et al ³³	$Brackel et al^{32}$	Buonsenso et al ³¹	Buonsenso et al^{26}	Osmanov et al ⁴⁰	Say et al ⁴¹	Smane et al ⁴²	Sterky et al ³⁸	*Except asthma. †Only for blood drawing. ‡Except overweight.	



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TABLE 2. Heterogeneity and Methodological Limitations Found in Studies Investigating Children and Adolescents With Persistent Symptoms After SARS-CoV-2 Infection

Heterogeneity between studies

Studies vary considerably in:

- Age range of participants
- · Proportion of participants with preexisting medical conditions
- Inclusion criteria
 - Laboratory confirmed COVID
 Severity of disease
- Time points of assessment
- Outcome measurement
 - Number and range of symptoms assessedDuration of follow-up
- Data collection method
- Methodologic limitations

No control group

- Small cohort or small number seropositive
- · No data on preexisting medical conditions
- Inclusion criteria
 - ° Includes self-reported SARS-CoV-2 infection
 - Not all cases laboratory confirmed infection
 - Includes only/mostly asymptomatic or mild infection
- Outcome
 - Timing of SARS-CoV-2 infection not specified
 - Duration of symptoms not specified
 - ° Self-/parent-reported symptoms, no clinical assessment
 - Few clinical outcomes assessed
 - No mental health outcomes
- Bias
 - Selection bias
 - Misclassification bias
 - Recall bias
- Nonresponse bias

A third important limitation is selection bias as many studies had a low response rate (13% in a recent study).³⁷ As those with persisting symptoms might be more likely to respond to surveys, this can lead to a substantial overestimation of the prevalence of long COVID. Also, as children and adolescents with mild symptoms might not seek testing, selection and misclassification bias could also lead to an overestimate.

Another limitation is that almost all studies include a wide range of age groups. It is likely that the incidence and characteristics of long COVID vary between adolescents and younger children. As the risks and benefits of COVID vaccines differs between these age groups, more studies are needed that provide age-specific data. Furthermore, none of the studies investigated the impact of initial disease severity on the risk of long COVID. Finally, all studies are likely to have been done before the delta variant becoming dominant, which may have a different risk of long COVID.

Adding to the confusion has been the use of the term long COVID to encompass those with objective complications of COVID (such as pulmonary fibrosis or myocardial dysfunction), those with mental health problems,^{21,22} and those with more subjective and nonspecific symptoms reminiscent of postviral chronic fatigue syndrome or myalgic encephalomyelitis. A separation of postintensive care syndrome, postviral fatigue syndrome, and long-term COVID syndrome has been suggested for the adult population and could be adopted for children.⁵⁴

CONCLUSIONS

In summary, the evidence for long COVID in children and adolescents is limited, and all studies to date have substantial limitations or do not show a difference between children who had been infected by SARS-CoV-2 and those who were not. The absence of a control group in the majority of studies makes it difficult to separate symptoms attributable to long COVID from pandemic-associated symptoms.^{30,34,36}

In light of the large number of children and adolescents infected with SARS-CoV-2, the impact of even a low prevalence of persisting symptoms will be considerable. However, in the majority of studies, symptoms did not persist longer than 12 weeks.^{33–35,41} Consistent with this, 1 study that did find a difference between cases and controls in persisting symptoms (at 4 weeks post COVID) reported that by 8 weeks, most symptoms had resolved, suggesting long COVID might be less of a concern in children and adolescents than in adults.³⁵ Interestingly in one study, more than half of adolescents in the uninfected control group reported symptoms at 12 weeks despite only 8% reporting symptoms at the time of testing for SARS-CoV-2.³⁷

The relative scarcity of studies of long COVID and the limitations of those reported to date mean the true incidence of this syndrome in children and adolescents remains uncertain. The impact of age, disease severity and duration, virus strain, and other factors on the risk of long COVID in this age group also remains to be determined.

In light of the importance of long COVID in the risk-benefit equation for policy decisions on COVID vaccines for children and adolescents, further studies to accurately determine the risk of long COVID are urgently needed.⁵⁵ These should include rigorous control groups, including children with other infections and those admitted to hospital or intensive care for other reasons. Longitudinal cohort studies should include regular testing for SARS-CoV-2 to confirm infection, meticulous capture of symptoms, follow-up times that are both consistent and sufficiently long to account for intermittent symptoms, and recording of preexisting medical conditions. More research to identify underlying immunological mechanisms of long COVID is also needed.

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