Prevalence and clinical presentation of long COVID in children: a systematic review

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Abstract
A systematic literature review was conducted up to 15th February 2022 to summarize long COVID evidence and to assess prevalence and clinical presentation in children and adolescents. Articles reporting long COVID prevalence and symptoms based on original data in the paediatric population were included. Case series quality was assessed through the JBI Critical Appraisal Checklist. For observational studies, adherence to STROBE checklist was evaluated. Twenty-two articles were included: 19 observational studies (12 cohort/7 cross-sectional) and 3 case series. Nine studies provided a control group. We found a high variability in terms of prevalence (1.6–70%). The most frequently reported symptoms were fatigue (2–87%), headache (3.5–80%), arthro-myalgias (5.4–66%), chest tightness or pain (1.4–51%), and dyspnoea (2–57.1%). Five studies reported limitations in daily function due to long COVID. Alterations at brain imaging were described in one study, transient electrocardiographic abnormalities were described in a minority of children, while most authors did not evidence long-term pulmonary sequelae. Older age, female sex, and previous long-term pathological conditions were more frequently associated with persistent symptoms.

Conclusion: Long COVID evidence in children is limited, heterogeneous, and based on low-quality studies. The lockdown consequences are difficult to distinguish from long COVID symptoms. High-quality studies are required: WHO definition of long COVID should be used, controlled clinical studies should be encouraged, and the impact of new variants on long COVID prevalence should be investigated to ensure an objective analysis of long COVID characteristics in children and a proper allocation of healthcare system resources.

What is Known:
• Children rarely develop a severe respiratory disease in the acute phase of COVID-19.
• A limited number of patients develop a multisystem inflammatory condition that can lead to multiorgan failure and shock.

What is New:
• Persistent symptoms after SARS-CoV-2 infection are reported in children and limitations in daily function due to long COVID symptoms affect school attendance.
• Functional complaints of post-acute COVID are difficult to be distinguished from those due to social restrictions.

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Abbreviations
COVID-19 Coronavirus-associated acute respiratory disease called coronavirus disease 19
ECG Electrocardiography
IQR Interquartile range
LC28 Long COVID with symptoms persisting over 28 days
LC56 Long COVID with symptoms persisting over 56 days
Recently, a research definition of long COVID in children has been derived from a Delphi process and it is reported in Table 2 [6].

Children rarely develop a severe respiratory disease in the acute phase of COVID-19, though a limited number of patients exhibits a well-defined multisystem inflammatory condition, that can lead to multiorgan failure and shock, known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [7] or multisystem inflammatory syndrome in children (MIS-C) [8].

Since October 2020, parents’ concerns about persistent symptoms in children months after the acute SARS-CoV-2 infection have been emerging [9]. In November 2020, a case series from Sweden described a group of five girls with long COVID [10]. Since then, studies regarding long COVID in the paediatric population are accumulating although high variability in terms of definition, prevalence, and symptoms has been reported [11]. Therefore, we performed a systematic review of the literature to summarize the current evidence regarding this emerging condition in children, with a focus on prevalence and clinical presentation.

**Methods**

**Design**

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [12], Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [13] and Joanna Briggs Institute Critical Appraisal Checklist for Case Series (JBI) [14].

### Introduction

The challenges of coronavirus-associated acute respiratory disease called coronavirus disease 19 (COVID-19) are now extending to its long-term sequeliae. Since the beginning of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) [1] pandemic outbreak, evidence of persisting symptoms has emerged in adults with a prevalence of long COVID up to 80% [2]. The range of symptoms is extensive and the most common reported are fatigue, headache, attention disturbance, hair loss, and dyspnoea [2]. Several health organizations have issued different definitions of this new syndrome in adults, as reported in Table 1 [3–5].

### Table 1  Long COVID definitions in adults

| Organization                                  | Duration of symptoms                      | Previous history          | Other criteria                                      |
|-----------------------------------------------|-------------------------------------------|---------------------------|----------------------------------------------------|
| National Institute of Health and Care Excellence (NICE) [3] | Ongoing symptomatic COVID-19 4 to 12 weeks | Acute COVID-19 Persistence of symptoms |
| Post COVID-19 syndrome                        | Over 12 weeks                             | Acute COVID-19 Persistence of symptoms |
| Center for Disease Control and Prevention (CDC) [4] | 4 weeks or more after the infection      | SARS-CoV-2 infection      |
| World Health Organization (WHO) [5]           | At least 2 months                         | Probable or confirmed SARS-CoV-2 infection |
|                                              |                                           | - Symptoms presenting 3 months after the onset of COVID |
|                                              |                                           | - Cannot be explained by an alternative diagnosis |
|                                              |                                           | - Impact on everyday functioning |
|                                              |                                           | - Symptoms may continue or develop after the infection |
|                                              |                                           | - May fluctuate or relapse over time |

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**JBI** Joanna Briggs Institute Critical Appraisal Checklist for Case Series

**N** Number

**N/A** Not applicable

**PIMS-TS** Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

**PRISMA** Preferred Reporting Items for Systematic Reviews and Meta-analyses

**SARS-CoV-2** Severe acute respiratory syndrome coronavirus type 2

**STROBE** Strengthening the Reporting of Observational Studies in Epidemiology

**PCR** Polymerase chain reaction

**SD** Standard deviation
and Meta-analyses (PRISMA) guideline recommendations [12]. The research was conducted through MEDLINE by PubMed and MedRxiv, for articles available up to 15 February 2022. References of all relevant articles were also evaluated, and pertinent articles were included. Search terms, limited to Title or Abstract, were as follows: “post-acute COVID-19,” “long COVID-19,” “SARS-CoV2,” “sequelae,” “COVID-19,” “children,” “child,” “paediatrics.”

**Inclusion and exclusion criteria**

The research was restricted to English language. Articles reporting long COVID prevalence and symptoms based on original data in paediatric population were included independently from the study design. Review articles, commentaries, editorials, and letters to the author with no original data were excluded. Sample dimension was not an exclusion criterion. Studies concerning PIMS-TS were excluded, except where the number of patients with PIMS-TS was minimal [13, 14].

**Data extraction**

Duplicate publications were removed, then two authors separately (RP and EC) checked the titles and abstracts and removed irrelevant studies according to the inclusion and exclusion criteria. Articles were categorized as cohort studies or case series and, according to the source of information, as based on surveys or questionnaires or on clinician-assessed data. From each study information about children population included, test used for SARS-CoV-2 infection diagnosis, follow-up time, long COVID definition, and clinical presentation were extracted. Studies including a minimal number of patients with PIMS-TS were included, and the prevalence of persistent symptoms was recalculated after excluding PIMS-TS cases for the sake of comparability.

**Quality assessment**

For observational studies, adherence to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [15] was assessed. Case series quality was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series [16].

**Ethics**

Ethics approval was not required for the systematic review component of this study.
Results

Study characteristics and quality

Overall, 214 articles have been initially retrieved, and after screening and selection, 22 have been included in the review (Fig. 1). The types of studies were as follows: 12 cohort studies (8 prospective [13, 14, 17–22], 3 retrospective [23–25], and 1 ambidirectional [26]), 7 cross-sectional studies [27–33], and 3 case series [10, 34, 35]. Seven studies relied on direct assessed data [13, 17, 23, 25, 31, 34, 35], including one study with a control group [31]. Fifteen studies were based on interviews or questionnaires, of these 2 were directed to paediatricians [28, 30] and 13 to caregivers or patients [10, 14, 18–22, 24, 26, 27, 29, 32, 33] among these 8 provided a control group [18–20, 22, 24, 26, 32, 33]. The median age of children ranged from 9.16 [31] to 17.6 years [32]. As described in Tables 3 and 4, terms and definitions were quite variable. The most frequently used definition relied on symptoms persisting more than 4 weeks from acute infection or hospital admission [13, 19, 20, 24, 26, 27, 31, 34]. However, other definitions used varied from symptoms persisting over 2 months [10, 19, 32] to 5 months [21]. Follow-up time ranged from 4 weeks [34] to 13 months [24]. Adherence to STROBE recommendations for observational studies and quality assessment of case series is reported in Figs. 2 and 3, respectively. The excluded studies and the PRISMA checklist are provided in the Appendix.

Reported prevalence of long COVID in paediatric studies

The prevalence of long COVID varies notably from 1.6 [34] to 70% [26] (Fig. 4). The lowest was reported in a French case series describing 7 cases of long COVID out of 661 children with a positive diagnosis of COVID-19 [34]. The highest prevalence was found in a Latvian study reporting ongoing symptoms after 4 weeks in 70% of the positive cohort [26]. A cross-sectional Italian study, based on the ISARIC questionnaire [36] to caregivers, showed a similar prevalence of 58.1% of children
### Table 3  Studies based on clinician-assessed data

| Author                      | Age years | Type of study      | Setting                        | Country   | Children | Diagnostic test | Long COVID (N) | Long COVID (%) | Follow-up | Definition                                      |
|-----------------------------|-----------|--------------------|--------------------------------|-----------|----------|-----------------|----------------|----------------|-----------|------------------------------------------------|
| Erol et al. [31]            | Median age 9.16 IQR 10.88–17.92 | Cross-sectional study Control group | Inpatients and outpatients SC HC | Turkey | 121 COVID-19 95 controls** to compare instrumental cardiac findings | Not known | 45             | Mean 5.6 m | Symptoms persisting at least 4 w after infection |
| Ashkenazi-Hoffnung et al. [17] | Mean age 12 SD 5 y | Prospective cohort study | Inpatients and outpatients SC SC HC | Israel | 90       | PCR Serological test | N/A           | N/A           | At least 4 m | Not expressed                                |
| Say et al. [13]             | Median age 3 years (IQR 1–8)  | Prospective cohort study | Inpatients and outpatients SC SC HC | Australia | 151 149 After excluding PIMS-TS | Not known | 12             | 8% 6.7%       | 6 m | Symptoms lasting over 4 w                        |
| Smane et al. [23]          | Median age 12 y (IQR 8–15) | Retrospective cohort study | Outpatients SC SC HC | Latvia | 92       | PCR 47          | 51%           | 3 m | Persistence of symptoms at least 1 m after infection |
| Heching et al. [25]        | Median age 14.4 y (range 1–18 y) | Retrospective cohort study | Outpatients SC SC HC | US | 82       | PCR or antigen test 53 | 65%           | 44.5 ± 36.2 d | Prolonged symptoms following acute infection |
| Morrow et al. [35]         | 4–18 y | Case series | Outpatients SC SC HC | US | 8 | Clinical diagnosis 4 Serological test 1 PCR 4 | 8 | N/A | Mean 7.2 m Range 2–11 m | Persistence of symptoms after acute infection |
| Morand et al. [34]         | Mean age 12 y [range 10–13 y] | Case series | N/A SC SC HC | France | 66 | 1 with SARS-CoV-2 infection | Clinical diagnosis 4 Serological test 2 PCR 1 | 1.6% | 4 w | Persisting symptoms more than 4 w from the acute infection without symptom-free interval |

*IQR interquartile range, N number, m months, SD standard deviations, y years, SC single centre, MC multi-centre, CW community-wide, HC health/hospital-centre, PCR polymerase chain reaction, N/A not applicable, PIMS-TS paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, US United States of America, d days, w weeks*
with persisting symptoms after 4 weeks from the acute infection. By excluding 3 patients diagnosed with PIMS- TS, the long COVID prevalence dropped to 56.7% [27]. The latter prevalence was consistent with data from a study based on clinical standardized examination in 92 outpatients at a median follow-up time of 55 days after acute COVID-19 [23]. Conversely, in a subsequent study, according to most of the interviewed Italian paediatricians, the persistence of symptoms after COVID-19 was less than 20% [30].

Clinical picture in children and adolescents

The clinical spectrum assessed across studies varied notably. The most frequently reported symptoms were the following: fatigue (2 [31] to 87% [28]), headache (3.5 [21] to 80% [19]), muscle or joint pain (0.7 [33] to 66% [14]), chest tightness or pain (1.3 [33] to 51% [25]), dyspnoea (2 [23] to 57.1% [34]), and taste or smell impairment (4.7 [21] to 84% [19]) (Fig. 5). Limitation in daily function affecting school attendance was reported in 5 studies [14, 15].

Fig. 2 Adherence to STROBE recommendations

Fig. 3 Case series quality assessment

| Morand et al. [14] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|-------------------|---|---|---|---|---|---|---|---|---|----|
| Ludvigsson JF [10] |   |   |   |   |   | N/A |   |   |   |    |
| Morrow et al. [35] |   |   | N/A |   |   |   |   |   |   |    |

1. Were there criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographic of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes of follow-up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?
from the largest cohort to date, in which children with a history of SARS-CoV-2 infection reported persistent symptoms more frequently than the control group with a percentage difference of 0.8% [24]. A Latvian study compared children with previous SARS-CoV-2 infection to children with other non-SARS-CoV-2 infections stating that symptoms persistence is more evident with COVID-19 than any different infection [26]. On the other hand, no significant difference has been found in a Swiss cohort that described symptoms lasting over 4 weeks in 4% of seropositive and over 12 weeks in 9%, comparable to the prevalence in the seronegative group (respectively 2% and 10%) [18].

Among controlled studies, the long COVID clinical spectrum is undefined. Stephenson et al. described tiredness (23% vs 14.2%) and headache (39% vs 24.2%) as more frequently reported within the case group, and no difference in the distribution of mental health and well-being scores was found between the two groups [22]. Similarly, headache and concentration difficulties, along with fatigue, were the most frequent symptoms in the case group of the LongCOVIDKidsDK study [32]. Besides, in a nationwide matched cohort study, fatigue, anosmia, and ageusia were significantly associated with previous SARS-CoV-2 infection, whereas concentration difficulties, headache, arthro-myalgias, and gastrointestinal symptoms were more frequent in the control group [24]. Both the latter
studies reported a better quality of life in children with a previous history of SARS-CoV-2 infection. The authors speculate that the lower sense of well-being in uninfected children could reflect the effects of social restrictions [24, 32].

**Alterations in imaging and function tests in long COVID children**

The persistence of long COVID symptoms has been associated with a hypometabolic pattern at positron emission tomography (PET) with 2-[18F]-fluorodeoxyglucose (FDG) of the brain, involving bilateral medial temporal lobes, brainstem, cerebellum, and the right olfactory gyrus in 7 French children with long COVID [34].

Data regarding possible cardiac involvement are contrasting. Erol and colleagues described a statistically significant difference in systolic blood pressure, left ventricular posterior wall diameter, relative wall thickness, and tricuspid annular plane systolic excursion values between children with a history of SARS-CoV-2 infection and controls [31]. In an Israeli prospective cohort study, no echocardiographic alterations were documented in long COVID

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Fig. 5  a Most frequently reported symptoms. b Other symptoms reported
Table 4 Questionnaire and survey-based studies

| Author and Year | Age years | Type of study | Setting | Country | Children | Diagnostic test | Long COVID (%) | Long COVID (N) | Follow-up | Definition |
|-----------------|-----------|---------------|---------|---------|----------|-----------------|----------------|---------------|-----------|------------|
| Stephenson et al. [22] | 11–17 | Prospective cohort study | Inpatients and outpatients CW | England | 6804 tested 3065 positives 3739 negatives | PCR | N/A | 66.5% PCR positive 53.4% PCR negative | 3 m | Presence of symptoms at 3 months post-testing |
| Molteni et al. [19] | 5–17 | Prospective cohort study | Inpatients and outpatients SC CW | UK | 1734 positives 1734 negatives | PCR Serological test | Positive: LC28 77 LC56 25 Negative with symptoms > 28 d: 15 | N/A | Symptoms lasting > 28 days LC28 > 56 days LC56 |
| Radtke et al. [18] | Median age 11 IQR 9–13 | Prospective cohort study | Inpatients and outpatients CW | Switzerland | 109 positives 1246 negatives | Serological test | Symptoms over 4 w: 10 positive 121 negative Over 12 w: 4 positive 28 negative | 6 m | Symptoms lasting over 12 w |
| Miller et al. [20] | 0–17 | Prospective cohort study | Outpatients MC CW | UK | 175 positives 4503 negatives | PCR (62.9%) Serological test (26.9%) Both (10.3%) | Symptoms | 3 m | Symptoms lasting over 4 w not explained by alternative diagnosis |
| Osmanov et al. [21] | Median age 10.4 y (IQR 3–15) Range 2 d–18 y | Prospective cohort study | Inpatients SC HC | Russia | 518 | PCR | 128 | 24.7% | Median 268 d (IQR 233–284) | Symptoms present at the time of follow-up interview and lasting over 5 months |
| Sterky et al. [14] | 0–18 | Prospective cohort study | Inpatients MC HC | Sweden | 55 53 After excluding PIMS-TS | PCR | 6 4 After excluding PIMS-TS | 10% 7.5% After excluding PIMS-TS | At least 4 m after admission (median 219 days, range 123–324 days) | Symptoms lasting at least 4 months after admission |
| Buonsenso et al. [27] | 11.4 SD 4.4 | Cross-sectional study | Outpatients and inpatients SC HC | Italy | 129 | PCR | 75 | 58.1% | Mean 162.5 d | Symptoms persisting over 30 d |
| Author                  | Age years          | Type of study        | Setting                          | Country | Children | Diagnostic test | Long COVID (N) | Long COVID (%) | Follow-up | Definition                                                                 |
|------------------------|--------------------|----------------------|----------------------------------|---------|----------|-----------------|----------------|----------------|-----------|-----------------------------------------------------------------------------|
| Parisi et al. [30]     | N/A                | Cross-sectional study| Outpatients and inpatients HC    | Italy   | 267 paediatricians | N/A             | N/A            | <20% according to 97.3% of paediatricians | N/A       | Persistence of symptoms after recovery (no timing expressed)               |
| Brackel et al. [28]    | Median age 13 (IQR 9–15) range 2–18 | Cross-sectional study| Survey to paediatricians HC     | Netherlands | 78% of Dutch paediatric department | PCR 47 (52.8%)  | 89             | N/A       | N/A                      | Symptoms persisting over 12 w and not explained by alternative diagnosis |
| Asadi-Pooya et al. [29] | 6–17 (mean 12.3 SD 3.31) | Cross-sectional study| Inpatients HC                   | Iran    | 58       | PCR             | 26             | 44.8%       | 3 m       | Symptoms persisting at least 3 months not present before acute COVID-19   |
| Ludvigsson [10]        | 9–15 mean age 12   | Case series          | Inpatients and outpatients SC HC | Sweden  | 5        | Clinically diagnosed | 5             | N/A            | N/A       | Symptoms lasting over 2 months                                              |
| Borch et al. [24]      | Mean age 12 y (range 6–17) | Retrospective cohort study | Case group HC                   | Denmark | Case group 15941, Control group 15080 | PCR            | Case group (6–17 y) 3374 out of 12065, Control group (6–17 y) 2245 out of 8248 | 4 w–13 m | Symptoms lasting at least 4 weeks after SARS-CoV-2 infection              |
| Kikkenborg Berg et al. [32] | Median age 17.6 y Range 16.5–18.6 y | Cross-sectional study | CW                              | Denmark | Case group 6630, Control group 21640 | PCR             | Case group 3159, Control group 12340 | 61.9%       | 12 m                    | At least one symptom lasting more than 2 m                               |
children, though lower performance at an exercise stress test was noted suggesting some degree of chronotropic incompetence [17]. Electrocardiographic (ECG) abnormalities were described in a minority of COVID-19 outpatients, and none of the subjects affected had echocardiographic alterations. The ECG abnormalities resolved over time and were not associated with severity of acute disease [25].

A mild obstructive reversible pattern at lung function test was evidenced in nearly half the children in the Israeliian cohort [17], whereas no long-term pulmonary sequelae were evidenced using lung ultrasound [38, 39] and pulmonary function tests [39, 40] in 3 studies [38–40].

**Risk factors for long COVID in children**

In the CLoCK study cohort, in both positive and negative groups, those with multiple symptoms were more likely to be female, adolescent, and to have poorer baseline physical and mental health status [22]. The same group of children was more likely to report problems with mobility, self-care, usual activities, and pain/discomfort after acute COVID-19 [22].

Older age as a risk factor for persistent symptoms after SARS-CoV-2 infection has been reported in 9 studies [17, 19–21, 23, 24, 26, 29, 32]. As concerns sex, in a Danish matched cross-sectional study, female subjects were more prone to show symptoms lasting more than 2 months than males, both in the case and control groups [32], whereas according to Roge et al., long COVID symptoms were more frequent among female patients, with the most significant difference in cognitive and neurological sequelae [26]. Furthermore, allergic disease [21] and previous long-term conditions [20] have been identified as possible risk factors for long COVID [20, 21].

Overweight has been described as a long COVID risk factor in adults [17]. Among studies included in our review, no statistical significant difference in terms of body mass index (BMI) was found between children reporting persistent symptoms and controls [17, 31]. Recently, Bloise et al. described obesity as a potential risk factor for long COVID syndrome also in the paediatric age [41].

No correlation between acute illness severity and duration of symptoms was noticed [27, 31], except in one study comprising only inpatients in which intensive care unit (ICU) admission was associated with long COVID [29].

**Management and follow-up of children with long COVID**

The need of rehabilitation plans for long COVID patients in adults has been claimed [42], whereas the effects of this syndrome in children are unclear and data on follow-up and
management are scarce. However, according to Dutch paediatricians, 29% of children with suspected long COVID required a multidisciplinary approach comprising physiotherapy and psychologist support [28]. In Italy, 86% of paediatricians stated that in their area, no reference centre dedicated to the assistance of the child recovering from COVID was available [30].

Discussion

In the present systematic review, 7 studies [13, 17, 23, 25, 31, 34, 35] with clinical data (including 549 children with history of SARS-CoV-2 infection) and 15 studies [10, 14, 18–22, 24, 26–30, 32, 33] based on interviews or questionnaires (including 28227 children with history of SARS-CoV-2 infection) were retrieved and analysed. Data are difficult to compare due to the large inter-study variability in terms of study design, follow-up timing, and definitions of long COVID which results in different inclusion criteria. The final picture is a broad discrepancy in prevalence both for symptoms and long COVID overall. The considerable variability of prevalence and symptoms burden could indicate that studies are assessing different diseases, suggesting the urge for a harmonized case definition. Fatigue, headache, arthralgia, shortness of breath, and alteration of smell or taste appear to be the most common symptoms. According to the WHO definition, the impact on everyday functioning is crucial to define long COVID. Interestingly, most of the studies relied solely on the persistence of symptoms and only five studies reported a limitation in daily function imputable to long COVID [14, 17, 28, 29, 32]. It is important to underline that most of the studies were based on proxy-reported information while clinician-assessed data were scant. Adolescent age, pre-existing long-term pathological conditions, and allergic disease have been identified as potential risk factors for persistent symptoms after acute illness [17, 19–24, 26, 29, 32]. However, a critical appraisal is necessary to understand these findings, as an example, younger children are less likely to be able to consistently report symptoms of relevance and these could lead to an underestimation of symptom prevalence in this age class. Since most of the data are derived from online surveys, a recall bias and selection bias must be considered, as symptomatic people could be more prone to participate and the answers might not be accurate.

Interestingly, persisting symptoms were described also in children with previous mild or asymptomatic COVID-19 and no correlation between the severity of acute illness and long COVID has been noted [27, 31].

Furthermore, it is unclear whether persisting symptoms are related to viral infection itself or they express the effects of pandemic, lockdown, and school suspension on children. Lockdown and social limitation negatively impacted on children and adolescent mental health [43]. This fact may explain why no statistical difference between seropositive and seronegative populations has been found in neurocognitive, pain, and mood symptoms [44]. Two studies reported better quality of life in SARS-CoV-2 infected children than controls, and the lower sense of well-being in uninfected children could reflect the psychological implications of the pandemic [24, 32]. Given that a control group is mandatory to understand the results to the fullest.

When a control group was provided, patients with a history of SARS-CoV-2 infection were more prone to show higher prevalence of persistence of symptoms [19, 20, 24, 26, 32, 33, 37], except in one study based on a small sample [18] (Fig. 4). Notably, the prevalence of symptoms declined over time, with headache and sleep disorders declining slower, which could be driven by a psychological mechanism [21]. Since the outbreak of the SARS-CoV-2 pandemic, several variants of concern have been identified. It seems that omicron cases are less likely to experience long COVID compared with delta cases in adults [45]. Currently, data on children and youths are lacking.

The symptoms observed affect cardio-respiratory, gastrointestinal, and neurological systems, and rehabilitation and psychologist support are needed [28]. Therefore, a multidisciplinary approach appears necessary to sustain children and adolescents. NICE guidelines recommend investigation in people presenting with new or ongoing symptoms 4 weeks or later after acute COVID-19, and these include a full blood count, kidney and liver function tests, a C-reactive protein test, and an exercise tolerance test [3]. Currently, no structured follow-up has been set and reference centres for paediatric population are lacking [30].

The mechanisms underlying post COVID condition are not clearly defined; however, several pathogenesis models have been put forward. One of the most supported hypotheses is based on the persistence of the virus or a virus component [46]. Several studies have demonstrated a prolonged SARS-CoV-2 shedding in the respiratory tract, faeces, and intestinal biopsies, even in asymptomatic patients [47, 48]. This could lead to an exacerbated immune response resulting in increased levels of proinflammatory cytokines, including interleukin (IL)-6, IL-1β, and TNF [49, 50]. A persistent proinflammatory state could explain organ damage and prolonged symptoms, such as fatigue, headache, and smell impairment [46, 48]. Moreover, several types of autoantibodies are produced during SARS-CoV-2 infection due to a molecular mimicry mechanism between self-antigens and spike epitopes [51]. Autoantibodies against G-protein coupled receptors (GPCRs) have been associated with post COVID-19 condition. Since GPCRs can alter the neuronal and vascular process, the autoantibody production could explain some of the neurological and cardiovascular symptoms in patients with long COVID [48].
Limitations

Our review may have limitations, including that some articles might have been missed. Considering that the literature regarding long COVID is rapidly increasing, a continuous updating of evidence is mandatory. Methodological issues were frequent among the included studies: matched cohort studies were limited, rarely a comparison with other viral illness was provided, and most of the data were based on questionnaire-based studies. Symptoms prevalence mainly relies on self-reporting and online surveys; hence, recall and selection biases must be considered. Furthermore, most of the studies included in our review were published prior to the WHO post COVID-19 definition, resulting in a heterogeneous delineation of the condition among studies. Lastly, the exclusion of children with PIMS-TS, who typically complain more severe and persistent symptoms, could have an impact on the long COVID prevalence estimation.

Conclusion

Evidence on long COVID in children is limited, heterogeneous, and based on low-quality studies. Given that an accurate prevalence of the condition remains undefined, it is difficult to distinguish between functional complaints of post-acute COVID syndrome and social restriction effects.

Further high-quality studies are required to define the optimal management of this emergent condition and to establish which resources are needed to face long COVID syndrome and the overall lifelong negative effects of SARS-CoV-2 pandemic in children and adolescents. Since WHO provided a research definition of long COVID, its use should be promoted in future studies to harmonize data. Controlled clinical studies should be encouraged over questionnaire-based ones to ensure an objective analysis of the actual prevalence and long COVID characteristics in children. Moreover, the impact of new variants on long COVID prevalence needs to be investigated to ensure healthcare systems properly allocate their resources.

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