National Institute for Health and Care Excellence

COVID-19 rapid guideline: managing the long-term effects of COVID-19

[J] Evidence review for children and young people

NICE guideline NG188

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Guideline version (Final)

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COVID-19 rapid evidence review: Managing the long-term effects of COVID-19 for children and young people

November 2021

Literature search

The guideline on managing the long-term effects of COVID-19 is a living guideline. This means that weekly searches of newly published literature are undertaken for continuous evidence surveillance and stored in a database. Published studies, including pre-print and final published versions were screened using the inclusion and exclusion criteria in the relevant review protocols (see Appendix 1). One reviewer screened titles and abstracts, with a second reviewer checking 10% of entries. Having identified the evidence, 1 reviewer assessed the full text references of potentially relevant evidence to determine whether they met the inclusion criteria for this evidence review. All uncertainties were discussed and referred to an adviser if needed. See Appendix 4 for the study flow chart of included studies and Appendix 8 for the list of excluded studies, with reasons for exclusion.

Review question 1

What risk factors are associated with developing post-COVID-19 syndrome?

Children and young people are included as a subgroup in the protocols but we have included these subgroups in this separate evidence review to highlight the evidence in children and young people as requested by stakeholders at the scoping workshop.

The review protocol is shown in Appendix 2.

Included studies

There were 4 studies included in the review (1 prospective cohort study, 1 retrospective cohort study, 1 survey, and 1 systematic review). Details of these studies are described in Table 1.

Table 1: Included studies for review question 1

Study	Country, study design, dates	Population (n)	Study type	Risk of bias	Main results
Buonsenso 2021a	Worldwide but 68.8% lived in the UK and 18.4% in the USA. Survey. 1/1/20 to 31/1/21	Children who had long term effects (symptoms lasting ≥4 weeks) (n=510)	LongCOVIDKids online survey	High: retrospective, self-selection bias, 209/510 had suspected but not confirmed COVID	56% had ≥ pre-existing conditions, 16% had allergic diseases
Ludvigsson 2020	No country limits. Systematic review. 2/11/2020	Children with long-term effects of COVID-19 (n=0)	Systematic review.	Low	The investigators could find no relevant data on long COVID-19in children
Osmanov 2021	Russia. Prospective cohort study. 2/4/2020 to 26/8/2020	Children admitted to the hospital with RT-PCR confirmed COVID-19infection (n=518)	Survey by telephone with parents	High: the follow-up timepoints were not defined and the dropout rate was 39%	Children aged 6-18 years were more likely to get long COVID-19compared to children aged 2-5 years. Allergic diseases were also a predictor.
Stephenson 2021	UK. Cohort study. 1/9/20 to 31/3/21	Children aged 11-17 years who tested + for COVID-19on PHE's database (n=3065)	Questionnaire was sent out to participants at 3-months post-test	High: children were self-selected, and response rate was 13.3%. Could be some recall bias because the number of retrospective accounts is unknown	Those more likely to have more symptoms of post-COVID-19 syndrome tended to be female, older, have poorer baseline health.

Key results

The systematic review (Ludvigsson 2020) was undertaken in 2020, before the other studies in this review were published. Therefore, the investigators could find no relevant data. Two primary studies (Osmanov 2021, Stephenson 2021) suggest that older children are more likely to have symptoms of long-COVID-19 compared to younger children. One or more pre-existing condition, allergic diseases, eczema and asthma were reported to be risk factors for long term effects in 2 studies (Buonsenso 2021a, Osmanov 2021).

Table 2: Pre-existing conditions of children with long term effects of COVID-19

	Buonsenso 2021a	**Osmanov 2021**
≥1 pre-existing condition	56.30%	44.70%
Allergic diseases (any)	15.90%	23.50%
Asthma	14.50%	2.30%
Food Allergy	Not reported	13%
Eczema	12.40%	8.80%
Allergic Rhinitis	Not reported	8.90%
Hyper-mobility	10%	Not reported
Gastrointestinal problems	Not reported	9.30%
Neurological conditions	Not reported	8.80%
Neurological disorders	Not reported	8.40%
Anxiety	7.50%	Not reported
Headaches	7.10%	Not reported
OCD/Depression/Anxiety	7.10%	Not reported

Autism	5.70%	Not reported
ADHD/ADS	5.50%	Not reported
Excessive weight and obesity	Not reported	4.90%
Heart diseases	0.40%	4.10%
Renal/Kidney problems	Not reported	3.50%
Respiratory diseases (not including asthma)	Not reported	3.10%
Other endocrine illness (not diabetes)	Not reported	2.30%
Neurodisability	Not reported	2.10%

Subgroups

One study (Stephenson 2021) found that there were 2 subgroups of children with long term effects at 3 months as shown in Table 3. The first subgroup, class 1, had a very low prevalence of most symptoms. Class 2 children had multiple symptoms dominated by tiredness, headache, shortness of breath and dizziness. The probability of a child being in class 1 was 70% and the probability of being in class 2 was approximately 30%.

Those who were in class 2 were more likely to be female, older, to have poorer baseline physical and mental health and, at 3-months, to be more likely to have problems with mobility, self-care, usual activities and pain/discomfort. They also had higher Strengths and Difficulties Questionnaire (SDQ) total difficulties, Clinical Frailty Scale (CFS) scores, and lower Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWS) scores.

Table 3: Physical symptom clustering at 3 months

	Class 1 (%)	Class 2 (%)
Male	82.4	17.6
Female	65.9	34.1
11-15 years	75.3	24.7
16-17 years	67.7	32.3
Very poor/poor/OK previous physical health	62.8	37.2
Good/very good previous physical health	74.8	25.2
Very poor/poor/OK previous mental health	60.4	39.6
Good/very good previous mental health	79.2	20.8
EQ-5DY mobility	37.5	62.5
EQ-5DY self-care	40.3	59.7
EQ-5DY usual activities	40.3	59.7
EQ-5DY pain/discomfort	35.4	64.6
SDQ total difficulties, median (IQR)	9 (6, 14)	15 (10, 19)
Chalder fatigue scale, median (IQR)	11 (11, 14)	17 (13, 21)
SWEMBS, median (IQR)	21.5 (19.3, 25.0)	19.3 (17.4, 22.4)

Strengths and limitations

The limitations of this evidence are that there were few studies and they had a high risk of bias due to issues around participant selection and recall bias. The lack of control groups across the studies also prevented establishing a cause-effect link between COVID-19 and these symptoms.

The Buonsenso 2021a study was based on survey data which prevented measurement of the incidence of long-term effects in children, and not all children received a microbiologically confirmed diagnosis of COVID-19. However, the guideline scope includes patients regardless of whether or not they received a positive test. The small number of children requiring hospitalisation in this study did not allow the investigators to determine how initial severity affected long term effects in children.

The Osmanov 2021 study included patients from a single city and included only hospitalised children, not representative of the paediatric population. The parents/caregivers were interviewed in this study and not children themselves. There is also a risk of selection bias due to recruitment of the hospitalised population and recall bias in reporting symptoms which were non-existent at the time of the follow-up and potential selection bias with those with symptoms more likely to agree to survey.

The Stephenson 2021 study was limited by a self-selected sample with a low response rate and potential response bias for example, towards those continuing to experience symptoms at 3 months being more motivated to participate, resulting in an over-representation of symptom prevalence. It is also possible that recall bias influenced the reporting of symptoms at the time of testing as well as physical and mental health prior to testing, in particular, if tested positive.

The Ludvigsson 2020 systematic review was limited by its 2020 search date when no evidence was available on children and young people.

A modified GRADE approach was carried out to assess the certainty of the body of evidence. As all of the data from the studies were descriptive, a narrative approach to GRADE was undertaken. All outcomes were rated as very low certainty. This is due to the high risk of bias of most of the studies but also the inability to measure imprecision.

Expert panel discussion

For the expert panel discussion on overall risk factors for post COVID-19 syndrome, please see separate evidence review.

The expert panel considered the impact of the evidence on risk factors for post-COVID-19 syndrome in children and young people on current recommendations, but concluded that the evidence was of low certainty and would not impact the recommendations or inform any new recommendations.

Review questions 2 and 3

These 2 review questions have been analysed together as the average follow-up time is not reported for most studies, and so a combined overall summary is provided.

Review questions 2
What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 for a duration of 4 to 12 weeks?

Review questions 3
What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 beyond 12 weeks?

The review protocols are shown in Appendix 2.

Included studies

Eight studies were included in this review. Six studies measured individual signs and symptoms and were comprised of 1 cohort study (some data was prospective and other data was retrospective), 2 prospective cohort studies, 2 surveys, and 1 cross-sectional study. Details of these studies are described in Table 4. Two studies (1 prospective cohort study and 1 survey) measured broad categories of signs and symptoms and are therefore less detailed. Details of these studies are described in Table 5. One retrospective cohort study investigated the signs and symptoms of paediatric inflammatory multisystem syndrome (PIMS-TS), which has been associated with COVID-19 illness. This study is summarised in Table 8. One retrospective case-control study investigated the time course or incidence of new post-COVID-19 conditions after COVID-19 diagnosis, see Table 10.

Table 4: Included studies for review questions 2 and 3: individual signs and symptoms

These 6 studies measured each individual sign and symptoms.

Study	Country, study design, dates	Population (n)	Study type	Risk of bias	Main results (most common 5 symptoms)
Brackel 2021	The Netherlands. Survey. 18/12/2020 to 6/2/2021	All paediatricians in hospitals. Post-COVID-19 children had symptoms "months after initial COVID-19 infection" (n=89)	Survey on: manifestation, severity, and involvement of the multidisciplinary team	High: retrospective study and prone to recall bias. Hospitals so more severe disease	Loss of smell, fatigue, headache, short of breath, skipped meals
Buonsenso 2021a	Worldwide but 68.8% lived in the UK and 18.4% in the USA. Survey. 1/1/20 to 31/1/21	Children who had long COVID-19 (symptoms lasting ≥4 weeks) (n=510)	LongCOVIDKids online survey	High: retrospective, self-selection bias, 209/510 had suspected but not confirmed COVID-19	Tiredness and weakness/ hypersomnia, fatigue, headache, abdominal pain, muscle aches and pains
Buonsenso 2021b	Italy. Cross-sectional study. 1/3/2020 to 1/1/2021	Children ≤18 years diagnosed with COVID-19 using PCR analysis on nasopharyngeal swab (n=129)	Caregivers were interviewed by paediatricians either by phone or out-patient visit about their child's health using a questionnaire	High: retrospective study and therefore prone to recall bias. Outcomes were also prone to self-reporting bias.	Fatigue, headache, muscle aches and pains, lack of concentration/ delirium, skin rash/ red welts
Molteni 2021	UK. Prospective cohort study. 24/3/2020 to 22/2/2021	App collecting data from parents of children who tested positive (n=77)	Information was reported by parents	Moderate: parents were self-selected and may not represent all parents	Loss of smell, fatigue, headache, short of breath, skipped meals
Osmanov 2021	Russia. Prospective cohort study. 2/4/2020 to 26/8/2020	Children admitted to the hospital with RT-PCR confirmed COVID-19 infection (n=518)	Survey by telephone with parents	High: the follow-up timepoints were not defined and the dropout rate was 39%	Fatigue, headache, tiredness and weakness/ hypersomnia, diarrhoea, abdominal pain

Study	Country, study design, dates	Population (n)	Study type	Risk of bias	Main results (most common 5 symptoms)
Stephenson 2021	UK. Cohort study. 1/9/20 to 31/3/21	Children aged 11-17 years who tested + for COVID-19 on PHE's database (n=3065)	Questionnaire was sent out to participants at 3-months post-test	High: children were self-selected, and response rate was 13.3%. Could be recall bias from some	Tiredness and weakness/ hypersomnia, short of breath, headache, dizziness/ light headedness, loss of smell

Key results

The signs and symptoms of each study which children experienced are shown below. To capture the most common symptoms, we only include symptoms that >11% of children had in at least 1 study. The most common symptoms are towards the top:

Table 5: Signs and symptoms of long-term effects of COVID-19 in children

	Buonsenso 2021a	Brackel 2021	Molteni 2021	Stephenson 2021	Osmanov 2021	Buonsenso 2021b
Tiredness and weakness/ hypersomnia	87.1%	Not reported	Not reported	39%	2.99%	3.1%
Fatigue	80.4%	87%	44.16%	Not reported	10.69%	10.9%
Headache	78.6%	38%	28.57%	23.2%	3.5%	10.1%
Abdominal pain	75.9%	33%	15.58%	3.9%	2%	2.3%
Muscle aches and pains	68.4%	28%	12.99%	5.4%	0.82%	10.1%
Joint pains	60.6%	Not reported	Not reported	Not reported	1.22%	6.70%
Lack of concentration/ delirium	60.6%	45%	5.19%	6.50%	0.41%	10.10%
Short of breath	Not reported	55%	16.88%	23.40%	1.39%	6.20%
Post-exertional malaise	53.7%	Not reported	Not reported	Not reported	Not reported	Not reported

	Buonsenso 2021a	Brackel 2021	Molteni 2021	Stephenson 2021	Osmanov 2021	Buonsenso 2021b
Skin rash/ red welts	52.4%	7%	5.19%	1.60%	1.61%	6.90%
Irritability (unexplained)	51.4%	Not reported	Not reported	Not reported	Not reported	Not reported
Dizziness/ light headedness	48%	3%	12.99%	13.70%	1.03%	Not reported
Nausea	45.7%	Not reported	10.39	Not reported	1.2%	Not reported
Loss of smell	Not reported	1%	45.45%	13.50%	1.5%	Not reported
Sore throat	45.1%	Not reported	12.99%	9.50%	Not reported	Not reported
Diarrhoea and vomiting	42.4%	Not reported	3.9%	Not reported	Not reported	Not reported
Conjunctivitis/ sore eyes	40.4%	Not reported	11.69%	5.90%	0.4%	Not reported
Palpitations	40.2%	18%	Not reported	Not reported	1.06%	3.80%
Red and cracked lips	39.4%	Not reported	Not reported	Not reported	Not reported	Not reported
Chest pain	Not reported	35%	6.49%	7.10%	0.62%	3.10%
Short term memory loss	32.7%	13%	Not reported	Not reported	Not reported	Not reported
Fever	29.6%	2%	9.09%	1.60%	Not reported	Not reported
Persistent cough	29.6%	1%	6.49%	3.20%	0.99%	5.40%
Blisters on hands and feet	28%	Not reported	7.79%	Not reported	Not reported	Not reported
Swollen neck glands	25.1%	Not reported	Not reported	Not reported	Not reported	Not reported
Diarrhoea	Not reported	24%	Not reported	3%	2%	1.5%
Flu-like symptoms	23.7%	Not reported	Not reported	Not reported	Not reported	Not reported
Swollen hands and feet	21%	Not reported	Not reported	Not reported	Not reported	Not reported
Throat clearing	21%	Not reported	Not reported	Not reported	Not reported	Not reported

	Buonsenso 2021a	Brackel 2021	Molteni 2021	Stephenson 2021	Osmanov 2021	Buonsenso 2021b
Skipped meals	Not reported	Not reported	16.88%	9.7%	Not reported	Not reported
Ulcers	15.5%	Not reported	Not reported	Not reported	Not reported	Not reported
Chills	Not reported	Not reported	Not reported	8.8%	Not reported	Not reported

GRADE profiles for all studies reporting prevalence of symptoms are available in Appendix 7.

Strengths and limitations

The limitations of this evidence are that 5 out of 6 of these studies have a high risk of bias and the remaining study has a moderate risk of bias. Buonsenso 2021a and Brackel 2021 were surveys and had a high risk of bias because they were retrospective and therefore prone to selection bias. Half of the children in Buonsenso 2021a had suspected but not confirmed COVID-19. Brackel 2021 was prone to recall bias. Stephenson 2021, had a high risk of bias because the children were self-selected, the response rate was only 13.3%, and there could have been some recall bias. Osmanov 2021 had a high risk of bias because it had a dropout rate of 39% and the follow-up timepoints were not defined. Buonsenso 2021b had a high risk of bias because it was retrospective cross-sectional study and therefore it is prone to selection bias, recall bias, and self-reporting bias. Molteni 2021 had the lowest risk of bias of these 6 studies because it was a prospective cohort survey that used an app. It had a moderate risk of bias because parents were self-selected.

Most studies were limited by the risk of selection and recall bias, due to self-selection and self-reported outcomes.

The risk of recall bias arose in reporting symptoms which were non-existent at the time of the follow-up and selection bias arose with parents of children with symptoms more likely to agree to survey.

Some studies were limited by self-selected samples with low response rates (Stephenson 2021) and potential response bias for example, towards those

continuing to experience symptoms at 3 months being more motivated to participate, resulting in an over-representation of symptom prevalence.

A modified GRADE approach was carried out to assess the certainty of the body of evidence. As all of the data from the studies were descriptive, a narrative approach to GRADE was undertaken. All outcomes were rated as very low certainty. This is due to the high risk of bias of most of the studies but also the inability to measure imprecision. Some outcomes were additionally downgraded for inconsistency due to different study designs.

Table 6: Included studies for review questions 2 and 3: categories of signs and symptoms

These 2 studies measured broad categories of signs and symptoms.

Study	Country, study design, dates	Population (n)	Approach	Risk of bias	Main results (most common category)
Miller 2021	UK. Survey. 15/6/2020 to 16/3/2021	Children aged ≤17 years and reporting COVID-19 symptoms lasting ≥4 weeks. Must have had COVID-19 confirmed via positive swab result or tested positive for COVID-19 IgG (n=80)	Symptoms were coded into categories	High: parents were self-selected. Results were prone to self-reporting bias as well as recall bias because it was a retrospective study	Fatigue, fever, or pain
Sterky 2021	Sweden. Retrospective cohort study. 13/3/2020 to 31/8/2020	The presence of a nasopharyngeal sample RT-PCR positive for severe acute COVID-19 (n=55)	Structured telephone interviews with the children and/or their guardians ≥4 months after being admitted	High: this is a retrospective study and therefore prone to selection bias. The post-acute data was collected retrospectively and was prone to recall bias	Fatigue, fever, or pain

Key results

The categories of signs and symptoms of each study are shown below. The most common symptoms in Miller 2021 (the largest of the 2 studies) are towards the top.

Table 7: Broad categories of signs and symptoms

	Miller 2021	Sterky 2021
Fatigue, fever, or pain	27.50%	16.36%
Ear, nose, and throat (including reduced taste/smell)	22.50%	3.64%
Respiratory	21.20%	5.45%
Neurological (including cognitive impairment/'brain fog' and headache)	16.20%	5.45%
Dermatological	15%	Not reported
Gastrointestinal	13.80%	5.45%
Cardiovascular (including palpitations)	11.20%	1.81%
Psychiatric (including depression/dysphoria)	10%	5.45%
Muscular	8.80%	Not reported
Other	6.20%	Not reported

GRADE profiles for all studies reporting prevalence of symptoms are available in Appendix 7.

Strengths and limitations

Miller 2021 and Sterky 2021 were both retrospective studies and therefore prone to selection bias and recall bias. Miller 2021 involved parents who were self-selected and therefore may not represent children with long COVID-19 in the general population. Therefore, both studies had a high risk of bias. Both studies have a small number of participants (Miller 2021, n=80; Sterky 2021 n=55), which may lead to the results being imprecise. Furthermore, they measured signs and symptoms using broad categories, which has limited diagnostic usefulness because they lack details of specific signs and symptoms.

A modified GRADE approach was carried out to assess the certainty of the body of evidence. As all of the data from the studies were descriptive, a modified approach to GRADE was undertaken. For the modified GRADE approach, the 10 most common symptoms, with the range of percentages of children who experienced each symptom across the studies was reported. All outcomes were rated as very low certainty. This is due to the high risk of bias of most of the studies but also the inability to measure imprecision.

Table 8: Included studies for review questions 2 and 3

This study looked at the signs and symptoms of paediatric inflammatory multisystem syndrome (PIMS-TS).

Study	Country, study design, dates	Population (n)	Approach	Risk of bias	Main results (most common 2 signs or symptoms)
Penner 2021	UK. Retrospective cohort study. 4/4/2021 to 1/9/2020	Children ≤18 years, fulfilling the UK RCPCH diagnostic criteria for PIMS-TS (n=46)	Patients were prospectively reviewed by multiple specialties in a PIMS-TS multidisciplinary outpatient clinic.	Moderate: this was a retrospective study and therefore prone to selection bias	43.48% could walk less than 3rd centile, 36.13% had proximal myopathy or lower limb weakness, 34.78% had bilateral or unilateral dysmetria, 32.61% had abnormal eye movements or saccades

Key results

The table below shows the signs and symptoms of PIMS-TS at 6 weeks and 6 months. The most common symptoms are towards the top.

Table 9: signs and symptoms of PIMS-TS at 6 weeks and 6 months

	Signs and symptoms at 6 weeks	Signs and symptoms at 6 months
Could walk less than 3rd centile expected distance for their age and sex	43.48%	39.13%
Proximal myopathy or lower limb weakness	36.13%	17.39%
Bilateral or unilateral dysmetria	34.78%	26.09%

Abnormal eye movements or saccades	32.61%	15.21%
Abnormal posturing	19.57%	Not recorded
Difficulty in tandem walking	13.04%	Not recorded
Dysphonia	13.04%	Not recorded
Hyper-reflexia	10.87%	19.57%
Persistent gastrointestinal symptoms	Not recorded	13.04%

Strengths and limitations

The limitations of this study were that it was relatively small, and retrospective and therefore prone to selection bias. For example, the clinically guided investigations were retrospectively collected, which accounts for variations in follow-up data among participants. Its strength is in the length of follow up providing some insight into contrasting signs and symptoms at 6 weeks and 6 months.

Table 10: Included studies for review questions 2 and 3: new post-COVID-19 conditions or diseases

This study looked at new post-COVID-19 diseases in children who have had COVID-19 compared to children who did not have COVID-19.

Study	Country, study design, dates	Population (n)	Approach	Risk of bias	Main results (most common 2 signs or symptoms)
Chevinsky 2021	USA, Retrospective case-control	Children identified with or without COVID-19 using ICD-10 and discharge codes (n=2673)	Data from new ICD-10 codes appearing 1 to 4 months after COVID-19	High: during the COVID-19 pandemic, control cases are more likely to be severe as mild cases more likely to stay at home. ICD-10 codes are sometimes misclassified	Children with COVID-19 were not more likely to experience new post-COVID-19 diagnoses or conditions than children without COVID-19

Key results

Children with COVID-19 were not more likely to experience new post-COVID-19 diagnoses or conditions than children without COVID-19.

GRADE profiles for all studies reporting prevalence of symptoms are available in Appendix 7.

Strengths and limitations

The limitation of this study is that it had a high risk of bias: During the COVID-19 pandemic, for the control arm, children with mild conditions were more likely to stay at home and not come to the attention of the investigators. This is because the parents of the children were less likely to come out of self-isolation and risk catching COVID-19. As a consequence, the control cases would be expected to have more severe diseases than normal. This effect should not be seen for the post-COVID-19 arm because the participants had already had COVID-19. Therefore, the severity of new post-COVID diseases could have been underestimated.. Potential misclassification among case-patients and control-patients could have occurred because of the use of ICD-10-CM codes rather than laboratory data. For example, clinicians might have miss-coded some cases of COVID-19 as being influenza due to 'other unidentified influenza virus'.

Expert panel discussion

This section describes how the expert panel considered the evidence on review questions 2,3 and 4 in relation to the recommendations within the guidance. This section includes the expert testimony for review question 4 because no evidence was found for that review question.

Experts who provided expert testimony provided their opinions in the form of PowerPoint presentations and a question-and-answer session afterwards. The expert panel also had the included studies explained to them during a presentation. The expert panel then drafted recommendations after taking into consideration both expert testimony and study evidence.

Benefits and harms

The panel noted the evidence indicating that children sometimes have a lack of concentration, short term memory loss, and/or difficulty doing everyday tasks ≥4 weeks after acute COVID-19 illness. Expert witnesses and the panel agreed there was a lack of recognition among healthcare professionals and the public that children can be affected by ongoing symptomatic COVID-19 or post-COVID-19 syndrome. For example, worse achievement or absenteeism at school is sometimes erroneously attributed to other causes, leading to an under-referral of cases to dedicated clinics, multidisciplinary teams (MDTs) and multidisciplinary rehabilitation services.

The expert witness and panel overwhelmingly agreed that worse performance or absenteeism at education, work, or training was a “red flag” for both children and adults. For example, in the studies above, common symptoms of long-COVID-19 include tiredness, fatigue, and lack of concentration. The panel agreed that it was important to highlight this because worse achievement or absenteeism could be wrongfully attributed to other causes. The panel agreed to use the term “worse achievement” because this encompasses a range of attainments, such as academic, athletic, attention to detail or other abilities that are important to that person.

The panel also agreed to retain the list of common symptoms of ongoing symptomatic COVID-19 and post-COVID-19 syndrome, which is consistent with the evidence and encompasses the common symptoms for all age groups, however they did note that cardiac and respiratory symptoms were less common in children than adults and agreed that this should be noted in the common symptoms list.

Expert witness testimony advised that many children with new or ongoing symptoms after acute COVID-19 were experiencing anxiety caused by unnecessary investigations and referrals to different specialists. Therefore, the panel advised that the NICE guideline on shared decision making should be signposted to. The panel agreed there should not be a recommendation cautioning against unnecessary investigations or referrals because there was already under-referral to dedicated clinics or MDTs.

The panel suggested that a dedicated integrated multidisciplinary assessment service should investigate children with ongoing symptoms after acute COVID-19. This is to increase coordinated and rapid care. It is also to prevent referral to a series of different specialists and many unnecessary and/or repeated investigations, which can cause anxiety for people and their families. This was the advice from expert witness testimony for both children and adults.

Based on expert advice and in the panel’s opinion, it was considered helpful for GPs to be able to contact a dedicated paediatrician who is involved with a local dedicated clinic or MDT.

Certainty of the evidence

The evidence base for children and young people remains uncertain due to the small number of studies, the small size of them, and their risk of bias. Furthermore, there was heterogeneity across the studies in terms of how they selected participants who had symptoms of post-acute COVID-19. For example, some studies only included children with “long COVID-19” and others included all children who had COVID-19 and measured symptoms experienced after certain amount of time by that whole population overall. Most studies had a high risk of bias due to their retrospective design with the inherent risk of selection bias, and largely self-reported outcomes with an increased risk of recall bias.

Preferences and values

The panel were not aware of any systematically collected data on preferences and values of children, young people and their parents or carers but identified worse performance or absenteeism in education or training as being important to them. Therefore, the panel decided that advice and information should be given on who to contact if people are worried about new, ongoing or worsening symptoms, or if they are struggling to return to education or training.

The panel also noted the expert testimony advising that many children with new or ongoing symptoms after acute COVID-19 were experiencing anxiety caused by unnecessary investigations and referrals to different specialists. The panel inferred that after ruling out acute or life-threatening complications and alternative diagnoses, most children and their parents or carers would prefer to avoid unnecessary investigations and would prefer to be referred to a dedicated integrated multidisciplinary assessment service. The panel agreed that shared decision making should be used to decide whether they need a further assessment.

Resource and other considerations

Resource use was not assessed.

Other considerations

The panel agreed to retain the advice to consider using a screening questionnaire as part of the initial consultation to help capture the person’s symptoms, which applies to all age groups. It was considered important to emphasise that the purpose of the screening questionnaire is to facilitate discussion with the patient, and their family or carer, about their symptoms and the impact that the long-term effects of COVID-19

has on them, to help make a decision about whether referral to a dedicated clinic or MDT would be appropriate.

Review question 4

What investigations should be carried out to determine appropriate management or treatment of symptoms?

The review protocol is shown in Appendix 2.

Included studies

No studies were found for review question 4.

Expert panel discussion

Details of the expert testimony covering investigations is included in the expert panel discussion of the review questions 2 and 3 above.

Appendix 1 Methods used to develop the guidance

Please see the methods chapter for details on how this guideline was developed.

Appendix 2 Review protocols

Review question 1: What risk factors are associated with developing post-COVID-19 syndrome?

Criteria	**Notes**
Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) from the onset of acute COVID-19 illness.
Exposure	Any
Comparators	Not applicable
Outcomes	Risk factors or factors that are associated with post-COVID-19 syndrome (as defined by the study)
Settings	Any

Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes)
	• Health care workers

Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. Preferred: • Systematic reviews of cohort studies

	• Cohort studies (prospective or retrospective) • Cross-sectional studies
Countries	Any
Timepoints	Not applicable
Other exclusions	None

Review question 2: What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 for a duration of 4 to 12 weeks?

Criteria	**Notes**
Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) from 4 to 12 weeks after the onset of acute COVID-19 illness.
Interventions/service configuration/information and support [delete/amend as appropriate]	Not applicable
Comparators	Not applicable
Outcomes	Prevalence of symptoms or clusters of symptoms (ongoing physical and mental health) reported 4-12 weeks following onset of acute COVID-19 illness including, but not limited to: Signs and symptoms: • respiratory symptoms such as chronic cough, shortness of breath, cardiovascular symptoms and disease such as chest tightness,

	tachycardia, palpitations, protracted loss or change of smell and taste • mental health problems including but not limited to depression, anxiety and PTSD symptoms and cognitive difficulties • Neuropsychiatric or psychiatric symptoms • Neurological symptoms including weakness, numbness, continuing headaches, seizures, cognitive symptoms visual loss, autonomic symptoms, vestibular symptoms • Myalgia or joint pain • Evidence of end organ damage across a range of organs • gastrointestinal disturbance with diarrhoea • fatigue, weakness and sleeplessness • skin rashes • evidence of systemic inflammation Conditions • Autonomic conditions • Respiratory conditions such as lung inflammation and fibrosis • Cardiovascular conditions such as myocarditis and heart failure • liver and kidney dysfunction • clotting disorders and thrombosis • Lymphadenopathy • neurological disorders including neuropathy

Settings	Any

Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes)
	• Health care workers

Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. • Systematic reviews of observational studies • Prospective and retrospective observational studies • Descriptive studies; case series, case reports • Mixed method study designs
Countries	Any
Timepoints	Any
Other exclusions	None

Review question 3: What is the prevalence of symptoms or clusters of symptoms (physical and mental health) and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health), among people who have symptoms of COVID-19 beyond 12 weeks?

Criteria	**Notes**

Population	People experiencing symptoms or clusters of symptoms (ongoing physical and mental health) continuing after 12 weeks from the onset of acute COVID-19 illness
Interventions/service configuration/information and support [delete/amend as appropriate]	Not applicable
Comparators	Not applicable
Outcomes	Prevalence of symptoms or clusters of symptoms (ongoing physical and mental health) reported 12+ weeks following onset of acute COVID-19 illness including, but not limited to: Signs and symptoms: • respiratory symptoms such as chronic cough, shortness of breath, cardiovascular symptoms and disease such as chest tightness, tachycardia, palpitations, protracted loss or change of smell and taste • mental health problems including but not limited to depression, anxiety and PTSD symptoms and cognitive difficulties • Neuropsychiatric or psychiatric symptoms • Neurological symptoms including weakness, numbness, continuing headaches, seizures, cognitive symptoms visual loss, autonomic symptoms, vestibular symptoms • Myalgia or joint pain • Evidence of end organ damage across a range of organs • gastrointestinal disturbance with diarrhoea • fatigue, weakness and sleeplessness

	• skin rashes • evidence of systemic inflammation Conditions • Autonomic conditions • Respiratory conditions such as lung inflammation and fibrosis • Cardiovascular conditions such as myocarditis and heart failure • liver and kidney dysfunction • clotting disorders and thrombosis • Lymphadenopathy • neurological disorders including neuropathy
Settings	Any

Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes
	• Health care workers

Study types	Any

	The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. • Systematic reviews of observational studies • Prospective and retrospective observational studies • Descriptive studies; case series, case reports • Mixed method study designs
Countries	Any
Timepoints	Any
Other exclusions	None

Review question 4: What investigations should be carried out to determine appropriate management or treatment of symptoms?

Criteria	**Notes**
Population	Adults and children who are experiencing new or ongoing symptoms or clusters of symptoms (physical and mental health): • 4-12 weeks from onset of acute COVID-19 illness • 12 weeks from onset of acute COVID-19 illness
Diagnostics tests or assessments	Diagnostic tests or assessments appropriate for the presenting symptoms and the care setting that can be used to: • rule out or confirm other diagnoses • Understand end organ damage effects
Comparators	Any or no comparator
Outcomes	• Post COVID-19 syndrome (as defined by the study)

	• Other diagnoses • Dual diagnoses and other multimorbidities (e.g. post-COVID-19 syndrome plus another condition)
Settings	Any

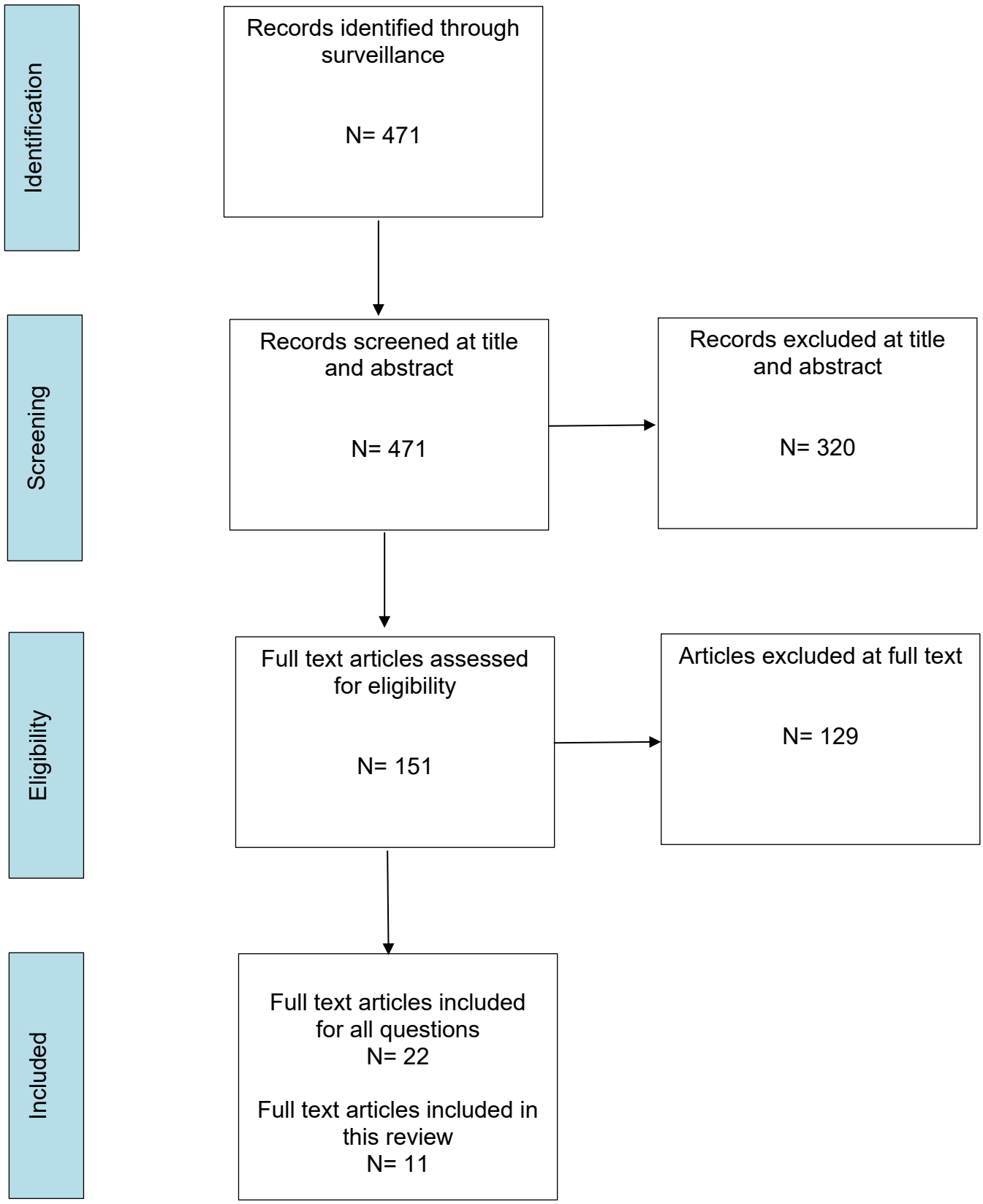
Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes)
	• Health care workers

Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. • Cohort studies • Case series • Cross sectional studies
Countries	Any
Timepoints	Any
Other exclusions	None

Appendix 3 Literature search strategy

Database strategies
Full details are available on request.

Appendix 4 Study flow diagram



Appendix 5 Included studies

Review question 1

Study
Buonsenso, D; Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children; Preprints; 2021
Ludvigsson, Jonas F; Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2020
Osmanov Ismail, M; Spiridonova, Ekaterina; Bobkova, Polina; Gamirova, Aysylu; Shikhaleva, Anastasia; et al; Team - Sechenov StopCOVID, Research; Risk factors for long COVID-19in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study; medrxiv preprint
Stephenson T, Pereira SP, Shafran R, De Stavola B, Rojas N, McOwat K, Simmons R, Zavala M; Long COVID the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study; Research Square pre-prints; 2021

Review questions 2 and 3

Study
Brackel, Caroline L H; Lap, Coen R; Buddingh, Emilie P; van Houten, Marlies A; van der Sande, Linda J T M; Langereis, Eveline J; Bannier, Michiel A G E; Pijnenburg, Marielle W H; Hashimoto, Simone; Terheggen-Lagro, Suzanne W J; Pediatric long-COVID: An overlooked phenomenon?.; Pediatric pulmonology; 2021
Buonsenso, D; Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children; Preprints; 2021
Buonsenso, Danilo; Munblit, Daniel; De Rose, Cristina; Sinatti, Dario; Ricchiuto, Antonia; Carfi, Angelo; Valentini, Piero; Preliminary Evidence on Long Covid in children.; Acta paediatrica (Oslo, Norway : 1992); 2021
Chevinsky, Jennifer R; Tao, Guoyu; Lavery, Amy M; Kukielka, Esther A; et al; Late conditions diagnosed 1-4 months following an initial COVID-19 encounter: a matched cohort study using inpatient and outpatient administrative data - United States, March 1-June 30, 2020.; Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 2021
Miller, Faith; Nguyen, Vincent; Navaratnam Annalan, MD; Shrotri, Madhumita; Kovar, Jana; Hayward Andrew, C; et al; Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales; medrxiv preprint
Molteni, Erika; Sudre, Carole; Helene; Canas, Liane; Santos; Bhopal Sunil, S; Hughes, Robert; C; Antonelli, Michela; S; et al; Illness duration and symptom profile in a large cohort of symptomatic UK school-aged children tested for SARS-CoV-2; medrxiv preprint
Osmanov Ismail, M; Spiridonova, Ekaterina; Bobkova, Polina; Gamirova, Aysylu; Shikhaleva, Anastasia; Andreeva, Margarita; et al; Team - Sechenov StopCOVID, Research; Risk factors for long COVID-19in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study; medrxiv preprint
Penner, Justin; Abdel-Mannan, Omar; Grant, Karlie; Maillard, Sue; Kucera, Filip; Hassell, Jane; Eyre, Michael; Berger, Zoe; Hacohen, Yael; Moshal, Karyn; GOSH PIMS-TS MDT, Group; 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study.; The Lancet. Child & adolescent health; 2021
Stephenson T, Pereira SP, Shafran R, De Stavola B, Rojas N, McOwat K, Simmons R, Zavala M; Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study; Research Square pre-prints; 2021

Sterky, Ellinor; Olsson-Akefeldt, Selma; Hertting, Olof; Herlenius, Eric; Alfven, Tobias; Ryd Rinder, Malin; Rhedin, Samuel; Hildenwall, Helena; Persistent symptoms in Swedish children after hospitalisation due to COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2021

Appendix 6 Evidence tables

All studies are in the same evidence table section because 3 studies that are included in review question 1 also appear in review questions 2 and 3 (Buonsenso 2021a, Osmanov 2021, and Stephenson 2021).

Review questions 1, 2, and 3

Brackel 2021 (in review questions 2 and 3)

Bibliographic Reference	Brackel, Caroline L H; Lap, Coen R; Buddingh, Emilie P; van Houten, Marlies A; van der Sande, Linda J T M; Langereis, Eveline J; Bannier, Michiel A G E; Pijnenburg, Marielle W H; Hashimoto, Simone; Terheggen-Lagro, Suzanne W J; Pediatric long-COVID: An overlooked phenomenon?.; Pediatric pulmonology; 2021

Study details

Study design	Survey With a small case series of 6 children.
Study start date	18-Dec-2020
Study end date	06-Feb-2021
Aim of the study	To determine how many children with long COVID-19 are referred by GPs to hospital specialists.
Country/ Geographical location	Netherlands
Study setting	Hospital and community.
Population description	They conducted a national survey asking paediatricians to share their experiences on long-COVID-19 in children. They furthermore described a case series of six children with long-COVID-19 to explore the clinical features in greater detail.
Inclusion criteria	Paediatricians work in secondary and tertiary care hospitals. The survey targeted all paediatricians. The survey and case series included children who had long COVID-19. The children in the case series were under the care of the Pediatric Department at the Emma Children's Hospital, Amsterdam University Medical Center, Tergooi Hospital, and the Catharina Hospital.
Exclusion criteria	None
Intervention/test/approach	The survey aimed to achieve a representative distribution of at least 70% of the 73 hospitals across the Netherlands with paediatric departments. All patient data were anonymised. The survey, consisting of five questions with sub-questions, focused on four key areas: (1) the occurrence of Paediatric Long-

	COVID, (2) the clinical manifestation, (3) the severity of disease and impact on daily activity, and (4) the wider multidisciplinary team involvement. Additional information, including patient age, the investigation used to diagnose COVID-19and whether hospital admission was required were also collected. The respondents were given a definition of long-COVID-19as well as a list of predominant symptoms in adults, and were able to consult their patient records to accurately describe relevant patient cases. It was defined as cases, similar to those in adults, where symptoms such as persistent tiredness, headaches, dyspnea, concentration problems, depression, skin lesions, and gastro-intestinal complaints persisted months after initial COVID-19 infection. They were also able to fill in “other complaints.” Survey responses were excluded from the study if data regarding the number of patients, mode of diagnosis, disease course, and hospital admission were incomplete.
Comparator (where applicable)	None
Methods for population selection/allocation	In the Netherlands, when a child is sick, unless their condition is acutely life-threatening, they are seen by their family doctor. Here, the decision is made if a referral to a paediatrician is necessary since the symptoms or consequences are sufficiently serious, or the presentation not fully understood. Paediatricians work in secondary and tertiary care hospitals. The survey targeted all paediatricians. **Survey** A total number of 89 children suspected of long-COVID-19 were described with a median age of 13 years (IQR: 9–15). Of these 89, 47 (52.8%) of the reported children had a positive PCR test, 31 (34.8%) positive serology tests, and 34 (38.2%) could be diagnosed clinically. It is important to note that there is a certain overlap in these groups, a number of patients were reported to have both positive PCR and serology, and/or medical history fitting a previous COVID-19 infection. In eight (9.0%) children it was unknown how COVID-19 had been diagnosed. **Case series** This illustrative case series consists of six children (four males), referred by general practitioners to paediatricians. All patients fulfilled the described criteria for long-COVID-19in adults, with symptoms still present 12 weeks after the acute phase, a positive diagnosis of COVID-19 (either by laboratory testing or positive family history, combined with complaints fitting COVID-19).
Methods of data analysis	This was a survey and a small case series. The results of the survey were presented as percentages.
Attrition/loss to follow-up	None
Source of funding	Not provided

Results	**The survey** Their study shows that long-COVID-19 is also present in children and that the main symptoms resemble those previously described in adults. The most common long-term complaint was fatigue (87%), followed by dyspnea in more than half of the children. Many patients reported some degree of cognitive dysfunction, with 45% reporting concentrating difficulties, 13% reporting memory loss, and a further 2% describing brain fog. A further 38% suffered from headaches. Only two children presented with persistent fever, and only one had a loss of smell and taste. It is important to note that 18% of all children were admitted to the hospital due to their long-COVID-19 disease presentation, of which the exact reasons were unknown to the investigators. At the time of Long-COVID-19 diagnosis, 48% reported mild limitations (e.g., can go to school but excessively tired), with 36% experiencing severe limitations demonstrated by limited or no school attendance, while only 8% of the reported patients had no disruption to their life due to their symptoms. 29% patients required active input from the wider multidisciplinary team: 25% required physical therapy, and 16% were seen by a psychologist. Three patients required a referral to a paediatric cardiologist for unspecified reasons. One patient had kidney failure and was subsequently seen by a pediatric nephrologist. It is unclear if there is a causal link with the diagnosis of long-COVID. **Table of signs and symptoms, most common at the top, N=89, survey, median age 13 years, reported "months after initial COVID-19 infection"**

Sign/symptom	Percentage who experienced it
Fatigue	87%
Short of breath	55%
Lack of concentration/ delirium	45%
Headache	38%
Chest pain	35%
Abdominal pain	33%
Muscle aches and pains	28%
Diarrhoea	24%
Palpitations	18%
Short term memory loss	13%
Skin rash/ red welts	7%

	<table><tr><td>Dizziness/ light headedness</td><td>3%</td></tr><tr><td>Fever</td><td>2%</td></tr><tr><td>Brain fog</td><td>2%</td></tr><tr><td>Weight loss</td><td>2%</td></tr><tr><td>Loss of smell</td><td>1%</td></tr><tr><td>Persistent cough</td><td>1%</td></tr><tr><td>Myocarditis</td><td>1%</td></tr></table> **Case series** Shortness of breath was the most common symptom reported by all patients during the acute COVID-19 illness. Three patients (patients 1, 2, and 5) were initially treated for a suspected asthma exacerbation with little effect seen in patients 2 and 5. Patient 1 had a history of asthma and reported an acute worsening of his pre-existing asthma symptoms, in addition to other complaints, after the acute viral infection, experienced in March 2020. He benefited from short acting beta-agonists but still experienced many complaints. Patient 4 was treated unsuccessfully with a course of azithromycin following continued complaints and persisting fever, three months after acute COVID-19. Patients 3, 5, and 6 are still experiencing extreme fatigue, resulting in school absence. Patients 3 and 6 are treated by a specialist in paediatric rehabilitation, while patients 2 and 5 are treated by a physical therapist. Patient 6 was living independently before COVID-19 diagnosis, but had to move back in with her parents due to her long-lasting symptoms.
Study limitations (Author)	They only collected data from paediatricians working in general and university hospitals, and not from family doctors. They expect that the more severe cases of long-COVID-19will be referred to the paediatrician and that milder cases may be underrepresented in their study. The type of symptom may also prompt referral, which could be a reason for the high percentage of patients suffering from fatigue and breathlessness. Second, due to privacy considerations, limited clinical data was collected in the questionnaire. Therefore, data on comorbidities, pre-existing disease, height, weight, psychological status, and diagnostic workup are missing. Third, only retrospective data were obtained from paediatricians. While they were able to consult their records, this may still have led to a recall bias, and thus an underestimation of total cases, and potentially an overrepresentation of severe cases.
Study limitations (Reviewer)	Nothing further to add.

Study arms

Children who had long COVID-19 (N = 89)
Survey

Children who had long COVID-19 (N = 6)
Case series

Characteristics
Study-level characteristics

Characteristic	Study (N = 89)
Age (years) median Nominal	13 (IQR 9-15)

Brackel, 2021

Bibliographic Reference	Brackel, Caroline L H; Lap, Coen R; Buddingh, Emilie P; van Houten, Marlies A; van der Sande, Linda J T M; Langereis, Eveline J; Bannier, Michiel A G E; Pijnenburg, Marielle W H; Hashimoto, Simone; Terheggen-Lagro, Suzanne W J; Pediatric long-COVID: An overlooked phenomenon?.; Pediatric pulmonology; 2021

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Not applicable
Assessment questions	Were the outcomes measured in a valid and reliable way?	No *(Retrospective study therefore the results are prone to recall bias and the more severe cases were more likely to be remembered.)*
Assessment questions	Was appropriate statistical analysis used?	Yes

Section	Question	Answer
Overall bias and directness	Risk of bias judgment	High *(Retrospective study and prone to recall bias.)*
Overall bias and directness	Directness	Directly applicable *(However, this study covers the more severe cases of COVID-19 that were referred to hospital. It does not cover cases only managed by GPs.)*

Buonsenso 2021a (in review questions 1, 2 and 3)

Bibliographic Reference	Buonsenso, D; Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children; Preprints; 2021

Study details

Study design	Survey
Study start date	01-Jan-2020
Study end date	31-Jan-2021
Aim of the study	To further understand the burden of long COVID-19 in children.
Country/ Geographical location	LongCOVIDKids developed an online platform where parents from all over the world can access and anonymously report their child's experience. 351 (68.8%) of them lived in the UK and 94 (18.4%) in the USA.
Study setting	Any.
Population description	Children who had long COVID-19.
Inclusion criteria	Children who had long COVID-19.
Exclusion criteria	None
Intervention/test/approach	In order to assess the presence of persisting symptoms in children with previous COVID-19, the parents non-profit association LongCOVIDKids developed an online platform where parents from all over the world can access and anonymously report their child's experience. The 'Long COVID Kids Rapid Survey 2' was designed as a follow-up to a pilot survey (that established quantity and type of symptoms) as a means to establish clusters of symptoms rather than the full breadth of symptoms as well as the effects on the mental and physical health of the child as a result of Long COVID-19. Certain symptoms were deliberately excluded as they were not considered relevant to the clusters under consideration. Links to the survey site on JotForm were disseminated on the closed Facebook group LongCOVIDKids. Parents' consent was required before

	answering questions on their children with COVID-19 persistent symptoms. In the 'Long COVID Kids Rapid Survey 2', participants were asked to self-declare the following main information on their children: how COVID-19 was confirmed and details at infection, including need of hospitalisation, age, sex and ethnicity; month of initial infection; course of symptoms, if any, from initial infection; activity before after infection; mental health status and comorbidities before COVID-19; displayed symptoms since COVID-19; behavioural/activity/habits changes after COVID-19; need of medical care after COVID-19; parents' perspectives of need of medical care for their children and type of care; parents' perspective on child's need of support to be readmitted at school after COVID-19. The full version of the survey is available at: https://form.jotform.com/210431051528039?fbclid=IwAR3uYxbqOAFcOO8o73Dhc5kolP8aaTx0wY_ba7MvIQ83UxHEy6eBLpH720 For the purpose of this study, they used data from the 'Long COVID Kids Rapid Survey 2' collected between 13 February 2021 and 06 March 2021. Only those children with symptoms lasting longer than 4 weeks were included.
Comparator (where applicable)	None
Methods of data analysis	The Confirmation status of COVID-19 infection was asked about as "Has your child had confirmed or suspected COVID-19 infection?". The possible answers to that question were: "Clinical Diagnosis", "Lateral Flow", "Positive PCR Swab", and "Unconfirmed by a test or medical professional but we think we had it." We will initially report the counts for the original possible answers, and then in tables we will use a simplified version by merging "Positive PCR Swab" and "Lateral Flow" as "Positive Test". Time from infection was estimated (with a 15-day uncertainty) by subtracting the 15th day of the reported month of (confirmed or suspected) infection from the date of response to the survey. Children with an estimated time from infection below 1.5 months were excluded to ensure that all included children had had symptoms for longer than 4 weeks. In practice this implied excluding all children infected on February 2021 and those infected on January 2021 and reported on February 2021. They produced summary tables and graphs aiming at the description of the study sample, the symptoms and changes in Long-COVID-19 children, looking further at changes in their physical activity levels and mental health. They cross-tabulated variables by confirmation status of COVID-19 infection and by the pre-existence of comorbidities.
Attrition/loss to follow-up	None
Source of funding	The authors stated that there was no funding.
Results	Data on 510 children who had had COVID-19 for more than 4 weeks were reported by their parents. 351 (68.8%) of them live in the UK and 94

(18.4%) in the USA. They got COVID-19 between January 2020 and January 2021 at a mean age of 10.3 years (standard deviation 3.8). 287 (56.3%) were female. For 297 (58.2%) children COVID-19 has been confirmed by a positive PCR test (N=141), a positive (antibody) lateral flow test (N= 4) or clinical diagnosis (N=156). For 209 (41%) children, COVID-19 was suspected but has not been confirmed by a test or medical professional; most of those children are from UK and were infected around March 2020, at a time when access to tests, particularly for non-severe cases, was difficult in most countries.

At their initial COVID-19 infection, only 22 (4.3%) children were hospitalised; 62 (12.2%) were asymptomatic, 378 (74.1%) were managed at home, and 48 (9.4%) went to hospital but were not admitted. 223 (43.7%) children had no pre-existing condition. 411 (80.6%) children had no pre-COVID mental health concern or diagnosis.

Pre-existing conditions of children with long-COVID, N=510, survey, mean age 10.3 years, reported at a mean of 8.2 months (SD 3.9)

Condition	Percentage of children who had it
≥1 pre-existing condition	56.3%
Allergic diseases (any)	15.9%
Asthma	14.5%
Eczema	12.4%
Hyper-mobility	10%
Anxiety	7.5%
Headaches	7.1%
OCD/Depression/Anxiety	7.1%
Autism	5.7%
ADHD/ADS	5.5%
Epilepsy	1.8%
Coeliac	1.6%
Dyspraxia	1.2%
Ehlers-Danlos syndrome	1.2%
Epstein Bar	1.2%
POT's	1.2%
Hypertonia	1%
IBS	0.8%
Sensory Processing Disorder	0.8%
Down's syndrome	0.6%
Lyme Disease	0.6%

TICS/Tourettes	0.6%
Abdominal migraines	0.4%
Cerebral palsy	0.4%
Gluten sensitivity	0.4%
Hayfever	0.4%
Heart murmur	0.4%
HPV Virus	0.4%
HSV virus	0.4%
Pandas	0.4%
Stomach pain	0.4%
Urticaria	0.4%
Heart diseases	0.4%

Persistence of symptoms in children since COVID-19

Overall, children had persisting COVID-19 for a mean of 8.2 months (standard deviation 3.9). Most frequent symptoms were: Tiredness and weakness (444 patients, 87.1% of sample), Fatigue (410, 80.4%), Headache (401, 78.6%), Tummy pain or cramps (387, 75.9%), Muscle aches and pains (349, 68.4%), Muscle and joint pain (309, 60.6%), Post-exertional malaise (274, 53.7%), A rash (267, 52.4%), Unexplained irritability (262, 51.4%), and Dizziness (245, 48%). 484 (94.9%) children had at least four symptoms. 129 (25.3%) children have suffered constant COVID-19 infection symptoms, 252 (49.4%) have had periods of apparent recovery and then symptoms returning, and 97 (19%) had a prolonged period of wellness followed by symptoms. Among those who had no pre-COVID-19 condition it was slightly less frequent to have constant COVID-19 (23.8% versus 26.5%) or alternating recovery/symptom episodes (48.4% versus 50.2%).

Signs and symptoms, most common at the top, N=510, survey, mean age 10.3 years, reported at a mean of 8.2 months (SD 3.9)

Sign/symptom	**Percentage who experienced it**
Tiredness and weakness/ hypersomnia	87.1%
Fatigue	80.4%
Headache	78.6%
Abdominal pain	75.9%
Muscle aches and pains	68.4%
Joint pains	60.6%
Lack of concentration/ delirium	60.6%
Post-exertional malaise	53.7%
Skin rash/ red welts	52.4%
Irritability (unexplained)	51.4%

Dizziness/ light headedness	48%
Nausea	45.7%
Sore throat	45.1%
Diarrhoea and vomiting	42.4%
Conjunctivitis/ sore eyes	40.4%
Palpitations	40.2%
Red and cracked lips	39.4%
Short term memory loss	32.7%
Fever	29.6%
Persistent cough	29.6%
Blisters on hands and feet	28%
Swollen neck glands	25.1%
Flu-like symptoms	23.7%
Swollen hands and feet	21%
Throat clearing	21%
Ulcers	15.5%
Tremor/ twitching	10.8%
Word repetition	10.2%
Tics	9.2%
Stuttering	7.8%
Swearing	5.1%
Growling	4.7%
Appendicitis	1.4%
Sepsis	1.4%
Peritonitis	0.2%

Changes in children since COVID-19 infection

Long-COVID-19 children have suffered complex changes since COVID-19 infection. The most frequently reported changes were in (direction of change was not provided): Energy levels (425 patients, 83.3% of sample), Mood (300, 58.8%), Sleep (287, 56.3%), and Appetite (253, 49.6%). The latter changes were significant on children with confirmed/unconfirmed COVID-19 and occurred similarly on those with or without pre-existing conditions. Overall, all children have had at least 1 change and 325 (63.7%) children have had at least 4 changes since their COVID-19 infection. The proportion of those with at least 4 changes is above 60% independently of whether they had had pre-COVID-19 conditions.

Changes in Physical Activity Levels

Most children were physically active before their COVID-19 infection. During the first 6 weeks after infection, 262 (51.4%) children did participate in some level of activity, 217 (42.5%) did not, and for 31 (6.1%) children their parents were unsure. Families reported that their children activity levels were worse than before infection. Only 51 (10%) children have returned to previous levels of activity. 108 (21.2%) are currently unable to

	enjoy any activity, and 154 (30.2%) enjoy occasional activity but usually have an increase of symptoms after. Overall, the more physically active they were before COVID-19, the higher the proportion of them who returned to previous activity levels, although these rates are very low: only 17 (11.8%) of those who practiced daily sports before COVID-19 returned to previous levels. **Changes in Mental Health** Parents reported a significant prevalence of Neuropsychiatric symptoms among their children with persisting symptoms. In more detail, several parents reported Lack of concentration (309 children, 60.6% of sample), Difficulty remembering information (234, 45.9%), Difficulty in doing everyday tasks (204, 40%), Difficulty processing information (167, 32.7%), and Short term memory issues (167, 32.7%). 279 (54.7%) children have had at least 3 mental health issues (excluding “None of the above” and “Other”), 45 (8.8%) children have had 2 issues, 54 (10.6%) children have had 1 issue, and 132 (25.9%) children have had no issues (excluding “None of the above” and “Other”). Only 64 (28.7%) of those with no pre-COVID-19 conditions haven’t had any mental health/cognitive issues since their COVID-19 infection.
Study limitations (Author)	This study has several limitations to address. First, it is an online survey that was only shared through an online platform and not systematically proposed to consecutively diagnosed children within specific settings, therefore determining a selection bias. Also, this survey has been launched on the page of Long COVID Kids UK, which was created with the purpose to provide awareness and support to families with children with long COVID-19. Therefore, parents of children with persisting symptoms may have had more interest in participating in this survey, and this can explain the large number of children with persisting symptoms in this cohort, when compared with other cohorts. Therefore, they were not able to define the incidence of Long COVID-19 in children. Another limitation is that not all children received a microbiologically confirmed diagnosis. This is mainly due to unpreparedness of health systems and difficulties in access to test, particularly during the first months of the pandemic, and because of different decision-rules practices in different settings. Also, the small number of children requiring hospitalisation did not allow the investigators to determine how initial severity affected long COVID-19 in children. Last, the lack of a control group cannot allow the investigators to determine a cause-effect link between COVID-19 and these symptoms.
Study limitations (Reviewer)	Nothing further to add.

Study arms
Children who had long COVID-19 (N = 510)

Characteristics
Study-level characteristics

Characteristic	Study (N = 510)
Age (years) mean Mean (SD)	10.3 (3.8)
Gender (%) Female Nominal	56.3

Buonsenso, 2021

Bibliographic Reference	Buonsenso, D; Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children; Preprints; 2021

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Not applicable
Assessment questions	Were strategies to deal with confounding factors stated?	Not applicable
Assessment questions	Were the outcomes measured in a valid and reliable way?	No *(Retrospective survey therefore prone to recall bias. Parents of children who had persisting long COVID-19 were more likely to seek the website out and use it.)*
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	High *(Issues with recall bias and self-selection of parents.)*

Section	Question	Answer
Overall bias and directness	Directness	Directly applicable

Buonsenso 2021b (in review questions 2 and 3)

Bibliographic Reference	Buonsenso, Danilo; Munblit, Daniel; De Rose, Cristina; Sinatti, Dario; Ricchiuto, Antonia; Carfi, Angelo; Valentini, Piero; Preliminary Evidence on Long Covid in children.; Acta paediatrica (Oslo, Norway : 1992); 2021

Study details

Study design	Cross-sectional study
Study start date	01-Mar-2020
Study end date	01-Jan-2021
Aim of the study	To assess persistent symptoms in paediatric patients previously diagnosed with COVID-19.
Country/ Geographical location	Italy
Study setting	Community
Population description	Children previously diagnosed with COVID-19.
Inclusion criteria	All children ≤18 year old diagnosed with microbiologically confirmed (PCR analysis on nasopharyngeal swab) COVID-19 (through a nasopharyngeal swab from March 2020 to October 2020) in Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy). Only children with a SARS-CoV-2 infection diagnosed for more than 30 days were included.
Exclusion criteria	Patients >18 years old or with severe neurocognitive disability were excluded, since this would have not allowed a proper assessment of signs and symptoms included in the survey.
Intervention/test/approach	Caregivers were interviewed about their child's health using a questionnaire developed by the Long COVID-19 ISARIC study group, for evaluation of persisting symptoms. Participants were interviewed by two paediatricians, either by phone or in the outpatient department, from 1 September 2020 to 1 January 2021. For those assessed in the outpatient settings, the same survey was used and symptoms reported were collected even if not present at the moment of the visit (e.g. tachycardia). Also, investigations were not performed at the moment of the assessment, in order to rule-out other causes, although the survey has a section to ask whether other possible causes have been detected in the meantime.
Comparator (where applicable)	None

Methods for population selection/allocation	Participants were categorised into groups according to symptoms status during the acute phase (symptomatic/asymptomatic), need for hospitalisation and time from COVID-19 diagnosis to follow-up evaluation (<60, 60–120,>120 days). Numerical variables were compared using t test or ANOVA and categorical variables with chi-square or Fisher's exact test where appropriate. All analyses were performed using R version 4.0.3 (R Foundation).
Methods of data analysis	Numerical variables were compared using t test or ANOVA and categorical variables with chi-square or Fisher's exact test where appropriate. All analyses were performed using R version 4.0.3 (R Foundation).
Attrition/loss to follow-up	None
Source of funding	Not mentioned.
Results	One hundred and twenty-nine children diagnosed with COVID-19 between March and November 2020 were enrolled (mean age of 11 ± 4.4 years, 62 (48.1%) female). Six children with severe neurocognitive impairment were excluded due to impossibility to report signs/symptoms included in the survey. Hundred and nine children (84.5%) were interviewed by phone call, and the remaining during outpatient assessment. During the acute COVID-19, 33 children (25.6%) were asymptomatic, and 96 (74.4%) had symptoms. Overall, 6 (4.7%) children were hospitalised, and 3 (2.3%) needed paediatric intensive care unit admission. After the initial diagnosis of COVID-19, three developed multisystem inflammatory syndrome (2.3%) and two myocarditis (1.6%). Patients were assessed on average 162.5 ± 113.7 days after COVID-19 microbiological diagnosis. 41.8% completely recovered, 35.7% had one or two symptoms and 22.5% had three or more. Insomnia (18.6%), respiratory symptoms (including pain and chest tightness) (14.7%), nasal congestion (12.4%), fatigue (10.8%), muscle (10.1%) and joint pain (6.9%), and concentration difficulties (10.1%) were the most frequently reported symptoms. These symptoms, described both in children with symptomatic and asymptomatic acute COVID-19, were particularly frequent in those assessed >60 days after the initial diagnosis. Twenty out of 30 children (66.6%) assessed between 60 and 120 days after initial COVID-19 had at least one persisting symptom (13 had one or two symptoms, seven had three or more); 35 of 68 children (27.1%) had at least one symptom 120 days or more after diagnosis (21 had one or two symptoms, 14 had three or more). Twenty-nine out of the 68 (42.6%) children assessed ≥120 days from diagnosis were still distressed by these symptoms.

	Signs and symptoms, most common at the top, N=129, cross-sectional study, mean age 11 years, reported at a mean of 162.5 days (SD 113.7) **Sign/symptom** / **Percentage who experienced it** Insomnia / 18.6% Nasal congestion/rhinorrhoea / 12.4% Fatigue / 10.9% Headache / 10.1% Muscle aches and pains / 10.1% Lack of concentration/ delirium / 10.1% Weight loss / 7.7% Skin rash/ red welts / 6.9% Joint pains / 6.7% Constipation / 6.2% Short of breath / 6.2% Persistent cough / 5.4% Disturbed smell / 4.6% Palpitations / 3.8% Disturbed taste / 3.1% Chest pain / 3.1% Tiredness and weakness/ hypersomnia / 3.1% Abdominal pain / 2.3% Changes in menstruation / 1.5% Diarrhoea / 1.5%
Study limitations (Author)	Limitations of the study include the single-centre design with a relatively small sample size. All patients were interviewed once at a mean of 162.5 days (SD 113.7) which is a considerable variation, and a control group of children without COVID-19 was not included.
Study limitations (Reviewer)	This is a retrospective study and is therefore prone to recall bias. For example, it is possible that some participants were reflecting on symptoms that they experienced over 100 days ago. The study is also prone to self-reporting bias. For example, some participants might not wish to discuss some symptoms due to various reasons, such as embarrassment.

Study arms
Children with COVID-19 (N = 129)

Characteristics
Study-level characteristics

Characteristic	Study (N = 129)
Age (years) mean age Mean (SD)	11 (4.4)
Gender (%) Female Nominal	48.1

Buonsenso, 2021

Bibliographic Reference	Buonsenso, Danilo; Munblit, Daniel; De Rose, Cristina; Sinatti, Dario; Ricchiuto, Antonia; Carfi, Angelo; Valentini, Piero; Preliminary Evidence on Long Covid in children.; Acta paediatrica (Oslo, Norway : 1992); 2021

Critical appraisal - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Yes
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Not applicable
Assessment questions	Were strategies to deal with confounding factors stated?	Not applicable
Assessment questions	Were the outcomes measured in a valid and reliable way?	No *(Retrospective study and therefore prone to recall bias. Outcomes were also prone to self-reporting bias.)*
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	High *(There are some concerns with the*

Section	Question	Answer
		way data was collected.)
Overall bias and directness	Directness	Directly applicable

Chevinsky 2021 (in review questions 2 and 3)

Bibliographic Reference	Chevinsky, Jennifer R; Tao, Guoyu; Lavery, Amy M; Kukielka, Esther A; Click, Eleanor S; Malec, Donald; Kompaniyets, Lyudmyla; Bruce, Beau B; Yusuf, Hussain; Goodman, Alyson B; Dixon, Meredith G; Nakao, Jolene H; Datta, S Deblina; Mac Kenzie, William R; Kadri, Sameer; Saydah, Sharon; Giovanni, Jennifer E; Gundlapalli, Adi V; Late conditions diagnosed 1-4 months following an initial COVID-19 encounter: a matched cohort study using inpatient and outpatient administrative data - United States, March 1-June 30, 2020.; Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 2021

Study details

Study design	Case–control studies
Trial registration (if reported)	**Not reported**
Study start date	01-Mar-2020
Study end date	30-Jun-2020
Aim of the study	To investigate the time course or incidence of late new COVID-19–related health conditions (post-COVID-19 conditions) after COVID-19 diagnosis.
Country/ Geographical location	USA
Study setting	Community: ex-hospital inpatients and outpatients.
Population description	Children and adults who had COVID-19.
Inclusion criteria	Case-patients were identified from the Premier Healthcare Database Special COVID-19 Release (PHD-SR; release date, 20 October 2020), an administrative all-payer database, which includes inpatient data from 922 hospitals and outpatient data from 934 hospitals, including 269 clinics with representation in all US Census regions, using standard International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), discharge codes of U07.1 (COVID-19, virus identified) during April–June 2020 or B97.29 (Other coronavirus as the cause of disease classified elsewhere [recommended before the April 2020 release of U07.1]) during March–April 2020. An index encounter was defined as the initial COVID-19 encounter (for case-patients)

	or a patient's matched encounter (for control-patients) during 1 March–30 June 2020. Index encounter date was defined as the hospital discharge date for an inpatient encounter or encounter date for an outpatient encounter. The discharge date was used as a reference point for inpatient encounters for 2 primary reasons: (1) discharge date is commonly used as a reference point to assess for complications after a hospitalisation and therefore could be a clinically useful point of reference and (2) this approach could limit the inclusion of acute symptoms and conditions in the findings by establishing a baseline for all inpatients after the hospitalisation.
Exclusion criteria	Prior to matching, they excluded patients without at least 1 encounter preceding their index encounter in PHD-SR, who died during their index encounter, or who were pregnant at their index encounter. Potential control-patients who were diagnosed with COVID-19 during the 4 months after their index encounter were also excluded prior to matching.
Intervention/test/approach	ICD-10-CM codes recorded during encounters were classified to Clinical Classification Software Refined (CCSR) categories, which aggregates ICD-10-CM codes into clinically meaningful categories to form disease groupings. Diagnoses from encounters before (using the historical data from January 2019 to the index encounter date) and during the index encounter were classified as underlying or acute COVID-19 conditions. New persistent conditions (those newly starting during the index encounter and persisting after the index encounter) and exacerbations of underlying conditions (those starting prior to the index encounter and worsening during or after the index encounter) were not assessed in this analysis because of challenges differentiating underlying conditions, acute conditions, and exacerbations in inpatient administrative data. Late conditions were defined as conditions not previously recorded as underlying or acute COVID-19 conditions during January 2019 through the index encounter date that occurred during 31–120 days (1–4 months) after the index encounter. Five CCSR categories were excluded from the late-conditions analysis: pregnancy, perinatal, congenital malformations, external causes of morbidity, and factors influencing contact with health services (e.g., encounter for administrative purposes). Late conditions were identified using CCSR categories based on timing of occurrence after the index encounter date: 31–60 days, 61–90 days, and 91–120 days. The timeline was established using a variable that determined the days between each visit, allowing for a continuous timeline. Adjusted (for the matched variables with pairs as strata) odds

	ratios (aORs) and 95% confidence intervals (CIs) were calculated using a conditional logit model for new conditions in case-patients compared with control-patients to identify post-COVID-19 conditions that could be unique to patients with COVID-19 rather than searching for pre-established outcomes, which could introduce additional bias. Among these statistically significant post-COVID-19 conditions, the most common were selected for adult case-patients based on the highest incidence proportion to identify conditions that could be the most frequent new health conditions experienced 31–120 days after COVID-19 diagnosis.
Comparator (where applicable)	Not applicable - there was no intervention that was tested.
Methods for population selection/allocation	Clinical diagnoses established during January 2019 to the index encounter date in PHD-SR provided historical data on underlying conditions. Case-patients and control-patients were identified by using propensity score nearest-neighbour matching, a statistical technique for maximising efficiency and for better isolating the effect of COVID-19 on the patient experiencing new conditions from the effect of other included variables. The match was based on propensity scores computed from patient demographics (age, sex, race, ethnicity, insurance status), clinical factors (number of previous inpatient encounters and conditions diagnosed before and at the index encounter), facility characteristics (urbanicity, region), and month of the index encounter. Inpatients and outpatients were matched separately. Outpatient encounters included the following facility settings: same-day surgery, emergency, observation, diagnostic testing, and recurring visits for services including dialysis, chemotherapy infusion and radiation, presurgical testing, and clinic. Inpatient encounters included exclusively a hospital facility setting. All other settings were excluded.
Methods of data analysis	A sensitivity analysis was conducted that restricted the control cohort to adult control-patients with a respiratory Clinical Classifications Software Refined (CCSR) category during the index encounter to examine if results were consistent with the larger study's findings. The larger analysis was not restricted to control-patients with a respiratory CCSR category during the index encounter because many respiratory illnesses, like influenza, have been less common during the pandemic and healthcare-seeking patterns during the pandemic have been dissimilar to healthcare-seeking patterns in previous years, potentially introducing bias when matching to patients with respiratory viruses in previous years. SAS (version 9.4; SAS Institute) was used for analyses. This activity was reviewed by the US Centers for Disease Control and Prevention and was deemed exempt from institutional review board oversight per 45 CFR §46.101(b)(4) and exempt from patient informed consent per 45 CFR

	§164.506(d)(2)(ii) (B) because the disclosed Premier Healthcare Database Special COVID-19 Release (PHD-SR) data are considered deidentified.
Attrition/loss to follow-up	None
Summary of findings	During 1 March–30 June 2020, from a total of 216 878 patients with a COVID-19 encounter, 27 589 inpatient case-patients and 46 857 outpatient case-patients were matched with their respective control-patients based on patient demographics, clinical factors, facility characteristics, and month of index encounter. Among the 27 589 inpatient match pairs, 305 match-pairs were in children (aged <18 years) and 27 284 match-pairs were in adults (aged ≥18 years). Among the 46 857 outpatient match-pairs, 2368 match-pairs were in children and 44 489 match-pairs were in adults. **Children** Children with COVID-19 were not more likely to experience new diagnoses than children without COVID-19. Children with COVID-19 were not more likely to experience post-COVID-19 conditions than children without COVID-19. **Adults** For adults, the incidence of post-COVID-19 conditions was predominantly in the 31–60-day range rather than in the 61–90- or 91–120-day ranges. Adults with an initial inpatient COVID- 19 encounter were significantly more likely to experience the following diagnoses in the 31–60 days after discharge compared with hospitalised adults without COVID-19: nonspecific chest pain (aOR = 1.3; 95% CI = 1.0–1.7), respiratory system symptoms (aOR = 1.4; 95% CI = 1.1–1.8), circulatory system symptoms (aOR = 1.3; 95% CI = 1.1–1.7), and nervous system symptoms (aOR = 1.3; 95% CI = 1.1–1.6). Among 27284 inpatient adult case-patients, 7.0% newly experienced 1 or more of 5 identified the most-common post-COVID conditions during 31–120 days: respiratory symptoms (e.g., shortness of breath), nervous system symptoms (e.g., altered mental status), urinary tract infections, circulatory symptoms (e.g., tachycardia), and nonspecific chest pain (Table 3). Outpatient adult case-patients were more likely to experience a range of diagnoses corresponding to multiple body systems compared with outpatient adult control-patients. During 31–60 days, adults with an outpatient index encounter for COVID-19 were more likely than outpatient control-patients to experience acute pulmonary embolism (aOR = 2.8; 95% CI = 1.3–6.0). During 31–120 days, 7.7% of 44 489 adults with an initial outpatient encounter for COVID-19 newly experienced 1 or more of 10 identified post-COVID-19 conditions: respiratory symptoms (e.g., shortness of breath), abdominal pain and other digestive/abdominal symptoms (e.g., diarrhoea), nonspecific chest pain, nervous

	system symptoms (e.g., altered mental status), headache (including migraine), circulatory symptoms (e.g., tachycardia), fluid and electrolyte disorders (e.g., hypokalaemia), malaise and fatigue, nausea and vomiting, and urinary tract infections. Among 44 489 adult case-patients with an outpatient index encounter, 1222 (2.8%) were later hospitalised during 31–120 days with the most-common diagnoses including pneumonia and fluid and electrolyte disorders. The results of the sensitivity analysis that restricted the control cohort to adult control-patients with a respiratory CCSR category during the index encounter were consistent with the study findings with identification of new diagnoses in multiple body systems for adult case-patients. Among 27 284 inpatient adults and 44 489 outpatient adults who had a diagnosis of COVID-19, 7.0% and 7.7%, respectively, were newly diagnosed with 1 or more identified post-COVID-19 conditions (31–120 days following their initial COVID-19 encounter as defined above) in a large administrative all-payer database. Because this study compared COVID-19 case-patients with control-patients who did not have COVID-19, it is probable that the identified post-COVID-19 conditions in adults are related to COVID-19 rather than to other factors such as age or care setting. Furthermore, the findings of a sensitivity analysis suggest excess risk for adult patients with COVID-19 for experiencing conditions in multiple body systems compared with adults with other respiratory diseases.
Source of funding	Not mentioned.
Study limitations (Author)	The findings in this report are subject to at least 6 limitations. First, because the study relied on healthcare encounter information it might be subject to information bias and might not fully reflect hospitalisation acuity or exact timing of condition onset. Patients with minor to moderate symptoms without COVID-19 might be less likely than patients with COVID-19 to seek care for multiple reasons, including fear of SARS-CoV-2 exposure in a medical facility, causing potential overestimation of odds ratios for post-COVID-19 conditions. As COVID-19 is a novel disease, there may be additional reasons that healthcare providers would arrange for follow-up encounters with their patients who experienced COVID-19 compared with patients without COVID-19. Second, potential misclassification among case-patients and control-patients could have occurred because of the use of ICD-10-CM codes rather than laboratory data. Third, there could be changes in diagnostic or treatments patterns over time that could have affected the incidence of new conditions.

	Fourth, these findings were not representative of all patients with SARS-CoV-2 infection or COVID-19 disease; recent surveys in the United Kingdom suggest that 14% of patients who tested positive for SARS-CoV-2 infection still had symptoms at 12 weeks, suggesting that additional persistent symptoms might exist that start at the time of acute infection. Persistent symptoms, starting at the time of acute disease, were not assessed in this analysis. Individual patients might experience significant additional new conditions as well as rare complications that were not represented within these findings, and some symptoms (e.g., cognitive impairment or post exertional malaise) and conditions might not be well captured by ICD-10-CM codes. Fifth, this study included 2673 children, nearly 90% of whom presented with an index outpatient encounter; studies with a larger paediatric population might find associated post-COVID-19 conditions in children that were not found in this study, such as multisystem inflammatory syndrome in children or other post-COVID-19 conditions. Finally, if patients did not seek healthcare services or if patients received care outside of hospitals submitting data to PHD-SR, information about their condition was not captured, leading to potential missing data about prior or subsequent health conditions.
Study limitations (Reviewer)	Nothing further to add.

Study arms

Children who had COVID-19 and were inpatients (N = 305)

Children who did not have COVID-19 and were inpatients (N = 305)

Children who had COVID-19 and were outpatients (N = 2368)

Children who did not have COVID-19 and were outpatients (N = 2368)

Characteristics

Arm-level characteristics

Characteristic	Children who had COVID-19 and were inpatients (N = 305)	Children who did not have COVID-19 and were inpatients (N = 305)	Children who had COVID-19 and were outpatients (N = 2368)	Children who did not have COVID-19 and were outpatients (N = 2368)
<1 year Mean (SD)	129 (42.3)	120 (39.3)	638 (2639)	622 (26.3)
2–11 years Mean (SD)	97 (31.8)	106 (34.8)	833 (35.2)	891 (37.6)

Characteristic	Children who had COVID-19 and were inpatients (N = 305)	Children who did not have COVID-19 and were inpatients (N = 305)	Children who had COVID-19 and were outpatients (N = 2368)	Children who did not have COVID-19 and were outpatients (N = 2368)
12–17 years Mean (SD)	79 (25.9)	79 (25.9)	897 (37.9)	855 (36.1)
% Female (%) Nominal	43.6	44.6	50.6	52.7
White, Non-Hispanic Nominal	26.9	31.5	20.6	20.7
Black non-Hispanic Nominal	23.9	21.3	22	20.9
Asian, non-Hispanic Nominal	30.2	30.2	1.7	1.3
Hispanic Nominal	14.1	13.4	43.2	44.3
Other non-Hispanic Nominal	4.9	3.6	12.5	12.7

Chevinsky, 2021

Bibliographic Reference	Chevinsky, Jennifer R; Tao, Guoyu; Lavery, Amy M; Kukielka, Esther A; Click, Eleanor S; Malec, Donald; Kompaniyets, Lyudmyla; Bruce, Beau B; Yusuf, Hussain; Goodman, Alyson B; Dixon, Meredith G; Nakao, Jolene H; Datta, S Deblina; Mac Kenzie, William R; Kadri, Sameer; Saydah, Sharon; Giovanni, Jennifer E; Gundlapalli, Adi V; Late conditions diagnosed 1-4 months following an initial COVID-19 encounter: a matched cohort study using inpatient and outpatient administrative data - United States, March 1-June 30, 2020.; Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 2021

Critical appraisal - CASP Critical appraisal checklist for case-control studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	No *(The data was collected using ICD-10-CM codes, which were not designed to capture the signs, symptoms, and long-term effects of COVID-19.)*
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	Yes
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	N/A
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	Yes
(B) What are the results?	7. What are the results of this study?	See data above.
(B) What are the results?	8. How precise are the results?	N/A
(B) What are the results?	9. Do you believe the results?	No, because the data was collected using ICD-10-CM codes, which were not designed to capture the signs, symptoms, and long-term effects of COVID-19.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The data was collected using ICD-10-CM codes, which were not designed to capture the signs, symptoms, and long-term effects of COVID-19)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes

Ludvigsson 2020 (in review question 1)

Bibliographic Reference	Ludvigsson, Jonas F; Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2020

Study details

Study design	Systematic review
Aims/ review questions	The aim of this paper was to describe five children with long COVID-19, based on parental reports, and complement those cases with a systematic literature review of long COVID-19.
Search date	02-Nov-2020
Country/ Geographical location	The systematic review had no country limits. The 5 children in the case report were from Sweden.
Setting(s)	For the systematic review, there were no relevant studies that had children with COVID-19. The 5 children in the case report were in the community but one was later admitted to hospital for peri-myocarditis.
Population description	Children with long-term effects of COVID-19. They defined long COVID-19 as persistent symptoms that lasted for 2 months or more.
Inclusion criteria	**Systematic review** Papers on long COVID-19 in children. **Case reports** Children who had long COVID-19. The parents of the 5 children had contacted the investigators.
Exclusion criteria	Papers/children were excluded if they did not have COVID-19 in the period prior to investigation.
Intervention/test/approach	For the case reports: Clarifying parental reports. The different areas of data gathered were decided after hearing the histories of the families.
Comparator (where applicable)	None
Searching methods	A librarian at the Karolinska Institutet University Library, Stockholm, Sweden, performed a systematic literature review of the MEDLINE, EMBASE and Web of Science databases to identify papers on long COVID-19 in children. In addition, the librarian also performed a search of medical papers filed on medRxiv/bioRxiv up to the same date. This is a pre-print database for biology papers, which is operated by the Cold Spring Harbor Laboratory, a private research and educational institution in New York, USA. They used search terms for COVID-19 and SARS-CoV-2 and children and also added following terms, and variants of these terms, to specifically catch publications that discussed long COVID-19: chronic, post-acute, post-COVID-19, long COVID-19, long haulers, persistent, sequelae or complications.
Methods of data analysis	Case reports: Narrative synthesis of results. Systematic review: N/A - no relevant studies were found.

Methods to investigate heterogeneity	N/A - no relevant studies were found.
Risk of bias assessment	N/A - no relevant studies were found. Risk of bias assessments were not performed.
Summary of findings	**Systematic review** Most of the 19 publications read in detail concerned general or specific medical aspects of COVID-19, but they did not describe any children with long COVID-19. Other publications concerned how COVID-19 may influence different aspects of children's lives. In a systematic review, Ahmed et al. described the clinical characteristics of 662 children with multi-inflammatory syndrome in children (MIS-C), but reported no long-term consequences other than MIS-C. It was unclear if any of the MIS-C cases that the authors described occurred more than 2 months after the onset of COVID-19. Other studies focused on individual cohorts of children with MIS-C or COVID-19 and the need for intensive care, hospital admission or other aspects of MIS-C or COVID-19. In a brief report, Denina et al. followed up 28 children admitted to hospital with COVID-19. On average, children were followed up for an average of 35 days after discharge, but the authors did not state the average time lapse between hospital admission and follow-up. After they were discharged, none of the children demonstrated any clinical or laboratory abnormalities. The authors noted that no sequelae remained 4 months after discharge. Finally, the other studies identified in their review concerned COVID-19 in adults. Radmard et al. discussed neurological complications after COVID-19 and presented data on 33 patients. There was only one paediatric patient under the age of 18 and that individual was 17 years of age. No detailed follow-up data were provided. Although it was not explicitly stated, the median age of the 48 patients in the pre-print study by Savarraj et al. was 50 years and children were not mentioned. Yasin et al. reviewed respiratory symptoms and x-ray results in subjects with a mean age of 42 years, which included an unspecified number of children aged 12–17. It is unclear if any of the documented abnormalities at more than 15 day persisted for two or more months and were seen in children. The investigators were unable to access a case report of four adolescents with skin lesions, 2 weeks after the occurrence of a flu-like syndrome. The patients tested positive for SARS-CoV-2 antibodies, but it was not clear from the abstract if these potential cutaneous manifestations persisted for more than 2 months.

	Case reports Of the five children with potential long COVID-19, four were girls and their median age was 12 years (range 9–15). The children had experienced symptoms for between 6 and 8 months. All had been diagnosed with COVID-19 by their physician. None of the children had positive SARS-CoV-2 polymerase chain reactions, but the tests had been obtained more than 1.5 months after the onset of COVID-19. SARS-CoV-2 antibody testing had been carried out on four of the five children, but all the tests were negative. It was not necessary for any of the children to be admitted to hospital at the onset of COVID-19. Only one child had comorbidities before developing COVID-19 and that was a 12-year-old female with asthma, allergies and mild autism spectrum disorder. The most common symptoms 2 months after the onset of COVID-19 were fatigue, dyspnoea and heart palpitations or chest pain. These were seen in all five of the children. In addition, four of the five children complained of headaches, difficulties concentrating, muscle weakness, dizziness and a sore throat. The parents reported that three of the children experienced abdominal pain, memory loss, depression and skin rashes and muscle pain. Less common symptoms, experienced by two children, were remitting fever, sleep disorders, joint pain, diarrhoea and vomiting and hyperanaesthesia. A number of symptoms were each reported by one child after 2 months, and they were persistent deranged smell and taste, poor appetite, a chronic cough and numbness. Some of the children had improved after experiencing symptoms for 6–8 months, but all of them still suffered from fatigue and none of them had been able to return to school full time. Four reported daily problems of some kind while a fifth was reported to have ‘good and bad days’. The parents stated that two of the children had undergone cardiac examinations and two had seen, or were scheduled to see, a psychologist. The girl with prior comorbidities was hospitalised for 3 days for peri-myocarditis after being diagnosed with COVID-19. Several parents also reported that they or the children's siblings also had longstanding issues as a result of COVID-19. These included the mothers and two siblings of patient four.

	One parent noted that it was general knowledge on Internet-based social forums for long COVID-19 patients that mothers and their daughters often had long COVID-19 simultaneously.
Source of funding	Not mentioned.
Study limitations (Author)	They did not identify any report that specifically described long COVID-19 in children.
Study limitations (Reviewer)	The systematic review appears to have been conducted before any relevant studies had been published. The case report was not relevant to our systematic review because we were including studies at the level of cohort, surveys, or cross-sectional studies.
Other details	We did not include the data from the case reports because we already had sufficient data from cohort, surveys, and cross-sectional studies.

Outcomes
No outcomes
The systematic review found no relevant data

Ludvigsson, 2020

Bibliographic Reference	Ludvigsson, Jonas F; Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2020

ROBIS tool to assess risk of bias in systematic reviews

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low *(However, the investigators could find no relevant data on long COVID-19 in children.)*

Miller 2021 (in review questions 2 and 3)

Bibliographic Reference	Miller, Faith; Nguyen, Vincent; Navaratnam Annalan, MD; Shrotri, Madhumita; Kovar, Jana; Hayward Andrew, C; Fragaszy, Ellen; Aldridge Robert, W; Collaborative - Virus, Watch; Hardelid, Pia; Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales; medrxiv preprint

Study details

Study design	Cohort study
Trial registration (if reported)	Not reported
Study start date	15-Jun-2020
Study end date	16-Mar-2021
Aim of the study	To estimate the prevalence of post-acute COVID-19 symptoms in children.
Country/ Geographical location	UK (England and Wales)
Study setting	This was a household survey (community).
Population description	Children aged ≤17 years who had post-acute symptoms of COVID-19.
Inclusion criteria	Children aged ≤17 years at enrolment and reporting COVID-19 symptom episodes lasting 4 weeks or more through the weekly surveys. History of SARS-CoV-2 infection was defined where a child had i) reported a positive swab result, ii) had a positive swab as part of the VirusWatch survey, or iii) tested positive for SARS-CoV-2 IgG.
Exclusion criteria	None
Intervention/test/approach	They coded persistent symptoms into groups used by the National Institute for Health and Care Excellence: respiratory, cardiovascular, generalised (fatigue, fever, or pain), neurological (including cognitive impairment/'brain fog' and headache), gastrointestinal, psychological/psychiatric symptoms, ear, nose and throat (ENT) symptoms, dermatological or other symptoms. Age was coded into three groups: <2, 2-11 and 12-17 years. Presence of a long-term condition was coded as a binary variable based on information regarding long-term conditions or medications from the baseline questionnaire. A small-area level indicator of socio-economic deprivation, the Index of Multiple Deprivation (IMD; coded into quintiles) and region of residence was mapped to the household postcode.
Comparator (where applicable)	They compared the distribution of age, sex, region of residence and IMD quintile in the study cohort with that of the resident population of children in England and Wales, derived

	from 2019 population estimates provided by the Office for National Statistics.
Methods for population selection/allocation	They used data from VirusWatch, a household cohort study in England and Wales. Households were recruited starting in mid-June 2020 via a number of methods, including postcards or letters sent to the home address, social media and SMS. As of mid-March 2021, 47,813 individuals in 23,059 households had registered to take part. To participate, a household required internet access and an email address, and at least one household member had to speak sufficient English for survey completion. Participating households completed online weekly surveys (reporting a wide range of symptoms and SARS-CoV-2 swab test results), and monthly themed topic surveys. Parents consented on behalf of their children if children were <6 years old. VirusWatch also included a programme of nasopharyngeal swab sample collection, and blood collection via venepuncture or fingerprick sampling in a subset of 10,000 participants. They used data from the 3rd monthly survey (distributed on the 17th February 2021), which asked about persistent symptoms (the 'long COVID-19 survey'). All children aged ≤17 years at enrolment who had either a) answered the question about persistent symptoms in the 3rd monthly survey, or b) whose household had participated in at least 3 weekly surveys in a 5-week period, before the 20th January 2021, were included in their analysis. In the long COVID-19 survey, participants were asked: "In the last year (since February 2020) have any of the household members experienced any new symptoms that have lasted for four or more weeks even if these symptoms come and go, and that are not explained by something else (e.g., pre-existing chronic illness or pregnancy)?" Participants who responded 'yes' could also report the nature of the symptoms and the date of onset and resolution for the three most severe symptoms. They defined 'persistent symptoms' as a child having either answered yes to the above question in the long COVID-19 survey, or reporting symptom episodes lasting 4 weeks or more through the weekly surveys. If the date of onset of persistent symptoms was missing from the long COVID-19 survey, the 20th January 2021 was used as the onset date (5 weeks before the survey date). If information on persistent symptoms was derived from the weekly survey, the start date of the illness episode was used as the onset of persistent symptoms.
Methods of data analysis	They estimated the prevalence of persistent symptoms overall and in children with a history of SARS-CoV-2 infection according to age group, sex and presence of a long-term condition They fitted mixed effects logistic regression models for persistent symptom prevalence including these risk factors as the independent variables and household ID as the random

	intercept. They estimated the median duration of symptoms for children who had reported onset dates and that at least one symptom had ended. All analyses were carried out using Stata version 16 and RStudio version 3.4.3.
Attrition/loss to follow-up	The records of 689 children who had COVID-19 went missing (14.7%).
Summary of results	We included 4,678 children who met the inclusion criteria. Children aged 12-17 years were slightly over-represented in the VirusWatch child cohort compared to mid-year population estimates, as were children living in the Eastern regions of England. The child cohort was substantially less deprived than the population of children in England. 175 cohort children (3.7%) had evidence of past or present SARS-CoV-2 infection (Table 1). Of children with evidence of past infection, 110 had had a positive swab test (62.9%), 47 were positive on serology (26.9%) and 18 children had had a positive swab test and serology (10.3%). Seven children (of 175; 4%) had tested positive through the VirusWatch swabbing programme. Of the 476 children who reported at least one long-term condition, 385 (80.9%) reported having clinician-diagnosed asthma or using an inhaler (8.2% of the cohort). The overall prevalence of persistent symptoms was 1.7% (80/4678 children; 95% CI 1.4%, 2.1%), and 4.6% (8/174 children; 95% CI 2.0%, 8.9%) in children who had a history of SARS-CoV-2 infection before persistent symptom onset. Among children who reported persistent symptoms, the most common reported symptom types were general (fatigue, fever, or pain), ENT, and respiratory symptoms. Among the 22 children who had reported at least one ‘general’ symptom, fatigue was the most common, reported by 18 children (22.5% of children reporting persistent symptoms). The median duration of symptoms was 46 days (interquartile range 32-188) for the 18 children who reported start and end dates of symptoms. Children who had evidence of SARS-CoV-2 infection were over twice as likely to report persistent symptoms compared to children who had not (Table 2). Being a teenager, girl or having long-term conditions significantly increased the odds of persistent symptoms. The prevalence of persistent symptoms lasting ≥4 weeks in children during the second and third UK wave of the COVID-19 pandemic was1.7% overall, and 4.6% among children with a history of SARS-CoV-2 infection. Apart from children with a history of SARS-CoV2 infection, girls, teenagers and children

	with long-term conditions were more likely to report persistent symptoms. We used data from a large sample of children in England and Wales, which was representative of the general population of children in terms of age and sex, but less socio-economically deprived.
Source of funding	Medical Research Council. The study also received Facebook advertising credit to support a pilot social media recruitment campaign.
Study limitations (Author)	Given that the prevalence of persistent symptoms was low, larger studies are required to assess risk factors for persistent symptoms in children related to SARS-CoV-2 infection in more detail. Since only one monthly survey to date have included questions on persistent symptoms, they were not able to assess time to symptom resolution for all children (as some had continuing symptoms), however evidence from other studies indicates that the majority of children recover after two months. Furthermore, they were not able to compare the prevalence of persistent symptoms in children with SARS-CoV-2 infection to the proportion of children developing persistent symptoms after other respiratory infections.
Study limitations (Reviewer)	Parents were self-selected and may therefore not be representative of the general population. Results were prone to self-reporting bias as well as recall bias because it was a retrospective study. For example, the survey question was: “In the last year (since February 2020) have any of the household members experienced any new symptoms that have lasted for four or more weeks even if these symptoms come and go, and that are not explained by something else (eg, pre-existing chronic illness or pregnancy)?” Therefore, some participants could have been recalling symptoms that ended almost year ago.

Study arms
Children who had COVID-19 (N = 4678)

Population of children in England and Wales (N = 12653507)

Characteristics
Arm-level characteristics

Characteristic	Children who had COVID-19 (N = 4678)	Population of children in England and Wales (N = 12653507)
<2 years (%) Nominal	7	10.5
2–11 years (%)	53.9	57.9

Characteristic	Children who had COVID-19 (N = 4678)	Population of children in England and Wales (N = 12653507)
Nominal		
12–17 years (%) Nominal	39.1	31.7
% Female (%) Nominal	40.6	48.7

Miller 2021

Bibliographic Reference	Miller, Faith; Nguyen, Vincent; Navaratnam Annalan, MD; Shrotri, Madhumita; Kovar, Jana; Hayward Andrew, C; Fragaszy, Ellen; Aldridge Robert, W; Collaborative - Virus, Watch; Hardelid, Pia; Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales; medrxiv preprint

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	No *(The population was self-selected and prone to selection bias.)*
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Not applicable
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	Yes
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Yes
(B) What are the results?	7. What are the results of this study?	See data above.

Section	Question	Answer
(B) What are the results?	8. How precise are the results?	N/A
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See data above.
Overall bias	Overall risk of bias	High *(The participants (parents of children and children) were self-selected and therefore the data is prone to selection bias. Furthermore, the results were self-reported and prone to self-reporting bias as well as recall bias because it was a retrospective study.)*

Molteni 2021 (in review questions 2 and 3)

Bibliographic Reference	Molteni, Erika; Sudre, Carole; Helene; Canas, Liane; Santos; Bhopal Sunil, S; Hughes, Robert; C; Antonelli, Michela; S; Murray, Benjamin; Klaser, Kerstin; Kerfoot, Eric; Chen, Liyuan; Deng, Jie; Hu, Christina; Selvachandran, Somesh; Read, Kenneth; Pujol, Joan; Capdevila; Hammers, Alexander; Spector, Timothy; Ourselin, Sebastien; Steves, Claire; J; Modat, Marc; Absoud, Michael; Duncan, Emma; L; Illness duration and symptom profile in a large cohort of symptomatic UK school-aged children tested for SARS-CoV-2; medrxiv preprint

Study details

Study design	Prospective cohort study
Study start date	24-Mar-2020
Study end date	22-Feb-2021
Aim of the study	The aim was to investigate illness duration and symptom prevalence, duration, and burden in UK school-aged children (age 5–17 years) testing positive for SARS-CoV-2, and similar data for symptomatic children testing negative.
Country/ Geographical location	UK
Study setting	Community
Population description	Children who had COVID-19.

Inclusion criteria	Children were considered symptomatic of SARS-CoV-2 if they were proxy-reported with relevant symptoms between 1 week before and 2 weeks after infection confirmation (either PCR or lateral flow antigen test).
Exclusion criteria	Data from children with reporting gaps longer than 1 week between symptomatic reports/periods were excluded.
Intervention/test/approach	Illness duration was calculated from the first symptom (having been previously asymptomatic) until recovery (return to asymptomatic or, if proxy-reporting ceased before becoming asymptomatic, final proxy report). Individuals who were proxy-reported as asymptomatic but subsequently re-reported with symptoms within 1 week of their last symptomatic report were considered unwell from initial presentation (i.e., relapsing or remitting illness), with illness duration calculated accordingly. Individual symptom prevalence and duration were assessed, with duration calculated from first to last report for that symptom. Symptom burden was calculated as the number of different symptoms reported at least once over defined timeframes (during first week, first 28 days, from day 28 until illness end, and entire illness duration). Illness with symptoms lasting for 28 days or more was termed LC28 and for 56 days or more was termed LC56. Thus, by virtue of census dates, LC28 could be determined for children whose symptoms commenced on or before Jan 24, 2021, and LC56 for children whose symptoms commenced on or before Dec 29, 2020 (peak positive specimen date). Hospital presentation comprised emergency department presentation or hospital admission following symptom commencement. Proxy-reporting density was defined as the number of episodes of proxy-reporting over illness duration, and proxy-reporting persistence was defined as proxy-reporting until return to asymptomatic. Several direct symptom questions were added to the app on Nov 4, 2020, but these data were not included in the main illness profile analyses. Free-text reporting was possible across the entire period. Free-text data were divided into themes using descriptive word frequency, and items within themes were independently scrutinised by two clinicians to ensure appropriateness. Individuals reporting symptoms within themes were then counted. Free-text data are reported as descriptive statistics and not included in illness profile analyses. Free-text data searching included neurological terms and symptoms potentially affecting attention, behaviour, learning or school performance or both; symptoms already assessed by direct questions were excluded. Illness profiles, including illness duration and symptom burden, were also assessed in children testing negative for SARS-CoV-2, using a randomly selected control cohort (matched 1:1 for age, gender, and week of testing), and compared with children who tested positive. Prevalence data for common winter circulating viruses were obtained from national public health databases.

	The primary outcome was illness duration and symptom burden in children who tested positive for SARS-CoV-2 and in matched children who tested negative, assessed overall as well as for younger and older children. Additionally, they assessed individual symptom prevalence and duration, hospital presentation, and the prevalence of prolonged illness duration.
Comparator (where applicable)	None
Methods for population selection/allocation	N/A - there was only 1 arm.
Methods of data analysis	Data are presented using descriptive statistics. Due to rarity (some percentages <5%), CIs were calculated using Poisson distribution. Comparisons of data between groups were done using Wilcoxon signed-rank test, two-tailed χ^2-tests, or Fisher's exact tests. They used Spearman correlation to assess correlation of illness duration with age. All analyses were done in Python version 3.7.
Attrition/loss to follow-up	None
Summary of results	Overall, 258 790 UK children aged 5–17 years were proxy-reported between March 24, 2020, and Feb 22, 2021. Positive SARS-CoV-2 testing was reported in 6975 children, of whom 1912 (666 younger and 1246 older children) had a calculable illness duration and requisite proxy-report logging. Because only 36 of these 1912 children had illness onset before Sept 1, 2020 (return-to-school), and given the limited testing access early in the UK pandemic,13 analyses were restricted to children with illness onset after Sept 1, 2020. 1734 (588 younger, 1146 older) children were proxy-logged on or before Jan 24, 2021, allowing LC28 to manifest. Similarly, 1379 (445 younger, 934 older) children had symptoms commencing on or before Dec 29, 2020, allowing LC56 to manifest. **Signs and symptoms, most common at the top, N=77, prospective cohort study, median age 14 years, reported at ≥28 days** This data was sent to us by the authors Sign/symptom — Percentage who experienced it Loss of smell — 45.45% Fatigue — 44.16% Headache — 28.57% Skipped meals — 16.88% Short of breath — 16.88% Abdominal pain — 15.58% Dizziness/ light headedness — 12.99% Sore throat — 12.99% Muscle aches and pains — 12.99%

Conjunctivitis/ sore eyes	11.69%
Nausea	10.39%
Fever	9.09%
Blisters on hands and feet	7.79%
Persistent cough	6.49%
Chest pain	6.49%
Lack of concentration/ delirium	5.19%
Skin rash/ red welts	5.19%
Diarrhoea and vomiting	3.90%
Hoarse voice	1.30%

Source of funding	Zoe Limited, UK Government Department of Health and Social Care, Wellcome Trust, UK Engineering and Physical Sciences Research Council, UK Research and Innovation London Medical Imaging and Artificial Intelligence Centre for Value Based Healthcare, UK National Institute for Health Research, UK Medical Research Council, British Heart Foundation, and Alzheimer's Society.
Study limitations (Author)	To be eligible for PCR testing, individuals were required to have fever, cough, anosmia, or a combination of these symptoms, criteria that were largely informed by adult symptomatology, which might miss some paediatric manifestations of COVID-19 (e.g., abdominal pain, reported in 27·8% of their younger children). Freetext data did not suggest common symptoms unique to children; qualitative analysis was not undertaken given its ad hoc collection and potential bias from additional direct questions after Nov 4, 2020 (i.e., once directly asked, a symptom was unlikely to be freetext reported). Additionally, they did not ask specifically about multisystem inflammatory syndrome in children (MIS-C). Only 74·5% of children testing positive and 46·4% of children testing negative were reported to have fever, cough, anosmia, or a combination of these symptoms. They do not know why the remaining children were tested. The positive predictive value of any symptom varies according to illness prevalence, and here is clearly subject to the pandemic dynamics. However, nearly a quarter of symptomatic children testing positive for SARS-CoV-2 during the UK's second wave did not report any of these symptoms. They also acknowledge that symptoms were proxy-reported rather than directly ascertained. This is common in clinical assessment of children, particularly younger children. They do not have linkage to general practice or hospital records to validate proxy-reported data. Crucially, proxy-reported children depended upon an adult with access and capacity to participate in the COVID-19 Symptom Study. They did not have information on the relationship of the contributor to the proxy-reported child, which could influence reporting. For example, an unwell contributor might be too ill to

	proxy-report for a child; however, our high proxy-reporting density and perseverance of all symptomatic children suggest that this was uncommon. Current or previous symptoms experienced by contributors might also influence their proxy-reporting.
Study limitations (Reviewer)	The parents who participated were self-selected. Therefore, they might not have been representative of the whole UK population of children who had COVID-19. For example, the children included in this study might have had relatively more serious symptoms, motivating parents to learn about the app and download it. Some parents could have entered the data retrospectively, leading to recall bias.

Study arms
Children with a positive SARS-CoV-2 test (N = 1734)

Characteristics
Study-level characteristics

Characteristic	Study (N = 1734)
Age (years) median Nominal	13
Gender (%) % Female Nominal	50.1

Molteni et al.

Bibliographic Reference	Molteni, Erika; Sudre, Carole; Helene; Canas, Liane; Santos; Bhopal Sunil, S; Hughes, Robert; C; Antonelli, Michela; S; Murray, Benjamin; Klaser, Kerstin; Kerfoot, Eric; Chen, Liyuan; Deng, Jie; Hu, Christina; Selvachandran, Somesh; Read, Kenneth; Pujol, Joan; Capdevila; Hammers, Alexander; Spector, Timothy; Ourselin, Sebastien; Steves, Claire; J; Modat, Marc; Absoud, Michael; Duncan, Emma; L; Illness duration and symptom profile in a large cohort of symptomatic UK school-aged children tested for SARS-CoV-2; medrxiv preprint

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	No *(The parents who downloaded and used the app were self-selected and may not represent all*

Section	Question	Answer
		children who had COVID-19.)
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	Can't tell *(Some parents may have entered the data retrospectively, which could have led to recall bias.)*
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Not applicable
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	Yes
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Yes
(B) What are the results?	7. What are the results of this study?	See data above.
(B) What are the results?	8. How precise are the results?	See data above.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See data above.
Overall bias	Overall risk of bias	Moderate *(There are some issues with recruitment.)*

Osmanov 2021 (in review questions 1, 2 and 3)

Bibliographic Reference	Osmanov Ismail, M; Spiridonova, Ekaterina; Bobkova, Polina; Gamirova, Aysylu; Shikhaleva, Anastasia; Andreeva, Margarita; Blyuss, Oleg; Taravi Yasmin, El-Taravi; DunnGalvin, Audrey; Comberiati, Pasquale; Peroni Diego, G; Apfelbacher, Christian; Genuneit, Jon; Mazankova, Lyudmila; Miroshina, Alexandra; Chistyakova, Evgeniya; Samitova, Elmira; Borzakova, Svetlana; Bondarenko, Elena; Korsunskiy Anatoliy, A; Konova, Irina; Hanson Sarah, Wulf; Carson, Gail; Sigfrid, Louise; Scott Janet, T; Greenhawt, Matthew; Whittaker Elizabeth, A; Garralda, Elena; Swann, Olivia; Buonsenso, Danilo; Nicholls Dasha, E; Simpson, Frances; Jones, Christina; Semple Malcolm, G;

Warner John, O; Vos, Theo; Olliaro, Piero; Munblit, Daniel; Team - Sechenov StopCOVID, Research; Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study; medrxiv preprint

Study details

Study design	Prospective cohort study
Trial registration (if reported)	Not provided
Study start date	02-Apr-2020
Study end date	26-Aug-2020
Aim of the study	To investigate the incidence of and risk factors for long-term COVID-19 outcomes in children post-hospital discharge.
Country/ Geographical location	Russia
Study setting	Hospital
Population description	Children (≤18 years old) admitted with suspected or confirmed COVID-19.
Inclusion criteria	Children admitted to the hospital during the first wave of the pandemic, between April 2, 2020 and August 26, 2020, with reverse transcriptase polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection were included.
Exclusion criteria	Children who did not have a COVID-19 infection confirmed using RT-PCR.
Intervention/test/approach	The parents of these children were contacted between January 31, 2021 and February 27, 2021 to complete a follow-up survey for this study. The acute-phase dataset included demographics, symptoms, co-morbidities, chest computer tomography (CT), supportive care, and clinical outcomes at discharge. Interviews were undertaken by a team of medical students with experience gained in previous COVID-19 research who underwent standardised training in telephone assessment, REDCap data entry and data security. Assessments were conducted via interviews with the parents/carers. Non-responders were contacted by telephone three times before considering them lost to follow-up. Information about the current condition and persisting symptoms was collected using the version 1.0 of the ISARIC COVID-19 Health and Wellbeing Follow-Up Survey for Children, to assess patients' physical and psychosocial wellbeing and behaviour, with local adaptations (addition of questions

	related to signs/symptoms presence which symptom duration), translated into Russian. The follow-up survey documented data on demographics, parental perception of changes in their child's emotional and behavioural status (including reasons for a change COVID-19, pandemic or both), previous vaccination history, hospital stay and readmissions, mortality (after the initial index event), history of newly developed symptoms between discharge and the follow-up assessment, including symptom onset and duration, and overall health condition compared to prior to the child's COVID-19 onset. To assess the prevalence of symptoms over time parents were asked the following: (a) Within the last seven days, has your child had any of these symptoms, which were NOT present prior to their COVID-19 illness? (If yes, please indicate below and the duration of the symptom/s). (b) Please report any symptoms that have been bothering your child since discharge that are not present today. Please specify the time of onset and duration of these symptoms. The baseline characteristics, including demographics, symptoms on admission and comorbidities were extracted from EMRs and entered into REDCap. For the purposes of this study, we defined "persistent symptoms" as symptoms present at the time of the follow-up interview and lasting for over 5 months. These were subcategorised into respiratory, neurological, sensory, sleep, gastrointestinal, dermatological, cardiovascular, fatigue and musculoskeletal. Allergic diseases were defined as a presence of any of the following: asthma, allergic rhinitis, eczema or food allergy. Severe disease was defined as having received non-invasive ventilation, invasive ventilation or admission to the paediatric intensive care unit (PICU) during the hospital admission. Health status before COVID-19 and at the time of the interview was assessed using a 0 to 100 wellness scale, where 0 was the worst possible health and 100 the best possible health. The survey was developed by the ISARIC Global Paediatric COVID-19 follow-up working group and informed by a wide range of global stakeholders with expertise in infectious diseases, critical care, paediatrics, epidemiology, allergy-immunology, respiratory medicine, psychiatry, psychology and methodology and patient representatives. The survey was distributed to the members of the patient group and suggestions from parents/carers were implemented.

Comparator (where applicable)	N/A
Methods for population selection/allocation	See inclusion criteria above.
Methods of data analysis	Descriptive statistics were calculated for baseline characteristics. Continuous variables were summarised as median (with interquartile range) and categorical variables as frequency (percentage). The chi-squared test or Fisher's exact test was used for testing hypotheses on differences in proportions between groups. The Wilcoxon rank-sum test was used for testing the hypotheses on differences between groups. They performed multivariable logistic regression to investigate associations of demographic characteristics, co-morbidities (limited to those reported in ≥5% of participants), presence of pneumonia during acute infection and severity of COVID-19 with persistent symptom categories presence at the time of the follow-up interview. They included all participants for whom the variables of interest were available in the final analysis, without imputing missing data. The differing denominators used indicate missing data. Odds ratios were calculated together with 95% confidence intervals (CIs). Upset plots were used to present the coexistence of persistent symptom categories. Two-sided p-values were reported for all statistical tests, a p-value below 0.05 was considered to be statistically significant. Statistical analysis was performed using R version 3.5.1. Packages used included dplyr, lubridate, ggplots2, plotrix and UpSetR.
Attrition/loss to follow-up	335 children dropped out of the study and were not available for follow-up (39%).
Summary of results	All 853 children hospitalised with suspected COVID-19 to the hospital between April 2, 2020 and August 26, 2020 were discharged alive. Of 836 patients with accurate contact information, parents of 518 RT-PCR positive children agreed to be interviewed (response rate 62%) and were included in the analysis. The median age was 10.4 years (IQR, 3-15.2; range, 2 days–18 years), 272 (52.2%) were girls. Median follow-up time since hospital admission was 268 days (IQR 233-284). Children had a median of 8 (IQR, 4-9) years of formal school education and a median of 4 (IQR, 3-5) family members were residing in the household. The most common pre-existing comorbidity in this cohort was food allergy (13%, 67/514), followed by allergic rhinitis and asthma (9.7%, 50/514), gastrointestinal problems (9.3%, 48/514), eczema (8.8%, 45/514) and neurological problems (8.4%, 43/514). Parents of 55.3% (284/514) children did not report any comorbidities. Fever (83.6%, 427/511), cough (55.7%, 284/510), rhinorrhea (54.3%, 278/512) and fatigue (38.9%, 197/506) were the most common presenting symptoms at the time of the

	hospital admission. 37.3%, 192/515 of patients had pneumonia during hospital stay, 2.7%, 14/515 had severe disease, which required non-invasive ventilation/invasive ventilation or admission to PICU. At the time of the follow-up interview, parents of 24.7% (128) children reported at least one persistent symptom, with fatigue 10.6% (53/496), insomnia 5.19% (26/501), disturbed smell 4.7% (22/467) and headache 3.5% (17/486) being the most common. The prevalence of the symptoms present at the time of discharge declined over time. Number of children with fatigue fell from 15.8% (82/518) at the time of discharge to 8.8% (45/513) 6-7 months later, altered sense of smell from 8.7% (45/518) to 4.7% (24/514), sleep disturbance 7.5% (39/518) to 5.8% (30/515), altered sense of taste from 5.6% (29/518) to 3.1% (16/515), headache from 4.6% (24/518) to 3.5% (18/517), and breathing difficulties from 3.9% (20/518) to 1% (5/517), respectively. With regard to persistent symptom categories, fatigue was the most commonly reported in 10.6% (53/498) of patients at the time of assessment, followed by sleep disturbance 7.2% (36/501), sensory problems 6.2% (29/467), gastrointestinal 4.4% (22/499) and dermatological 3.6% (18/496) problems. A smaller number of patients experienced neurological 3% (14/465), respiratory 2.5% (12/489), cardiovascular 1.9% (9/470) and musculoskeletal 1.8% (9/489) problems long-term. A total of 8.5% (44) participants reported persistent symptoms from more than one category at the time of the follow-up assessment. Most commonly co-occurring categories were fatigue and sleep problems in 1.9% (10) of children, and fatigue and sensory problems were present in 1.5% (8) of participants. 2.7% (14) of children had persistent symptoms from three or more different categories. The scores on the wellness scale for children with one or two or more persistent symptoms significantly declined when compared to before COVID-19 onset from 90 (80-100) to 82.5 (70-93.8) and from 90 (80-95) to 70 (60-80) ($p<0.001$ for all comparisons), respectively. Children who did not experience any persistent symptoms did not report any significant changes in wellness when asked to compare to how they felt before their acute COVID-19 illness. Parents related the following changes to COVID-19 illness, and not to the pandemic in general: less eating in 4.5% (23/512) of children, less sleeping in 3.5% (18/511) and more sleeping in 2% (10/511), reduced physical activity in 4.7% (24/512) and child becoming less emotional in 4.3% (22/511). In contrast, parents attributed changes to social activities to the pandemic in general rather than to the COVID-19 illness: 12% (58/485) of children were spending less time with their friends in person, while 13% (61/470) were spending more time with friends remotely, with less than one percent of parents attributing these changes to COVID-19 illness. 23% (110/478) of children were spending more time watching television, playing video/computer games or using social media for educational purposes, with 92.9% of parents associating these changes with the pandemic in general rather than the COVID-19 illness.

	In multivariable regression analysis, older age group was associated with persistent symptoms. When compared with children under two years of ages, those ages 6-11 years had an odds ratio of 2.74 (95% confidence interval 1.37 to 5.75) of persistent symptoms and those 12-18 years of age (OR 2.68, 95% CI 1.41 to 5.4) both vs. <2 years. Another predictor associated with persistent symptoms was allergic diseases (OR 1.67, 95% CI 1.04 to 2.67). Similar patterns were seen for children with co-existence of persistent symptoms from 2 or more categories: 6-11 years of age (OR 2.49, 95% CI 1.02 to 6.72), 12-18 years of age (OR 3.18, 95% CI 1.43 to 8.11) both vs. <2 years. They ran an additional regression analyses, using “age” as a continuous variable which brought similar result. When subgroup analyses were performed in the age group of six years and above, severe acute COVID-19 was associated with persistent symptoms (OR 6.14, 95% CI 1.27 to 43.94) and excessive weight and obesity with co-existence of persistent symptoms from 2 or more categories (OR 2.89, 95% CI 1.12 to 7.15). They found that a quarter of children and adolescents had persistent symptoms at the time of the follow-up with fatigue, sleep disturbance and sensory problems being the most common. Almost one in ten reported multi-system impacts with two or more categories of persistent symptoms at the time of the follow-up. Children in mid-childhood and adolescence (age 6-18) were at higher risk of persistent symptoms at the time of the follow-up. Although prevalence of symptoms declined over time, a substantial proportion experienced problems many months after discharge. Although many children experienced symptoms, such as fatigue, disturbed smell and taste, sleep and respiratory problems, hair loss and headaches at the time of the hospital discharge, they witnessed a steady decline in the symptom prevalence over time. This was particularly evident for fatigue and smell disturbance. Prevalence of some symptoms such as headache, and sleep problems declined slower, which may be driven by psychological mechanisms rather than pathophysiologic virus infection effects. They found that almost one in ten children had multisystem impacts with two or more categories of persistent symptoms present at the time of the follow-up. Age was significantly associated with persistent symptom presence at the time of the follow-up, with children above 6 years of age being at higher risk. They also found that in children of six years of age and above, severe acute COVID-19 was associated with persistent symptoms and excessive weight and obesity with multisystem involvement, but confidence intervals were wide and these findings require confirmation on a larger sample size to make any firm conclusions. They found that allergic diseases in children were also associated with a higher risk of long COVID-19. Apart from physical symptoms we assessed emotional and behavioural changes. Although most parents reported no

changes, one in twenty parents noticed changes in their children, which they attributed to COVID-19 illness rather than the general situation during the pandemic. These included changes in eating, sleeping, emotional wellbeing and physical activities. Over one in ten parents noted that their children were spending less time in face-to-face communication and more time interacting with their friends remotely and spending time online for both educational and non-educational purposes. These changes were largely attributed to the general situation during the pandemic rather than to the COVID-19 illness.

Pre-existing conditions of children with long-COVID-19, N=518, prospective cohort study, median age 10.4 years

Condition	Percentage of children who had it
≥1 pre-existing condition	44.7%
Allergic diseases (any)	23.5%
Food Allergy	13%
Gastrointestinal problems	9.3%
Allergic Rhinitis	8.9%
Neurological conditions	8.8%
Eczema	8.8%
Neurological disorders	8.4%
Excessive weight and obesity	4.9%
Heart diseases	4.1%
Renal/Kidney problems	3.5%
Respiratory diseases (not including asthma)	3.1%
Other endocrine illness (not diabetes)	2.3%
Asthma	2.3%
Neurodisability	2.1%
Haematological conditions	1.9%
Malnutrition	1.9%
Tuberculosis	1.8%

Other skin problems (not including eczema)	1.6%
Genetic conditions	1.2%
Immune system diseases	1.2%
Anxiety	1%
Depression	0.8%
Rheumatological conditions	0.8%
Diabetes	0.6%
Oncological conditions	0.6%

Signs and symptoms, most common at the top, N=518, prospective cohort study, median age 10.4 years, reported at 5 to 10 months

Sign/symptom	Percentage who experienced it
Fatigue	10.69%
Insomnia	5.19%
Disturbed smell	4.71%
Headache	3.5%
Disturbed taste	3.42%
Tiredness and weakness/ hypersomnia	2.99%
Hyperhidrosis	2.59%
Poor appetite	2.4%
Problems seeing/blurred vision	2.09%
Abdominal pain	2%
Diarrhoea	2%
Nasal congestion/	1.98%
Hair loss	1.8%
Skin rash/ red welts	1.61%
Constipation	1.6%
Loss of smell	1.5%
Short of breath	1.39%
Variations in heart rate	1.22%
Joint pains	1.22%
Nausea	1.2%
Palpitations	1.06%
Dizziness/ light headedness	1.03%
Persistent cough	0.99%

Muscle aches and pains	0.82%
Vomiting	0.8%
Chest pain	0.62%
Urination problems	0.6%
Tremor/ twitching	0.6%
Changes in menstruation	0.6%
Loss of taste	0.43%
“Pins and needles“	0.42%
Pain on breathing	0.41%
Lack of concentration/ delirium	0.41%
Cannot fully control movement	0.4%
Problems with balance	0.4%
Conjunctivitis/ sore eyes	0.4%
Bleeding	0.2%
Problems speaking or communicating	0.2%
Problems swallowing or chewing	0.2%
Lumps or rashes (purple/pink) on toes	0.2%
Fainting/ blackouts	0%
Seizures/fits	0%
Weight loss	0%

Source of funding	This study did not have external funding.
Study limitations (Author)	This cohort study has several limitations. First, the study population only included patients within Moscow, although regional clustering is common to many cohort studies published during the COVID-19 pandemic. Second, it included only hospitalised children, not representative of paediatric population. Third, we did not have a control group of previously hospitalised children not experiencing COVID-19 infection. Fourth, some patients may have developed additional comorbidities or complications since the hospital discharge, which were not appropriately captured and could potentially affect the wellbeing and symptom prevalence and persistence. Fifth, the parents/caregivers were interviewed in this study and not children themselves. There is also a risk of selection bias due to recruitment of the hospitalised population and recall bias in reporting symptoms which were non-existent at the time of the follow-up and potential selection bias with those with symptoms more likely to agree to survey. The reality of conducting research in outbreak conditions do not allow for appropriate co-enrolment of a control group, which is not practical. One of the issues which has not been addressed so far in clinical research is what control group of individuals admitted to hospital during this period when hospitals were overwhelmed with COVID-19 cases could provide a valid control group. The design

	of this study allows only to describe the feature of COVID-19 survivors and cannot involve a control group. A limitation of these findings is that symptom onset and duration was recalled at the single follow-up interview in our study; this may be overcome with repeated follow-ups at appropriate intervals to limit potential recall imprecision.
Study limitations (Reviewer)	39% of the children were lost to follow-up. This is a fairly high number considering that participants were called 3 times before being considered lost to follow-up. There could have been sometime different about those lost to follow-up. For example, they may have had mild or few symptoms, which the parents or children considered not worth discussing. The follow-up timepoints were not defined. Therefore, it is difficult to gauge how retrospective some of the data collection was. A long follow-up time would mean that the study was at risk of recall bias.

Study arms
Children admitted to hospital with COVID-19 (N = 853)

Characteristics
Study-level characteristics

Characteristic	Study (N = 853)
Age (years) median Nominal	10.4
Gender (%) % Female Nominal	52.2

Osmanov Ismail et al.

Bibliographic Reference	Osmanov Ismail, M; Spiridonova, Ekaterina; Bobkova, Polina; Gamirova, Aysylu; Shikhaleva, Anastasia; Andreeva, Margarita; Blyuss, Oleg; Taravi Yasmin, El-Taravi; DunnGalvin, Audrey; Comberiati, Pasquale; Peroni Diego, G; Apfelbacher, Christian; Genuneit, Jon; Mazankova, Lyudmila; Miroshina, Alexandra; Chistyakova, Evgeniya; Samitova, Elmira; Borzakova, Svetlana; Bondarenko, Elena; Korsunskiy Anatoliy, A; Konova, Irina; Hanson Sarah, Wulf; Carson, Gail; Sigfrid, Louise; Scott Janet, T; Greenhawt, Matthew; Whittaker Elizabeth, A; Garralda, Elena; Swann, Olivia; Buonsenso, Danilo; Nicholls Dasha, E; Simpson, Frances; Jones, Christina; Semple Malcolm, G; Warner John, O; Vos, Theo; Olliaro, Piero; Munblit, Daniel; Team - Sechenov StopCOVID, Research; Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study; medrxiv preprint

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	Yes
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	Can't tell *(The follow-up timepoints were not defined.)*
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Not applicable
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	No *(There was a dropout rate of 39%.)*
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Can't tell *(The follow-up timepoints were not defined.)*
(B) What are the results?	7. What are the results of this study?	See data above.
(B) What are the results?	8. How precise are the results?	See data above.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See data above.
Overall bias	Overall risk of bias	High *(The follow-up timepoints were not defined and the dropout rate was 39%.)*

Penner 2021 (in review questions 2 and 3)

Bibliographic Reference	Penner, Justin; Abdel-Mannan, Omar; Grant, Karlie; Maillard, Sue; Kucera, Filip; Hassell, Jane; Eyre, Michael; Berger, Zoe; Hacohen, Yael; Moshal, Karyn; GOSH PIMS-TS MDT, Group; 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study.; The Lancet. Child & adolescent health; 2021

Study details

Study design	Retrospective cohort study
Study start date	04-Apr-2021
Study end date	01-Sep-2020
Aim of the study	To analyse 6-month outcomes in a cohort of paediatric patients with paediatric inflammatory multisystem syndrome (PIMS-TS) treated at a large tertiary paediatric hospital in the UK. PIMS-TS is also known as multisystem inflammatory syndrome in children (MIS-C).
Country/ Geographical location	UK
Study setting	Hospital and after discharge.
Population description	Children who had been diagnosed with COVID-19 and who had been admitted to hospital.
Inclusion criteria	Patients aged 18 years or younger, fulfilling the UK Royal College of Paediatrics and Child Health (RCPCH) diagnostic criteria for PIMS-TS, and admitted to Great Ormond Street Hospital, London, UK, between April 4 and Sept 1, 2020, were included in this cohort study.
Exclusion criteria	Patients not fulfilling the UK Royal College of Paediatrics and Child Health (RCPCH) diagnostic criteria for PIMS-TS.
Intervention/test/approach	Patients were prospectively reviewed by multiple specialties in a PIMS-TS multidisciplinary outpatient clinic that had been set up in May, 2020. A new ward-based day-case service was established to accommodate sequential reviews and investigations by multiple specialties. Patients were seen by the multidisciplinary team at a minimum of two further timepoints after discharge from hospital: at 6 weeks and 6 months. Electronic clinical records were reviewed by two investigators who collected baseline and follow-up data. Recent SARS-CoV-2 infection was confirmed by RT-PCR of nasopharyngeal samples, positive serology, a clear epidemiological link to an infected contact, or a combination of the above. Serology testing evaluated IgG antibodies to the SARS-CoV-2 nucleocapsid protein and, from June, 2020, to the spike protein. After June, 2020, anti-spike protein antibody tests were done on all patients presenting with PIMS-TS. Retrospective analysis of patients with negative nucleocapsid antibody results was done on available stored samples. Follow-up serological assays were done on the anti-spike assay. All echocardiogram reports were reviewed by senior paediatric cardiologists. Abnormal echocardiogram results at presentation and follow-up were defined as: coronary artery aneurysms or dilatation (Z-score >2), pericardial inflammation,

	abnormal ventricular function (ejection fraction <0·55 or visualised hypokinesis), significant valvulopathy, or a combination of the above. Abnormal abdominal ultrasound or CT results were defined as: inflammatory liver changes, hepatosplenomegaly, ileocolitis, or significant peritoneal lymphadenopathy, or a combination of the above. Various outcomes were assessed by physicians and therapists at 6 months; here, we list the outcomes assessed as part of this study. The Expanded Disability Status Scale (range 0–10, with higher levels indicating higher levels of disability) was calculated by a senior paediatric neurologist. The 6-min walk test and the manual muscle test-8 (scored out of 80, with higher scores indicating better strength) were carried out by two senior physiotherapists. Published normative values from healthy child and adolescent controls were used to group the patient scores into centiles.8 Patient-reported outcome measures were assessed via the PedsQL 4.0 Generic Core Scales, which provide measures of physical, emotional, social, and school functioning. Patients were considered to have mild problems if scores fell between one and two SDs below the population mean, or severe problems if scores were more than two SDs below the population mean. For the Paediatric Index of Emotional Distress, a clinical cut-off score of 20 identified those patients who required further clinical assessment and intervention. Structured interviews were also done, asking parents or guardians the following questions: did they have concerns about a PIMS-TS relapse in their child? Have they taken any additional isolation precautions beyond current UK Government guidance? Did they feel that their child was vulnerable medically due to PIMS-TS? And would they (the parent or guardian only, not the child) be willing to be vaccinated with a COVID-19 vaccine once available?
Comparator (where applicable)	None
Methods for population selection/allocation	See inclusion criteria.
Methods of data analysis	Descriptive statistics were used to summarise key clinical, laboratory, and radiological features. Non-parametric statistical tests (Mann–Whitney U and Kruskal Wallis) were used for continuous distributions (age, body mass index [BMI], laboratory investigations, duration of mechanical ventilation and inotropic support, and duration of hospital stay), as appropriate given normality, and χ^2 or Fisher's exact tests were used for nominal data (sex, ethnicity, SARS-CoV-2 PCR and serology positivity, proportion of patients with proteinuria, hypertension, raised retinol binding protein [RBP]-to-creatinine ratio, abnormal faecal calprotectin, echocardiogram, abdominal imaging, evidence of thrombus on doppler ultrasound, ventilation and inotrope requirement, and

	treatment with methylprednisolone, intravenous immunoglobulin, or anakinra). Comparisons were made between patients aged 12 years and younger versus those older than 12 years, and patients with and without neurological findings.
Attrition/loss to follow-up	1 patient was lost to follow-up before the 6-week follow-up.
Summary of results	46 patients were included in this study. Median age at presentation was 10·2 years (IQR 8·8–13·3), 30 (65%) patients were male and 16 (35%) were female. 37 (80%) were from minority ethnic groups: 16 (35%) African-Caribbean, 11 (24%) South Asian, and ten (22%) from other backgrounds. The median duration of symptoms before initial treatment was 7·0 days (IQR 5·0–8·3). No differences in baseline clinical features were detected between patients aged 12 years and younger and those older than 12 years. Eight (17%) patients had comorbidities: four with autism, two with sickle-cell disease, one with asthma, one with type 1 diabetes, and one with spina bifida; one patient had both autism and sickle-cell disease. All patients had elevated markers of systemic inflammation at baseline. 12 (27%) of 45 had a positive SARS-CoV-2 PCR test on admission. 36 (86%) of 42 patients initially tested for SARS-CoV-2 IgG serology were positive, and one had an equivocal result. Two patients were neither PCR positive nor serology positive, but they had household contacts with COVID-19, thus meeting RCPCH diagnostic criteria. Nine (25%) of 36 patients had evidence of Epstein-Barr virus co-infection by PCR, either primary or reactivation, one of which progressed to haemophagocytic lymphohistiocytosis after PIMS-TS in a biphasic illness course. 15 (33%) of 46 children were found to have significant abnormalities on initial echocardiogram. 22 (48%) of 46 required inotropic support. One patient required extracorporeal membrane oxygenation. 38 (84%) of 45 patients had raised troponin and 31 (86%) of 36 had raised N-terminal pro-brain natriuretic peptide (NT-proBNP). 24 (52%) of 46 patients had neurological involvement at presentation. Symptoms reported were headaches (n=24), dysarthria or dysphonia (n=6), visual or auditory hallucinations (n=6), unsteady gait (n=5), and seizures (n=1; secondary to posterior reversible encephalopathy syndrome after steroid administration). Neurological abnormalities were encephalopathy or delirium (n=14), ataxia (n=4), peripheral neuropathy (n=3), abnormal eye movements or saccades (n=2), and facial asymmetry or weakness (n=1). Encephalopathy and hallucinations were present before intensive care admission and treatment with corticosteroids in all 24 patients. Seven (44%) of 16 patients who underwent

	neuroimaging (MRI scans of the brain with or without the spine) had abnormalities: splenial signal changes (n=4), microhaemorrhages (n=3), subcortical parietal white matter lesions (n=3), leptomeningeal enhancement (n=1), and cerebral oedema (n=1). 14 (93%) of 15 patients who underwent electroencephalography (EEG) had an excess of slow wave activity (ranging from mild to severe encephalopathy). Mild myopathic and neuropathic changes were seen in four of seven patients who underwent nerve conduction studies and electromyography (EMG). Children with neurological involvement were more likely to be ventilated (p=0·0060), for a longer duration (p=0·010), and require inotropic support (p=0·030), and have higher D-dimers at presentation (p=0·047). Renal involvement (raised creatinine, proteinuria, hypoalbuminaemia, or a combination of the above) was present in 42 (91%) of 46 patients during hospital stay. None required renal replacement therapy. Gastrointestinal involvement (abdominal pain, diarrhoea or vomiting, or abnormal abdominal imaging) was present in 45 (98%) of 46 patients before or during hospital stay. Nine (33%) of 27 patients who had abdominal imaging during admission had clinically significant abnormalities. Four (9%) of 46 patients were overweight (BMI >25 kg/m²) and median BMI was 18·4 kg/m² (IQR 16·7–21·6). Total 25-hydroxyvitamin D concentrations were insufficient (<50 nmol/L) in 33 (87%) of 38 patients, with a median of 21 nmol/L (IQR 14–43). Evidence of a prothrombotic state (raised fibrinogen or thrombi on doppler studies, or both) was present in 40 (87%) of 46 patients during hospital stay. Two (4%) of 46 patients had thrombi (unprovoked vena cava in one and line-associated internal jugular in the other). No pulmonary emboli were reported. 29 (63%) of 46 patients reported upper or lower respiratory symptoms, or both (cough, coryza, pharyngitis, or dyspnoea) before or during hospital stay. 16 (35%) of 46 patients needed mechanical ventilation, although the duration was typically short. 22 (48%) of 46 patients had dysphonia, anosmia, or dysphagia, or a combination of the above symptoms, at presentation before or during hospital stay. Dermatological or mucous membrane involvement (polymorphous rash, conjunctivital injection, or erythematous mucous membranes) was present in 39 (85%) of 46 patients before or during hospital stay.

	Patients showed improvement in both inflammatory markers (figure 2) and systems involvement at 6 weeks and 6 months of follow-up. There were no deaths. Three patients were re-admitted to hospital (four hospital admissions in total): one for PIMS-TS relapse with new-onset encephalopathy treated with steroids and intravenous immunoglobulin, and three for infectious complications (pneumonia, urosepsis, and skin and soft tissue infection). All 42 patients who underwent RT-PCR testing were negative for SARS-CoV-2 at 6 weeks, as were all eight tested at 6 months. 38 (90%) of 42 patients who had positive serology within 6 weeks remained seropositive at 6 months. One patient who was RT-PCR positive on multiple occasions at baseline never seroconverted, while one patient seroconverted between 6 weeks and 6 months. Four patients were antibody negative at 6 months after previously developing antibodies to SARS-CoV-2 (one was on rituximab treatment). Four patients continued to have low-level serum Epstein-Barr virus PCR titres at 6 months. At 6 months, and a minimum of 4 months off immunosuppression, 17 (39%) of 44 patients had persistently abnormal lymphocyte subsets; most notably, 13 (30%) of 44 had increased γδ cells, two (5%) also had elevated double negative T cells, and four (9%) had persistently low naive T cells. Systolic function and concentrations of troponin and NT-proBNP were normal in all patients by 6 months. By 6 months, echocardiograms in 44 (96%) of 46 patients had normalised. At 6 weeks, one patient had large coronary artery aneurysms (maximum Z-score 9·18), which remained stable at 6 months but required dual antiplatelet therapy, and one had a residual clinically insignificant pericardial effusion. One patient with underlying sickle-cell disease had marginally enlarged coronaries at 6 months (maximum Z-score 2·9), which were treated with aspirin and less evident at 6 weeks than at 6 months. At 6 weeks, 24 (52%) of 46 patients had abnormal neurological examinations: proximal myopathy or lower limb weakness (n=18), bilateral or unilateral dysmetria (n=16), abnormal eye movements or saccades (n=15), abnormal posturing (n=9), difficulty in tandem walking (n=6), hyper-reflexia (n=5), hyporeflexia (n=4), upgoing plantars (n=2), facial weakness (n=2), sensory abnormalities (n=2), and upper limb weakness (n=1). At 6 months, 18 (39%) of 46 patients had abnormal neurological examinations: bilateral or unilateral dysmetria (n=12), hyper-reflexia (n=9), proximal myopathy or

	lower limb weakness (n=8), abnormal eye movements or saccades (n=7), difficulty in tandem walking (n=4), abnormal posturing (n=3), hyporeflexia (n=2), upgoing plantars (n=2), sensory abnormalities (n=2), facial weakness (n=1), and upper limb weakness (n=1). The median Expanded Disability Status Scale score at 6 months was 0 (IQR 0–1; range 0·0–6·5). Only three of 15 patients who underwent EEG at 6 weeks had a mild excess of slow activity. At 6 months, no abnormalities were reported in three patients who had further EEGs. Three of four patients who underwent nerve conduction studies or an EMG at 6 weeks had abnormalities: severe axonal motor and sensory neuropathy (affecting peroneal and tibial nerves), mild or borderline axonal neuropathy, and denervation change in thyroarytenoid and cricoarytenoid. One patient had an EMG at 6 months, showing a mild non-length-dependent demyelinating neuropathy affecting the upper limbs. Creatinine universally normalised during follow-up. Proteinuria on urinalysis was found in four (9%) of 43 children tested at 6 weeks and in one (2%) of 44 at 6 months, with hypoalbuminaemia in another patient. At 6 weeks, two (5%) of 40 patients had a marginally raised urinary RBP-to-creatinine ratio, three (7%) of 42 had raised blood pressure above the 95th centile for their sex, age, and height, and two (5%) of 42 had raised blood pressure above the 99th centile. At 6 months, four (10%) of 42 patients had raised blood pressure above the 95th centile and none had raised blood pressure above the 99th centile. One patient with elevated blood pressure at 6 weeks was maintained on amlodipine. Persistent gastrointestinal symptoms with or without raised faecal calprotectin were reported in six (13%) of 46 patients at 6 months. Persistent abdominal pain was reported in four (9%) of 46 patients at 6 weeks and in three (7%) of 46 patients at 6 months. One patient had persistent diarrhoea for 6 months. One patient reported new-onset nausea and vomiting and one reported new onset diarrhoea at 6 months only. Faecal calprotectin was raised in ten (31%) of 32 children at 6 weeks and in one (7%) of 15 at 6 months. Four (20%) of 20 patients undergoing abdominal imaging had abnormalities reported at 6 weeks (one with persistent transverse colitis, one with ileitis, one with inflammatory liver changes, and one with splenomegaly), and splenomegaly persisted in one patient at 6 months. One patient underwent colonoscopy and gastroscopy, which showed patchy chronic inflammatory changes with increased lamina propria eosinophil density throughout the colon and ileum. Liver enzymes typically increased for up to 6 weeks before decreasing. Median BMI increased from 18 kg/m² (IQR 17–22) to 20 kg/m² (19–23) at 6 weeks, and 21 kg/m² (19–23) at 6 months. After supplementation (400–1000

	IU per day, depending on degree of deficiency), total 25-hydroxyvitamin D concentrations increased from 23 nmol/L (IQR 14–44) to 66 nmol/L (36–83) at 6 weeks and to 69 nmol/L (45–88) at 6 months. Both patients with thrombi completed a course of anticoagulation (one with dalteparin and the other with rivaroxaban) without any concerns. Fibrinogen concentrations typically normalised by 6 weeks and remained normal at 6 months. Only one patient had abnormal carbon monoxide gas transfer after correction for alveolar volume. Otherwise, the remaining 18 patients who met the criteria for follow-up testing had spirometry and plethysmography values within normal limits. At 6 weeks, self-reported symptoms were dysphonia (n=6), anosmia or dysgeusia (n=2), and dysphagia (n=1). Ear, nose, and throat (ENT) and speech and language therapy manifestations largely resolved by 6 months, with dysphonia in four children and anosmia or dysgeusia in two children, without clinically significant objective findings. One patient required ongoing voice therapy at 6 months following hyaluronic acid injection into the right vocal fold after presumed iatrogenic injury from extracorporeal membrane oxygenation. No abnormalities in the cribriform plate or olfactory tract were found on imaging of patients with anosmia. Three distinct rashes (hypopigmented [n=1], erythematous maculopapular [n=1], and dermographism [n=1]) were reported during follow-up in three patients, all thought to be unrelated to PIMS-TS. There were no cases of ongoing mucosal changes. The 6-min walk test done at 6 weeks showed that 20 (65%) of 31 patients walked less than the 3rd centile expected distance for their age and sex (table 3). At 6 months, 18 (45%) of 40 patients were below the 3rd centile. The median manual muscle test-8 score was 53 (IQR 43–64) at baseline and rose to 73 (65–78) at 6 weeks and to 80 (68–80) at 6 months. PedsQL responses revealed severe difficulties in physical functioning by parental report in five (13%) of 38 children and by self report in three (8%) children. PedsQL responses across emotional, social, school, and psychosocial dimensions are shown in table 4. Emotional lability was reported in 12 (26%) of 46 patients at 6 weeks and in seven (15%) of 46 patients at 6 months. The median Paediatric Index of Emotional Distress score at 6 months was 6 (IQR 5–13), with three (7%) of 46 patients scoring above the clinical cutoff of 20, indicating a risk of clinically significant emotional distress. From the structured interview, 14 (31%) of 45 parents reported anxiety about a possible PIMS-TS relapse in their child, ten (22%) of 45 reported concerns about medical

	vulnerability of their child as a result of admission to hospital with PIMS-TS, and nine (20%) of 45 reported taking additional isolation precautions beyond UK Government guidance. 33 (73%) of 45 parents expressed sentiments of SARS-CoV-2 vaccine hesitancy. 45 (98%) of 46 patients were back in full-time education by 6 months (virtually or face to face). There was over-representation of ethnic minority groups; however, age and sex did not affect the clinical phenotype. Increased rates of ventilation were secondary to fluid overload from vascular leak and a consequence of sedation requirements, and not generally due to respiratory involvement. No patient died within 6 months, but many had residual new deficits. The majority of patients had severe multisystem involvement during their initial illness including gastrointestinal (98%), neurological (52%), and echo abnormalities (33%), which mostly resolved by 6 months. At the 6-month follow-up, common sequelae included muscular fatigue; neurological sequelae such as proximal myopathy, dysmetria, and abnormal saccades; and anxiety and emotional lability. Biochemical markers or inflammation resolved, and SARS-CoV-2 serology status remained positive in most patients, despite immunosuppression.
Source of funding	The authors stated that there was no funding source for this study.
Study limitations (Author)	Limitations of this study include the single-centre design with a possibility of referral bias of the most unwell patients with PIMS-TS (i.e., those requiring intensive care). Paediatric controls, both after PICU discharge for other illnesses as well as those unaffected by illness during the COVID-19 pandemic, were not available for comparison and thus the findings must be viewed as hypothesis generating. Similarly, baseline pre-illness testing was not available for analysis to determine functional changes after illness. The study is limited by the retrospective collection of clinically guided investigations, which accounts for variations in follow-up data among participants. Given the rarity of this condition, longer-term prospective multicentre studies would help to validate our findings and further our understanding of PIMS-TS.
Study limitations (Reviewer)	Nothing further to add.

Study arms
Children with COVID-19 who were admitted to hospital (N = 46)

Characteristics
Study-level characteristics

Characteristic	Study (N = 46)
Age (years) median Nominal	10.2
Gender (%) % Female Nominal	35
White (%) Nominal	20
South Asian (%) Nominal	24
African-Caribbean (%) Nominal	35
Other (%) Nominal	22

Penner, 2021

Bibliographic Reference	Penner, Justin; Abdel-Mannan, Omar; Grant, Karlie; Maillard, Sue; Kucera, Filip; Hassell, Jane; Eyre, Michael; Berger, Zoe; Hacohen, Yael; Moshal, Karyn; GOSH PIMS-TS MDT, Group; 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study.; The Lancet. Child & adolescent health; 2021

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	No *(This was a retrospective study and therefore prone to selection bias.)*
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	Yes
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	Yes
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Yes
(B) What are the results?	7. What are the results of this study?	See data above.
(B) What are the results?	8. How precise are the results?	See data above.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See data above.
Overall bias	Overall risk of bias	Moderate *(This was a retrospective study and therefore prone to selection bias.)*

Stephenson 2021 (in review questions 1, 2 and 3)

Bibliographic Reference	Stephenson T, Pereira SP, Shafran R, De Stavola B, Rojas N, McOwat K, Simmons R, Zavala M; Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study; Research Square pre-prints; 2021

Study details

Study design	Cohort studies
Study start date	01-Sep-2020
Study end date	31-Mar-2021
Aim of the study	To describe the signs, symptoms, and risk factors for COVID-19.
Country/ Geographical location	UK
Study setting	Young people aged between 11 and 17 years in England.
Population description	Young people aged 11 to 17 years who had the SARS-CoV-2 test.
Inclusion criteria	Between September 2020 and March 2021, 234,803 young people aged between 11 and 17 years tested positive for

	SARS-CoV-2 in England. During the same period, there were 1,481,154 negatives tests among this age-group from 1,203,996 children and young people (CYP) (some had more than one negative test). The 234,803 test-positive CYP were matched with some oversampling to negative CYP according to their age at test, gender, month of test, and lower super output area (geographical area of ~ 1500 people), resulting in 102,402 test-positive individuals and 147,561 matched, negative individuals.
Exclusion criteria	Among those who tested negative, 76,689 individuals (100,154 tests) were excluded as they had a positive result before or (up to 31 March 2021) after their negative test. Using secure procedures, matched individuals were checked against the NHS PDS to exclude individuals who had died and to extract participants' postal addresses. 37 individuals were excluded because they had died since their COVID-19 test (6 test-positives, 31 test-negatives), while 11,193 test-positive individuals and 19,251 test-negative individuals were excluded because a residential address was not available. Finally, 246 young people were excluded because they were included in a previous pilot study.
Intervention/test/approach	91,016 test-positive CYP and 128,220 negative CYP were contacted. A letter was posted to all those selected, inviting them to take part in this study using an online link which provided them with details of the study, an option to consent online and complete a short recruitment questionnaire. The investigators began contacting individuals from April 2021 onwards. In this paper, they focus on those who were tested in January-March 2021 because only they could report symptoms 3 months post-test with minimal recall bias of symptoms at time of testing. For this group, a total of 50,846 individuals (23,048 test-positives, 27,798 test-negatives) were invited to participate. Participants who were tested between January-March 2021 were contacted 3 months after testing. Following online informed consent, the CYP self-completed an online (or paper) questionnaire about their physical and mental health at the time of the original test ("baseline") and at the time of completing the questionnaire; younger CYP and CYP with special educational needs or disability could request the help of their carer. The completed questionnaires were returned at a median time of 14.9 weeks after testing [25th ,75th centiles: 13.1, 18.9]. A total of 63 test-negative CYP reported having had a previous positive SARS-CoV-2 test and were excluded from analysis.

	The first questionnaire sent to CYP included demographic characteristics, elements of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric COVID-19 follow-up questionnaire and the recent Mental Health of Children and Young people in England surveys (https://tinyurl.com/NHSWave1FU). The follow-up questionnaires were identical but did not include questions on demographic characteristics. They were designed together with ISARIC Paediatric Working Group to produce a harmonised data collection tool, to facilitate international comparisons regarding the risk factors and profile of Long COVID-19 in CYP. The elements taken from the ISARIC Paediatric COVID-19 follow-up questionnaire included questions about physical symptoms, particularly cough and fever (the main acute symptoms in non-hospitalised CYP and gastrointestinal symptoms which were commonly reported in seropositive CYP. Other symptoms which might manifest later in Long COVID-19 (e.g., tiredness, headaches, myalgia etc.) were also included. They asked CYP to rate their general physical and mental health before their SARS-CoV-2 test, in two separate questions using a 5 category Likert scale; in analyses we recoded these variables into two categories (very poor/poor/ok versus good/very good). To measure mental health and wellbeing, the Strengths and Difficulties Questionnaire (SDQ) was summarised into the total difficulties score that excluded the prosocial dimension, along with the short 7-item version of the Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS). A higher SDQ total difficulties score is indicative of more problems, whereas a higher SWEMWBS score indicates a higher level of mental well-being. Quality of life/functioning was measured via the EQ-5D-Y and fatigue was measured by the 11-item Chalder Fatigue Questionnaire (CFQ).
Methods for population selection/allocation	The original study design was based on the calculation that 5,000 participants (2,500 test-positives, 2,500 test-negatives) would have 80% power to detect at least a 4% difference in symptom frequency at 5% significance, if test-negative participants had a 34% prevalence (based on available data at the time from the sKIDs study, accounting for attrition and possible lower baseline symptom prevalence. However, studying multiple symptoms and identifying risk factors for Long COVID-19 requires a larger sample size. For this reason, they amended their calculations to invite all available participants in England (except those tested in December 2020 due to funding constraints at present).
Methods of data analysis	To assess the representativeness of our study participants they compared their demographic characteristics (sex, age, region of residence) to those of the target population. The participants' demographic characteristics, physical symptoms

	at “baseline”, and physical symptoms, mental health status, well-being, quality of life/functioning, and fatigue 3-months post-test were compared by SARSCoV-2 test status. They carried out comparisons separately by age-groups (11-15y vs. 16-17y) as the prevalence of Long COVID-19 may vary by age (https://tinyurl.com/ONSPrevalence0721). They used latent class analysis to assess whether and how baseline and 3-month physical symptoms clustered among CYP, allowing for differential model parametrisation by SARS-CoV-2 test status (while analysing the data jointly by test status but separately by time). The number of classes was selected by comparing the Bayesian Information Criteria. Predicted class membership was estimated and used to assign CYP to their most likely class; this classification was then used to describe the characteristics of the latent classes. As this is mainly a descriptive study, we do not report p-values for comparisons by SARS-CoV-2 test status. They do report estimates of latent class prevalence by SARS-CoV-2 test status, as well as their ratio, with confidence intervals computed using the delta method21. To assess the impact of potential response bias, they reweighted all symptom frequencies according to the age, sex, region and SARS-CoV-2 test status of the responders.
Summary of results	**Study representativeness** A total of 6,804 CYP who had been tested between January and March 2021 participated in the study by completing the 3-month questionnaire. The overall response rate was 13.4%, with a similar proportion of test-positives (13.3%) and test-negatives (13.5%) contributing. More females and older CYP (16-17-year-olds) responded. Response rates also varied by region of England. Overall, there was little difference in demographic characteristics between test-positive and test-negative participants, reflecting the matched study design. **Physical symptoms and profile: baseline and 3-month post-test** At the time of testing, test-positive CYP had higher percentages of physical symptoms compared to test negative CYP; 35.4% of test-positives and 8.3% of test-negatives had any symptoms whilst 30.6% of test-positives and 6.2% of test-negatives had 3+ symptoms. The types of symptoms reported by test-positives and negatives were the same in the two age-groups: the most common symptoms among test-positives were sore throat, headache, tiredness and loss of smell while test-negatives had sore throat, headache, fever and persistent cough. The prevalence of these symptoms, however, varied by

SARS-CoV-2 test result (e.g. 26.3% of positives compared to 4.8% of negatives reported headaches).

Three months after the SARS-CoV-2 test, the presence of physical symptoms was higher than at baseline in both groups; 66.5% of test-positives and 53.4% of test-negatives had any symptoms whilst 30.3% of test-positives and 16.2% of test-negatives had 3+ symptoms. The symptom profile did not vary by age: for both 11-15y and 16-17y the most common symptoms among test-positives were tiredness, headache and shortness of breath and, among test-negatives, tiredness, headache and the unspecified category of "other". Again, the prevalence of tiredness and headache was consistently higher in the test positives, 39.0% and 23.2% versus 24.4% and 14.2% in negatives, respectively. Prevalence was higher for 16-17-year-olds; for example, 46.4% of test-positives reported being tired compared to 29.6% of test-negatives.

When they reweighted the percentage of reported symptoms at baseline and at 3 months post-test, broadly similar patterns were observed to those reported above.

Signs and symptoms, most common at the top, N=3065, retrospective case-control, age 11-17 years, reported at 3 months

Sign/symptom	Percentage who experienced it
Tiredness and weakness/ hypersomnia	39%
Short of breath	23.4%
Headache	23.2%
Dizziness/ light headedness	13.7%
Loss of smell	13.5%
Skipped meals	9.7%
Sore throat	9.5%
Chills	8.8%
Chest pain	7.1%
Lack of concentration/ delirium	6.5%
Earache or	6.2%
Conjunctivitis/ sore eyes	5.9%
Muscle aches and pains	5.4%
Abdominal pain	3.9%
Persistent cough	3.2%
Diarrhoea	3%
Fever	1.6%
Skin rash/ red welts	1.6%

Lumps or rashes (purple/pink) on toes	1.1%

Mental health, well-being, quality of life/functioning and fatigue 3-month post-test

There was no difference in the distribution of mental health scores (assessed by the SDQ total difficulties scores) and well-being (assessed by SWEMBS) between test positives and negatives, overall or in either age-group. The SDQ median (25th,75th centile) was 10 (6,15) for both test-positive and test-negative CYP aged 11-15y. For CYP aged 16-17y, the corresponding values were 11 (7,16) for test-positives and 12 (8,16) for test-negatives. Likewise, SWEMBS scores were similar among test-positives (Mean=21.5, SD=4.3) and test-negatives (Mean=21.4, SD=4.3). Similarly, fatigue (assessed by CFQ) showed no substantial differences between positives (Mean=13.3, SD=5.2) and negatives (Mean=12.5, SD=5.1).

However, older CYP (16-17y) did report slightly higher values: test-positives (Mean=14.0, SD=5.5) and test-negatives (Mean=13.4, SD=5.2). In terms of Health-Related Quality of Life (EQ-5D-Y) test positives in both age groups were more likely to report problems with mobility, doing usual activities, and pain/discomfort. Strikingly, while 40.8% of positives felt worried, sad or unhappy on the single item of the EQ-5D-Y, 39.2% of the negatives also reported feeling this way.

Physical symptom clustering at baseline and 3-months post-test

No evidence of clustering of baseline symptoms was found for either test-positive or test-negative participants. There was, however, evidence of clustering in symptoms reported at 3 months, with two subgroups emerging for both test-positive and test-negative CYP. In each, the largest subgroup (class 1) had very low prevalence of most symptoms, while the second subgroup (class 2) was characterised in both positives and negatives by multiple symptoms dominated by tiredness, headache, shortness of breath and dizziness. They refer to these classes as “few” and “multiple” symptoms classes.

The estimated probability (risk) of being in the multiple symptom class (class 2) was 29.6% (95% confidence interval, 27.4%, 31.7%) for test-positives and 19.3% (17.7%, 21.0%) for test-negatives and the risk ratio of being in class 2 versus class 1 comparing test-positives to test-negatives was 1.53 (1.35, 1.70).

For both test-positive and test-negative CYP, those assigned to class 2 were more likely to be female, older, to have poorer baseline physical and mental health (relative to the overall percentages of 19% and 30%) and, at 3-months, to be more

	likely to have problems with mobility, self-care, usual activities and pain/discomfort. They also have higher SDQ total difficulties and CFS scores, and lower SWEMBS scores.
Source of funding	National Institute for Health Research (NIHR), UK Research & Innovation (UKRI). NIHR Great Ormond Street Hospital Biomedical Research Centre.
Study limitations (Author)	This study has limitations. PCR-testing can result in some false negative and false positive results and they were unable to independently determine whether the test-negatives had previously had COVID-19 unless they had been tested although this is likely to account for only a minority of cases. They could not recruit based on ethnicity as this was not recorded at time of test but ethnicity was very similar in test-positives and negatives and geographical region served as a proxy for socio-economic status; both these variables are thought to influence COVID-19 in adults and could be important in Long COVID-19. As in any self-selected online study, the investigators acknowledged their response rate of 13.5%. It is possible that there is a response bias for example, towards those continuing to experience symptoms at 3 months being more motivated to participate, resulting in an over-representation of symptom prevalence. It is also possible that recall bias influenced the reporting of symptoms at the time of testing as well as physical and mental health prior to testing, in particular, if tested positive. However, they tried to minimise the impact of this bias by only considering CYP that reported on baseline ~ 3 months later. They did not assess whether symptoms were continuous for the entire 3 months, or whether they waxed and waned. Finally, the experiences of the CYP in January, February and March were likely to be highly varied with regard to school closure. At the time of testing, schools were closed, while, at 3 months after testing, schools had reopened albeit with social distancing, repeated testing and restriction of activities. Schools can be a source of both stress and support, and the return to school may partly explain some of the findings, in particular, the higher prevalence of symptoms at 3 months compared to baseline. The responders are largely representative of our target population though we have over-representation of girls and older CYP, with under-representation from North-West England and London. Inclusion of the comparator group was essential to place the findings within the wider context of the pandemic. These data also reflect symptomatology at a time when the Alpha variant was predominant in the UK. Whilst these findings may change with different variants, the prospective nature of this study makes it uniquely placed to detect such changes across the pandemic waves.
Study limitations (Reviewer)	Participants were self-selected so they might not be representative of the general population. For example, they might have had more symptoms or more severe symptoms

	and therefore could have been more motivated to participate. The response rate was 13.3%, which is very low. It is possible that the people who did not participate had fewer or more mild symptoms and therefore felt that it was not worth participating. The authors did not report when the symptoms occurred in relation to when data was collected. Therefore, there could have been some recall bias.

Characteristics

Study-level characteristics

Characteristic	Study (N = 3065)
Age 11-15 years (number)	1721
Age 16-17 years (number)	1344
Gender (%) % Female Nominal	63.46

Stephenson T, Pereira SP, Shafran R, De Stavola B, Rojas N, McOwat K, Simmons R, Zavala M, 2021

Bibliographic Reference	Stephenson T, Pereira SP, Shafran R, De Stavola B, Rojas N, McOwat K, Simmons R, Zavala M; Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study; Research Square pre-prints; 2021

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	No *(Participants were self-selected, and response rate was 13.3%.)*
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	Can't tell *(We do not know exactly when the symptoms occurred – there could be some recall bias.)*
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Not applicable
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	Yes
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Yes
(B) What are the results?	7. What are the results of this study?	See information above.
(B) What are the results?	8. How precise are the results?	See information above.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See information above.
Overall bias	Overall risk of bias	High *(Participants were self-selected, and response rate was 13.3%. Don't exactly know when the symptoms occurred – could be some recall bias.)*

Sterky 2021 (in review questions 2 and 3)

Bibliographic Reference	Sterky, Ellinor; Olsson-Akefeldt, Selma; Hertting, Olof; Herlenius, Eric; Alfven, Tobias; Ryd Rinder, Malin; Rhedin, Samuel; Hildenwall, Helena; Persistent symptoms in Swedish children after hospitalisation due to COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2021

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	Not reported
Study start date	13-Mar-2020
Study end date	31-Aug-2020
Aim of the study	To assess the extent, and type, of persistent symptoms in children aged 0–18 years.
Country/ Geographical location	Sweden
Study setting	Community
Population description	Children aged 0–18 years who were admitted to one of the two paediatric hospitals in the Stockholm Region due to COVID-19.
Inclusion criteria	The inclusion criteria were the presence of a nasopharyngeal sample RT-PCR positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Exclusion criteria	Children that tested positive, but were hospitalised for other reasons, were not included.
Intervention/test/approach	Information on any persisting health issues following hospitalisation, their perceived severity and their impact on daily activities was collected during structured telephone interviews with the children and/or their guardians. The children were followed up in December 2020 and January 2021, at least four months after being admitted (median 219 days, range 123–324 days). Three paediatricians reviewed the reported symptoms, in relation to the patient's age, and objective findings in their medical records. Symptoms were classified as mild, moderate or severe and by their uncertain or possible association with COVID-19.
Comparator (where applicable)	None
Methods for population selection/allocation	See inclusion criteria above.
Methods of data analysis	This was a survey.
Attrition/loss to follow-up	None (this was a retrospective study).
Summary of results	There were 147 SARS-CoV- 2-positive children hospitalised during the study period, and 60 were primarily admitted due to COVID-19. Of these 60 children, nine fulfilled the criteria of multisystem inflammatory syndrome in children (MIS-C) and two of these required intensive care. Other reasons for admissions included dehydration (38%), infection observation (35%) and need for inhalations (23%). A total of 55 were interviewed and analysed, as two were lost to follow-up and three declined to participate. We found that 12/55 (22%) had persistent

	symptoms and 8/12 had fatigue, which was the most common symptom. There were 6/12 with mild persistent symptoms with an uncertain relationship with COVID-19, including vague symptoms, such as parental reports of poor appetite despite good growth, an infant with a congested nose and intermittent increases in body temperature. A third (4/12), aged 4, 14, 15 and 16 years, had multiple severe symptoms that were possibly related to COVID-19. All four reported fatigue and headache or myalgia, and three reported cognitive difficulties. Their median admission was seven days, compared with four days for the overall group: three had a C-reactive protein value of more than 200mg/l during their initial illness, and two were diagnosed with MIS-C. All the severe cases had symptoms that had a major impact on their daily activities, including reduced school attendance and leisure activities. The groups were too small to determine statistically significant differences, but persistent symptoms seemed higher among children diagnosed with MIS-C. A tenth of the 55 children who were hospitalised due to COVID-19 reported persistent symptoms that were assessed to have a possible association with the SARS-CoV-2 infection more than four months after their acute illness. In this study, teenagers accounted for three of the four children with the most pronounced severe symptoms and the greatest impact on daily life.
Source of funding	Swedish Society of Medicine
Study limitations (Author)	Their conclusions were limited by the small sample and only included children admitted to the paediatric hospitals. This limits the generalisability to hospitalised children even though most children will have mild COVID-19. Children who tested positive for SARS-CoV-2 antibodies but had negative polymerase chain reaction results for SARS-CoV-2 were not included, and further assessment of persistent symptoms in children with MIS-C is warranted. Furthermore, self-reported symptoms may, to some extent, be difficult to validate and this makes it challenging to develop criteria for follow-up procedures.
Study limitations (Reviewer)	This was a retrospective study and therefore prone to selection bias. The data on persisting health issues were collected retrospectively and were prone to recall bias.

Study arms
Children who had COVID-19 (N = 55)

Characteristics
Study-level characteristics

Characteristic	Study (N = 55)
Age <1 year (number) Nominal	38
Age >15 years (number) Nominal	25
Age 6–12 years (number) Nominal	25
Age 13-18 years (number) Nominal	11
Gender (%) % Female Nominal	42

Sterky, 2021

Bibliographic Reference	Sterky, Ellinor; Olsson-Akefeldt, Selma; Hertting, Olof; Herlenius, Eric; Alfven, Tobias; Ryd Rinder, Malin; Rhedin, Samuel; Hildenwall, Helena; Persistent symptoms in Swedish children after hospitalisation due to COVID-19.; Acta paediatrica (Oslo, Norway : 1992); 2021

Critical appraisal - CASP Critical appraisal checklist for cohort studies

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Was the cohort recruited in an acceptable way?	No *(This was a retrospective study and is therefore prone to selection bias.)*
(A) Are the results of the study valid?	3. Was the exposure accurately measured to minimise bias?	Not applicable
(A) Are the results of the study valid?	4. Was the outcome accurately measured to minimise bias?	No *(The data on persisting health issues were collected retrospectively and were prone to recall bias.)*
(A) Are the results of the study valid?	5.(a) Have the authors identified all important confounding factors?	Not applicable
(A) Are the results of the study valid?	5.(b) Have they taken account of the confounding factors in the design and/or analysis?	Not applicable

Section	Question	Answer
(A) Are the results of the study valid?	6.(a) Was the follow up of subjects complete enough?	Yes
(A) Are the results of the study valid?	6.(b) Was the follow up of subjects long enough?	Yes
(B) What are the results?	7. What are the results of this study?	See data above.
(B) What are the results?	8. How precise are the results?	See data above.
(B) What are the results?	9. Do you believe the results?	Yes
(C) Will the results help locally?	10. Can the results be applied to the local population?	Yes
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Yes
(C) Will the results help locally?	12. What are the implications of this study for practice?	See data above.
Overall bias	Overall risk of bias	High *(This is a retrospective study and therefore prone to selection bias. The post-acute data was collected retrospectively and was prone to recall bias.)*

Appendix 7 GRADE profiles

CYP signs and symptoms: Children experiencing ongoing symptoms beyond the duration of acute COVID-19 illness (>4 weeks)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Prevalence of individual symptoms							
4388 (6 observational studies)	serious[a]	serious[b]	not serious	very serious[b]	none	Very low	Four studies (n=4222) found that 2.99%-87.10% of patients reported tiredness and weakness or hypersomnia. Five studies (n=1323) found that 10.69%-87% of patients reported fatigue. Six studies (n=4388) found that 3.50%-78.60% of patients reported headache and 2.00%-75.9% of patients reported abdominal pain. Six studies (n=4388) found that 0.82%-68.4% of patients reported muscle aches and pains. Five studies (n=3878) found that 1.39%-55.0% of patients reported shortness of breath. Four studies (n=3749) found that 1.0%-45.5% of patients reported loss of smell. Six studies (n=4388) found that 0.41%-60.6% of patients reported lack of concentration or delirium. Five studies (n=4259) found that 1.03%-48.0% of patients reported dizziness or light headedness. Two studies (n=3142) found that 9.7%-16.88% of patients reported skipped meals. Six studies (n=4388) found that 1.6%-52.4% of patients reported skin rash or red welts
Prevalence of categories of symptoms							

Certainty assessment							Summary of findings
135 (2 observational studies)	serious[a]	serious[b]	not serious	very serious[b]	none	Very low	Two studies (n=135) found that 16.36%-27.5% of patients reported general symptoms (including fatigue and fever). Two studies (n=135) found that 3.64%-22.5% of patients reported ear, nose, and throat symptoms (including reduced taste/smell). Two studies (n=135) found that 5.45%-21.2% of patients reported respiratory symptoms. Two studies (n=135) found that 5.45%-16.2% of patients reported neurological symptoms (including cognitive impairment/'brain fog' and headache). One study (n=80) found that 15% of patients reported dermatological symptoms. Two studies (n=135) found that 5.45%-13.80% of patients reported gastrointestinal symptoms. Two studies (n=135) found that 1.81%-11.20% of patients reported cardiovascular symptoms. Two studies (n=135) found that 5.45%-10% of patients reported psychiatric symptoms. One study (n=80) found that 8.80% of patients reported muscular symptoms.
Symptoms of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (follow-up: range 6 weeks to 6 months)							
46 (1 observational study)	serious[c]	not serious	not serious	serious[d]	none	Very low	One study found that the most common symptoms of PIMS-TS reported at 6 weeks and 6 months were abnormal neurological examination (52.17% at 6 weeks, 39.13% at 6 months); could walk less than 3rd centile (43.48%, 39.13%); proximal myopathy or lower limb weakness (36.13%, 17.39%); bilateral or unilateral dysmetria (34.78%, 26.09%); and abnormal eye movements or saccades (32.61%, 15.21%).
Prevalence of new post-COVID diagnoses or conditions							
2673 (1 observational study)	not serious	not serious	not serious	serious[e]	none	Very low	One study found that children with COVID were not more likely to experience new post-COVID diagnoses or conditions than children without COVID

CI: confidence interval

Explanations

a. Retrospective study design reliant on self-reported data. High risk of recall bias.
b. Unable to pool due to different study designs
c. Retrospective observational study and therefore prone to selection bias.
d. unable to assess statistical significance
e. Unable to measure precision

CYP risk factors: Children experiencing ongoing symptoms beyond the duration of acute COVID-19 illness (>4 weeks)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Risk factor: 1 or more pre-existing conditions							
1028 (2 observational studies)	serious[a]	not serious	not serious	serious[b]	none	Very low	In two studies, 44.7-56.3% of patients with long term effects of COVID had 1 or more pre-existing conditions
Risk factor: any allergic diseases							
1028 (2 observational studies)	serious[a]	not serious	not serious	serious[b]	none	Very low	In two studies, 2.3%-14.5% of patients with long term effects of COVID-19 had asthma
Risk factor: eczema							

Certainty assessment							Summary of findings
1028 (2 observational studies)	serious[a]	not serious	not serious	serious[b]	none	Very low	In two studies, 8.8%-12.4% of patients with long term effects of COVID-19 had eczema
Risk factor: female sex (follow-up: 3 months)							
3065 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	In one study, 34.1% of patients with COVID-19 were female
Risk factor: older child age (follow-up: 3 months)							
(1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	In one study, 24.7% of patients with long term effects of COVID-19 were aged 11-15 years and 32.3% were aged 16-17 years
Risk factor: baseline physical health (follow-up: 3 months)							
3065 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	In one study, 37.2% of patients with long term effects of COVID-19 had worse baseline physical health and 25.2% had good or very good baseline physical health
Risk factor: baseline mental health (follow-up: 3 months)							
3065 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	In one study, 39.6% of patients with long term effects of COVID-19 had worse baseline mental health and 20.8% of patients had good or very good baseline mental health

CI: confidence interval

Explanations

a. Retrospective observational study and therefore prone to selection bias.
b. Unable to measure precision

Appendix 8 Excluded studies

Study	Reason for exclusion
Addison, Alfred B, Wong, Billy, Ahmed, Tanzime et al. (2021) Clinical Olfactory Working Group Consensus Statement on the Treatment of Post Infectious Olfactory Dysfunction. The Journal of allergy and clinical immunology	- Indirect evidence
Aemaz Ur Rehman, Muhammad, Farooq, Hareem, Ali, Muhammad Mohsin et al. (2021) The Association of Subacute Thyroiditis with COVID-19: a Systematic Review. SN comprehensive clinical medicine: 1-13	- Covered in included systematic review
Al-Aly, Ziyad; Xie, Yan; Bowe, Benjamin (2021) High-dimensional characterization of post-acute sequalae of COVID-19. Nature	- Covered in included systematic review
Alemanno, Federica, Houdayer, Elise, Parma, Anna et al. (2021) COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID-rehabilitation unit experience. PloS one 16(2): e0246590	-Sample size less than 10,000
Aminian, Ali, Bena, James, Pantalone, Kevin M et al. (2021) Association of Obesity with Post-Acute Sequelae of COVID-19 (PASC). Diabetes, obesity & metabolism	- Sample size less than 10,000
Arnold David, T, Milne, Alice, Stadon, Louise et al. Are vaccines safe in patients with Long COVID? A prospective observational study. medrxiv preprint	- Duplicate
Augustin, Max, Schommers, Philipp, Stecher, Melanie et al. (2021) Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. The Lancet regional health. Europe 6: 100122	- Sample size less than 10,000
Augustin, Max, Schommers, Philipp, Stecher, Melanie et al. Recovered not restored: Long-term health consequences after mild COVID-19 in non-hospitalized patients. medrxiv preprint	- Duplicate
Badenoch James, B, Rengasamy Emma, R, Watson Cameron, J et al. Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis. medrxiv preprint	- Covered in included systematic review
Baricich, Alessio, Borg, Margherita B, Cuneo, Daria et al. (2021) Midterm functional sequelae and implications in rehabilitation after COVID19. A cross-sectional study. European journal of physical and rehabilitation medicine	- Sample size less than 10,000
Bell Melanie, L, Catalfamo Collin, J, Farland Leslie, V et al. Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT. medrxiv preprint	- Sample size less than 10,000
Bellan, Mattia, Soddu, Daniele, Balbo, Piero Emilio et al. (2021) Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA network open 4(1): e2036142	- Sample size less than 10,000

Biadsee, Ameen, Dagan, Or, Ormianer, Zeev et al. (2021) Eight-month follow-up of olfactory and gustatory dysfunctions in recovered COVID-19 patients. American journal of otolaryngology 42(4): 103065	- Sample size less than 10,000
Brackel, Caroline L H, Lap, Coen R, Buddingh, Emilie P et al. (2021) Pediatric long-COVID: An overlooked phenomenon?. Pediatric pulmonology	- Duplicate
Bultas, Margaret W and Fuller, Kelli (2021) Multisystem Inflammatory Syndrome in Children and COVID-19 Infections. NASN school nurse (Print): 1942602x211021136	- Study design: Narrative review with no data
Bultas, Margaret W and Fuller, Kelli (2021) Multisystem Inflammatory Syndrome in Children and COVID-19 Infections. NASN school nurse (Print): 1942602x211021136	- Study design: Narrative review with no data
Cabrera Martimbianco, Ana Luiza, Pacheco, Rafael Leite, Bagattini, Angela Maria et al. (2021) Frequency, signs and symptoms, and criteria adopted for long COVID: a systematic review. International journal of clinical practice: e14357	- Duplicate
Cabrera Martimbianco, Ana Luiza, Pacheco, Rafael Leite, Bagattini, Angela Maria et al. (2021) Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. International Journal of Clinical Practice	- Covered in included systematic review
Carenzo, Luca, Dalla Corte, Francesca, Haines, Ryan W et al. (2021) Return to Work After Coronavirus Disease 2019 Acute Respiratory Distress Syndrome and Intensive Care Admission: Prospective, Case Series at 6 Months From Hospital Discharge. Critical care medicine	- Study design: Case series (Prevalence)
Cennamo, Gilda, Reibaldi, Michele, Montorio, Daniela et al. (2021) Optical coherence tomography angiography features in post COVID-19 pneumonia patients: a pilot study. American journal of ophthalmology	- Scoping assessment - no impact on current recommendations
Chowdhury Zahin, Amin-Chowdhury, Harris Ross, J, Aiano, Felicity et al. Characterising long COVID more than 6 months after acute infection in adults; prospective longitudinal cohort study, England. medrxiv preprint	- Sample size less than 10,000
Clarke, Jonathan, Flott, Kelsey, Crespo Roberto, Fernandez et al. Assessing the Safety of Home Oximetry for Covid-19: A multi-site retrospective observational study. medrxiv preprint	- Population: Acute Covid-19
Collaborative - The, OpenSAFELY, Walker Alex, J, MacKenna, Brian et al. Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY. medrxiv preprint	- Not relevant to review protocols
Cousyn, L, Sellem, B, Palich, R et al. (2021) Olfactory and gustatory dysfunctions in COVID-	- Sample size less than 10,000

19 outpatients: a prospective cohort study. Infectious diseases now	
D'Cruz, R.F., Perrin, F., Waller, M. et al. (2021) Clinical, radiological, functional and psychological characteristics of severe COVID-19 pneumonia survivors: A prospective observational cohort study. Thorax 76(suppl1): a34-a35	- Study design: Conference abstract
Damanti, Sarah, Ramirez, Giuseppe Alvise, Bozzolo, Enrica Paola et al. (2021) 6-Month Respiratory Outcomes and Exercise Capacity of COVID-19 Acute Respiratory Failure Patients Treated With CPAP. Internal medicine journal	- Sample size less than 10,000
DARLEY David, R, Dore, Gregory, Byrne, Anthony et al. Limited recovery from post-acute sequelae of SARS-CoV-2 (PASC) at eight months of a prospective cohort. medrxiv preprint	- Sample size less than 10,000
Daugherty, Sarah E, Guo, Yinglong, Heath, Kevin et al. (2021) Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ (Clinical research ed.) 373: n1098	- Covered within included primary study
Davis Hannah, E, Assaf Gina, S, McCorkell, Lisa et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. medrxiv preprint	- Sample size less than 10,000
Daynes, Enya, Gerlis, Charlotte, Chaplin, Emma et al. Early experiences of rehabilitation for patients post-COVID to improve fatigue, breathlessness exercise capacity and cognition. medrxiv preprint	- Intervention: Rehabilitation on discharge
Daynes, Enya, Gerlis, Charlotte, Chaplin, Emma et al. (2021) Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. Chronic respiratory disease 18: 14799731211015691	- Intervention: Rehabilitation on discharge
Dennis, Andrea, Wamil, Malgorzata, Alberts, Johann et al. (2021) Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ open 11(3): e048391	- Sample size less than 10,000
Desgranges, Florian, Tadini, Eliana, Munting, Aline et al. Post-COVID-19 syndrome in outpatients: a cohort study. medrxiv preprint	- Sample size less than 10,000
Divanoglou, Anestis, Samuelsson, Kersti, Sj?dahl, Rune et al. Rehabilitation needs and mortality associated with the Covid-19 pandemic: a population-based study of all hospitalised and home-healthcare individuals in a Swedish healthcare region. medrxiv preprint	- Sample size less than 10,000
Donegani, Maria Isabella, Miceli, Alberto, Pardini, Matteo et al. (2021) Brain Metabolic Correlates of Persistent Olfactory Dysfunction after SARS-Cov2 Infection. Biomedicines 9(3)	- Study aim: Pathophysiology/mechanisms
Estiri, Hossein, Strasser, Zachary, Brat, Gabriel et al. Evolving Phenotypes of non-hospitalized	- Covered within included primary study

Patients that Indicate Long Covid. medrxiv preprint	
Evans Rachael, Andrea, McAuley, Hamish, Harrison Ewen, M et al. Physical, cognitive and mental health impacts of COVID-19 following hospitalisation: a multi-centre prospective cohort study. medrxiv preprint	- For consideration at future update pending further data
Fair Health (2021) A Detailed Study of Patients with Long-Haul COVID: An Analysis of Private Healthcare Claims.	- No data to extract
Faverio, Paola, Luppi, Fabrizio, Rebora, Paola et al. Six-month pulmonary impairment after severe COVID-19: a prospective, multicenter follow-up study. medrxiv preprint	- Scoping assessment - no impact on current recommendations
Froidure, Antoine, Mahsouli, Amin, Liistro, Giuseppe et al. (2021) Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respiratory medicine 181: 106383	- Sample size less than 10,000
Frontera Jennifer, A., Yang, Dixon, Lewis, Ariane et al. A Prospective Study of Long-Term Outcomes Among Hospitalized COVID-19 Patients with and without Neurological Complications. medrxiv preprint	- Sample size less than 10,000
Gaber T A-Z, K; Ashish, A; Unsworth, A (2021) Persistent post-covid symptoms in healthcare workers. Occupational medicine (Oxford, England)	-Sample size less than 10,000
Galal, islam, Hussein Aliae AR, Mohamed-Hussein, Amin - Mariam, T et al. Determinants of Persistent Post COVID-19 symptoms: Value of a Novel COVID-19 symptoms score. medrxiv preprint	-Sample size less than 10,000
Ganesh, Ravindra, Grach Stephanie, L, Bierle Dennis, M et al. The Female Predominant Persistent Immune Dysregulation of the Post COVID Syndrome: A Cohort Study. medrxiv preprint	- Sample size less than 10,000
Ghosn, Jade, Piroth, Lionel, Epaulard, Olivier et al. (2021) Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Sample size less than 10,000
Giovannetti, Guido, De Michele, Lucrezia, De Ceglie, Michele et al. (2021) Lung ultrasonography for long-term follow-up of COVID-19 survivors compared to chest CT scan. Respiratory medicine 181: 106384	- Scoping assessment - no impact on current recommendations
Gobbi, M, Brunani, A, Arreghini, M et al. (2021) Nutritional status in post SARS-Cov2 rehabilitation patients. Clinical nutrition (Edinburgh, Scotland)	- Scoping assessment - no impact on current recommendations
Guler, Sabina A, Ebner, Lukas, Beigelman, Catherine et al. (2021) Pulmonary function and radiological features four months after COVID-19: first results from the national prospective	- Sample size less than 10,000

observational Swiss COVID-19 lung study. The European respiratory journal	
Hallam F, Rankin R BJ (2021) Rehabilitation of adults who are hospitalised due to acute COVID-19 or Long COVID: physiotherapy service delivery.	- Study design: Expert opinion
Heightman, Melissa, Prashar, Jai, Hillman, Toby et al. Post-COVID assessment in a specialist clinical service: a 12-month, single-centre analysis of symptoms and healthcare needs in 1325 individuals. medrxiv preprint	- Sample size less than 10,000
Hirschtick, Jana L, Titus, Andrea R, Slocum, Elizabeth et al. (2021) Population-based estimates of post-acute sequelae of SARS-CoV-2 infection (PASC) prevalence and characteristics. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	- Sample size less than 10,000
Holmes, Elaine, Wist, Julien, Masuda, Reika et al. (2021) Incomplete Systemic Recovery and Metabolic Phenoreversion in Post-Acute-Phase Nonhospitalized COVID-19 Patients: Implications for Assessment of Post-Acute COVID-19 Syndrome. Journal of proteome research	- Scoping assessment - no impact on current recommendations
Hopkins, C, Surda, P, Vaira, L A et al. (2020) Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. Rhinology	- Sample size less than 10,000
Horn, Mathilde, Wathelet, Marielle, Fovet, Thomas et al. (2020) Is COVID-19 Associated With Posttraumatic Stress Disorder?. The Journal of clinical psychiatry 82(1)	- Sample size less than 10,000
Hoshijima, Hiroshi, Mihara, Takahiro, Seki, Hiroyuki et al. Incidence of Long-term Post-acute Sequelae of SARS-CoV-2 Infection Related to Pain and Other Symptoms: A Living Systematic Review and Meta-analysis. medrxiv preprint	- Covered in included systematic review
Humphreys, H., Kilby, L., Kudiersky, N. et al. (2021) Long COVID and the role of physical activity: a qualitative study. BMJ Open 11(3): 047632	- Qualitative studies: Separate search conducted by SIGN
Hunter, A., Hodgson, L., Leckie, T. et al. (2020) Socially distanced rehabilitation: A potential new normal for post-critical care recovery?. Intensive Care Medicine Experimental 8(suppl2)	- Scoping assessment - no impact on current recommendations
Hylton, H., Pfeffer, P.E., Robson, C. et al. (2021) Rapid design and implementation of a personalised holistic post-COVID recovery and rehab app. Thorax 76(suppl1): a236	- Study design: Conference abstract
Iftikhar, Hina; Doherty, Warren L; Sharp, Charles (2021) Long-term COVID-19 complications: a multidisciplinary clinic follow-up approach. Clinical medicine (London, England) 21(suppl2): 3-4	- Intervention: Rehabilitation on discharge
Iqbal, Ayman, Iqbal, Kinza, Arshad Ali, Shajeea et al. (2021) The COVID-19 Sequelae: A Cross-	- Sample size less than 10,000

Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. Cureus 13(2): e13080	
Iqbal, Fahad M, Lam, Kyle, Sounderajah, Viknesh et al. (2021) Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine 36: 100899	- Covered in included systematic review
Ismael, Flavia, Bizario, Joao C S, Battagin, Tatiane et al. (2021) Post-infection depressive, anxiety and post-traumatic stress symptoms: A prospective cohort study in patients with mild COVID-19. Progress in neuro-psychopharmacology & biological psychiatry: 110341	-Sample size less than 10,000
Iwu, C.J.; Iwu, C.D.; Wiysonge, C.S. (2021) The occurrence of long COVID: A rapid review. Pan African Medical Journal 38: 1-12	- Review of studies covered in development
Jacobs, Laurie G, Gourna Paleoudis, Elli, Lesky-Di Bari, Dineen et al. (2020) Persistence of symptoms and quality of life at 35 days after hospitalization for COVID-19 infection. PloS one 15(12): e0243882	- Sample size less than 10,000
Jewson, Jacob; McNamara, Alice; Fitzpatrick, Jane (2020) Life after COVID-19: The importance of a safe return to physical activity. Australian journal of general practice 49	- Supporting evidence
Ladds, Emma, Rushforth, Alex, Wieringa, Sietse et al. (2020) Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. BMC health services research 20(1): 1144	- Qualitative studies: Separate search conducted by SIGN
Ladds, Emma, Rushforth, Alex, Wieringa, Sietse et al. (2021) Developing services for long COVID: lessons from a study of wounded healers. Clinical medicine (London, England) 21(1): 59-65	- Qualitative studies: Separate search conducted by SIGN
Lemhofer, Christina, Gutenbrunner, Christoph, Schiller, Jorg et al. (2021) Assessment of rehabilitation needs in patients after COVID-19: Development of the COVID-19-rehabilitation needs survey. Journal of rehabilitation medicine	- Study design: Narrative review with no data
Li, Jian'an, Xia, Wenguang, Zhan, Chao et al. Effectiveness of a telerehabilitation program for COVID-19 survivors (TERECO) on exercise capacity, pulmonary function, lower limb muscle strength, and quality of life: a randomised controlled trial. medrxiv preprint	- Scoping assessment - no impact on current recommendations
Lopez-Leon, Sandra, Wegman-Ostrosky, Talia, Perelman, Carol et al. (2021) More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv : the preprint server for health sciences	- Covered in included systematic review
Mahmud, Reaz, Rahman, Md Mujibur, Rassel, Mohammad Aftab et al. (2021) Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. PloS one 16(4): e0249644	- Sample size less than 10,000

Makaronidis, Janine, Firman, Chloe, Magee, Cormac G et al. (2021) Distorted chemosensory perception and female sex associate with persistent smell and/or taste loss in people with SARS-CoV-2 antibodies: a community based cohort study investigating clinical course and resolution of acute smell and/or taste loss in people with and without SARS-CoV-2 antibodies in London, UK. BMC infectious diseases 21(1): 221	- Sample size less than 10,000
Malik, Jahanzeb, Zaidi Syed Muhammad, Jawad, Ishaq, Uzma et al. Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review. medrxiv preprint	- Covered in included systematic review
Mandal, Swapna, Barnett, Joseph, Brill, Simon E et al. (2020) 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax	- Sample size less than 10,000
Martin, Ines, Braem, Fred, Baudet, Lia et al. (2021) Follow-up of functional exercise capacity in patients with COVID-19: It is improved by telerehabilitation. Respiratory medicine 183: 106438	- Scoping assessment - no impact on current recommendations
Mattioli, Flavia, Stampatori, Chiara, Righetti, Francesca et al. (2021) Neurological and cognitive sequelae of Covid-19: a four month follow-up. Journal of neurology	- Sample size less than 10,000
Meije, Y, Duarte-Borges, A, Sanz, X et al. (2021) Long-term outcomes of patients following hospitalization for COVID-19: a prospective observational study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases	- Sample size less than 10,000
Miller, Faith, Nguyen, Vincent, Navaratnam Annalan, MD et al. Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales. medrxiv preprint	- Duplicate
Miskowiak, K W, Johnsen, S, Sattler, S M et al. (2021) Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity and association with illness variables. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 46: 39-48	- Sample size less than 10,000
Montefusco, Laura, Ben Nasr, Moufida, D'Addio, Francesca et al. (2021) Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. Nature metabolism	- Scoping assessment - no impact on current recommendations
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Appendix 9 Expert testimony

Expert testimony :Dr Mairi Stark

Section A: Developer to complete	
Name:	Dr Mairi Stark
Role:	Expert Witness - Consultant Paediatrician/RCPCH Scottish Officer
Institution/Organisation (where applicable):	Royal Hospital for Children & Young People Edinburgh
Guideline title:	Managing the long-term effects of COVID-19: update
Guideline Committee:	Expert Advisory Panel for the update of NG188
Subject of expert testimony:	Children and young people
Evidence gaps or uncertainties:	Signs and symptoms, case definition, assessment and investigations, management and service provision
Section B: Expert to complete	
Summary testimony:	

Service design in Scotland

The model of long COVID assessment hubs used in England would not work well in Scotland because there is a smaller paediatric population and therefore the numbers of children and young people with long COVID is low.

All children who have been in PICU are followed up – this is standard practice for any cause of severe illness. However, the numbers are very low.

Instead of a specialist clinic, children with symptoms of long COVID are initially seen by a paediatrician to ensure the correct diagnosis. If they were only seen in a COVID assessment centre there is a risk that a different underlying cause

could be missed. Long COVID in children is rare, so the symptoms are more likely to be due to another problem.

It is not necessary to treat long COVID differently to other post-viral conditions as there are similarities in symptoms. It would be preferable to have a MDT service for chronic fatigue and post-viral symptoms. This could focus on getting children and young people back to school, as outcomes improve when they reintegrate back into school. The Hospital Outreach team is important, for all children returning to education after a hospital stay.

It is not helpful to differentiate long COVID from chronic fatigue for service provision, as all patients need the support regardless of the underlying cause. The proposed pathway is rapid assessment by a general paediatrician to exclude alternative diagnosis, followed by support from physiotherapy, psychology, chronic fatigue nurse specialist and school outreach to reduce long-term effects and encourage graded increase in activities.

Questions from panel

Q. Is the 1.8% incidence of long COVID comparable with other similar conditions?

A. Chronic fatigue is around 2%. I work in large hospital, with main clinic for referrals and haven't seen any cases of long COVID in the last year.

Q. Is this an opportunity to get post-viral clinics established?

A. Need to be referred to a general paediatric clinic initially to get a full holistic assessment. Anyone with respiratory or cardiac problems would be referred to a specialist. It is important to have a pathway with rapid referral where it is needed. It is a good opportunity to establish a chronic fatigue service.

Q. How good is referral from GPs to paediatrics? Long COVID is not well recognised in children so it could be that referral to secondary care isn't happening?

A. Not aware of this as an issue. There is no increase in waiting times in Edinburgh. Patients are seen within four weeks if referral from GP is urgent.

Q. Does the interruption in schooling have an indirect impact, therefore post-COVID could be a major impact on children's health and wellbeing?

A. It doesn't matter what the cause of the illness is, the important thing is to manage the symptoms. There is a need to focus on hospital outreach teachers and get funding for that. Home teaching and support for phased return to in-school teaching is so important.

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Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.
Nil
Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form. **Note: If giving expert testimony on behalf of an organisation**, please ensure you use the DOI form to declare your own interests and also those of the organisation – this includes any financial interest the organisation has in the technology or comparator product; funding received from the manufacturer of the technology or comparator product; or any published position on the matter under review. The declaration should cover the preceding 12 months and will be available to the advisory committee. For further details, see the NICE policy on declaring and managing interests for advisory committees and supporting FAQs.

Expert testimony: Dr Elizabeth Whittaker

Section A: Developer to complete	
Name:	Dr Elizabeth Whittaker
Role:	Expert Witness – Practitioner Consultant paediatric infectious diseases and lecturer in paediatric infection and immunity

Institution/Organisation (where applicable):	St Mary's Hospital, Imperial College healthcare NHS Trust and Imperial College London
Guideline title:	Managing the long-term effects of COVID-19: update
Guideline Committee:	Expert Advisory Panel for the update of NG188
Subject of expert testimony:	Children and young people: • case definition • signs and symptoms • assessment and investigation • rehabilitation • care pathways/service organisation • lived experience

Evidence gaps or uncertainties:

• What are the physical, cognitive, psychological and psychiatric signs or symptoms of the long-term effects of COVID-19 in children and young people? What is the prevalence in children and young people?

• What assessments and investigations are used to identify the long-term effects of COVID-19 in children and young people? Are they different to those recommended in NG188?

• What is the most effective management and rehabilitation (for physical, cognitive, psychological and psychiatric symptoms) for children and young people with long-term effects of COVID-19 (links to service organisations and care pathways)

• What are the most effective modifications or support for children and young people with long-term effects of COVID-19 to continue with education?

• What care pathways and service organisation are you aware of for the assessment and management of the long-term effects of COVID-19 in children and young people, and which is most effective?

• Is there, or should there be a separate case definition for 'long COVID' in children?

Section B: Expert to complete

Summary testimony:

This expert testimony presented information and experiences of setting up and running services for children with ongoing symptoms of COVID-19 in London. In particular, the assessments and investigations undertaken, and care pathways for assessment and management.

Various datasets (ONS data, data from the Zoe app) show that ongoing symptoms of COVID-19 are prevalent in children and young people:

ONS data on persistent symptoms in people <16 were presented.

- 9.8-13% had symptoms at 5 weeks
- 7-8% had symptoms at 12 weeks.

Zoe data (Molteni et al., 2021)

- 4.4% had symptoms at 28 days
- 1.8% had symptoms at >56 days.

NHS services for children with post-COVID symptoms (London)

In London, services for children have been set up based partly on services for adults with ongoing symptoms of COVID-19 but tailored for young people. Young people seen in this service are often struggling with their mental health and may be anxious as a result of their symptoms.

These services have prioritised close working with local paediatric services through GPs and recognise the importance of involving family members in care.

Care pathway

Routes into the pathway: Children and young people can enter into the pathway in multiple ways (from emergency care, community providers or education providers).

GPs: GPs are the first stage in the pathway. This should be a face-to-face assessment. The experience in the London service is that a significant proportion of young people had pre-existing conditions. A holistic approach is therefore required, particularly as many children have had time off school as a result of their symptoms. GPs should have rapid access to paediatrician-led rapid triage to minimise wait.

Paediatrician-led rapid triage (PLRT): PLRT work with GPs to exclude other conditions and advise where diagnosis is unclear. If needed, paediatricians can refer into the virtual multidisciplinary team (MDT) assessment. A referral form has been created for this purpose

Virtual MDT assessment: The MDT should involve a broad range of disciplines. Allied Health Professionals (for example, dieticians, speech and language therapists, occupational therapists, physiotherapists) are important members of this team. The MDT in London consists of at least 6 members, with specialities tailored depending on the symptoms presenting. An MDT coordinator has been added to the London team for admin support. This assessment can result in a referral for face-to-face rehabilitation in severe cases. Alternate outcomes include referral to appropriate specialist services,

advice regarding further investigations, suggested treatment for symptom management, supportive guidance for self-management.

Self-management supportive options are varied. They can involve information leaflets, webinars, online group sessions. Parental group sessions are being considered for the future.

General observations: Fewer children and young people are being referred into this pathway than expected. This is a concern, and the reasons behind it are not yet known. Activities to address this:

- Active case finding
- Engagement with schools
- Education sessions with primary care (via Royal College of GPs RCGP, local primary care networks etc
- Dissemination of information to paediatric teams via other networks – e.g. North and South Thames Paediatric networks (NTPN, STPN)

However, it appears there may be other blockers to referral. Direct referrals are taken from primary care for the 16-18 year age group as they fall between paediatric and adult services.

Common symptoms and management

Case studies show that initial mild illness due to SARS-CoV-2 can result in ongoing symptoms of COVID-19. It is important not to miss other diagnoses during assessment for long-COVID.

People presenting into the pathway may not have laboratory evidence (PCR, antibody) of infection (15/29 people referred into TRACCS service showed no evidence of infection). Most people accessing services present with more than one symptom: most frequently fatigue, followed by headache, gastrointestinal symptoms, cardiorespiratory symptoms, and neuropsychiatric symptoms.

Most of these patients have treatment plans which involve groups or one-to-one sessions with a physiotherapist, psychologist or occupational therapist.

Some case studies were briefly presented, one of which included treatment with antihistamines (symptoms included a rash and abdominal pain).

Questions from panel

Q: The presence of neurological symptoms months after infection is interesting. This is also seen in long-COVID in adults. Is this a distinction between long-COVID in children and young people, and long-term effects of other viral infections?

A: We should be intentionally unbiased about how we think children and young people with long-COVID are going to present. We don't want to miss any new symptoms by expecting symptoms to align with what has been seen before in other conditions. There are overlapping symptoms with other conditions, but there are also clear distinctions. While some tools can be re-used in long-COVID, more research is needed in this area.

Q: Pulmonary and cardiovascular symptoms have been observed in children and young people with ongoing symptoms of COVID-19. Has organ damage been observed too?
A: There is a single published case study (Buonsenso et al., 2021) which reports having seen organ damage. However, we haven't observed this in London or England to date. This is a distinction from symptomatology in adults – even children who have been admitted to intensive care with COVID-19 don't follow the same path as adults, in particular thrombotic blood clotting complications are much less frequently seen. However, it's clear that investigations should still take place so that this isn't missed if it is present. These are built into the screening investigations required for referral to the pathway.

Q: The presentation stated that there is a blockage for referrals from primary care. Why might this be? Parents have very different experiences of getting referrals based on geography.

A: There is a problem with awareness. In London, we have done webinars, pamphlets, there are plans to go into schools to talk directly to children, young people and teachers. Active case finding could be the key. All of this requires resources, and while primary care services have done an incredible job throughout this pandemic, they may not have the resources to do this. It is true that there are people who are struggling to access care.

Q: One of the case studies included treatment with antihistamines. This seems to be increasingly common for ongoing symptoms of COVID-19. How many patients are using antihistamines? Do they help?

A: There is a published study from Russia (Osmanov et al., 2021) which shows that ongoing symptoms may affect children and young people with prior allergies (also noted in the CLoCK study not yet published). In London, treating with antihistamines has been trialled in patients with symptoms suggestive of urticaria or possible mast cell instability, as it is a relatively low risk treatment. Its effectiveness is uncertain (a trial is needed in this area, but will take time to produce results) – clinical experience suggests that it may work for some symptoms like rashes, but not for others like abdominal pain.

Q: Should the service provided by MDTs be made more easily accessible, rather than having to access through GPs? Could access be direct, with GPs contacted afterwards?

A: It's important that we investigate and continuously reassess the model that we're currently using, as we want to remove as many blocks to access as possible. It may be that opening up referrals more widely could overwhelm the service, but options like this one need to be considered. We have had discussions with primary care in London, and they were reluctant to refer directly in, and felt it was more appropriate that children and young people were assessed by a paediatrician first. However, if there are recognised delays in this pathway, we can reconsider this. 16-18 year olds are referred directly by

primary care into the pathway as they can otherwise fall between paediatric and adult services.

Q: There is a concern that difficulty in accessing MDTs (in some areas of the country, not necessarily everywhere) is driving parents to seek help through different channels. Sometimes this is private care, sometimes online advice about limiting diets or taking supplements. Do you think this could be diverting people away from pathways like the one in London, where they exist?

A: Yes, they could be. We are trying to address this: our educational material contains information about not changing your diet, as this can affect the weight and nutritional intake of a child or young person. We also ask private paediatricians to refer directly into the MDT, in order to reduce unnecessary investigations and transfers between healthcare professionals or departments, all of which can increase anxiety for the child or young person. We want people to come through our pathway as much as possible.

References to other work or publications to support your testimony' (if applicable):

Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2 (Molteni et al., 2021). https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00198-X/fulltext
Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection (Buonsenso et al., 2021) https://doi.org/10.1016/S2352-4642(21)00196-6

Risk factors for long covid in previously hospitalised children using the ISARIC Global follow-up protocol: A prospective cohort study (Osmanov et al., 2021); DOI: 10.1183/13993003.01341-2021

Disclosure:
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.

Nil

Declaration of interests: Please complete NICE's declaration of interests (DOI) form and return it with this form.

Note: If giving expert testimony on behalf of an organisation, please ensure you use the DOI form to declare your own interests and also those of the organisation – this includes any financial interest the organisation has in the technology or comparator product; funding received from the manufacturer of the technology or comparator product; or any published position on the matter under review. The declaration should cover the preceding 12 months and will be available to the advisory committee. For further details, see the NICE policy on declaring and managing interests for advisory committees and supporting FAQs.

Expert testimony: Professor Sir Terence Stephenson

Section A: Developer to complete	
Name:	Professor Sir Terence Stephenson
Role:	Expert Witness - Nuffield Professor of Child Health
Institution/Organisation (where applicable):	UCL Great Ormond Street Institute of Child Health
Guideline title:	Managing the long-term effects of COVID-19: update
Guideline Committee:	Expert Advisory Panel for the update of NG188
Subject of expert testimony:	Children and young people
Evidence gaps or uncertainties:	Physical and mental health symptoms Assessments and investigations Case definition

• What are the physical, cognitive, psychological and psychiatric signs or symptoms of the long-term effects of COVID-19 in children and young people? What is the prevalence in children and young people?

• What assessments and investigations are used to identify the long-term effects of COVID-19 in children and young people? Are they different to those recommended in NG188?

• What is the most effective management and rehabilitation (for physical, cognitive, psychological and psychiatric symptoms) for children and young people with long-term effects of COVID-19 (links to service organisations and care pathways)

• What are the most effective modifications or support for children and young people with long-term effects of COVID-19 to continue with education?

• What care pathways and service organisation are you aware of for the assessment and management of the long-term effects of COVID-19 in children and young people, and which is most effective?

• Is there, or should there be a separate case definition for 'long COVID' in children?

Section B: Expert to complete
Summary testimony:

Children & young people with Long Covid (CLoCk) study

This study looked at children and young people aged 11-17 who had a positive COVID PCR test, matched to those with a negative result. Requests were made to 150,000, with a 13% response rate (results for 6,804 children and young people, subjects and controls). An online questionnaire was completed three months after the test. Controls were matched by age, gender and where they lived.

At the time of the test the most common symptoms amongst those who tested positive were headache, tiredness, sore throat and loss of taste/smell.

For those who tested negative: Sore throat, headache, persistent cough, fever.

36% reported 1 symptom (vs 8% negative test), and 24% vs 4% reported ≥5 symptoms. This number rose to 66% (positive) vs 53% (negative) at 3 months for one symptom and 13% vs 6% ≥5 symptoms. The increase over time may be because people had more interest in completing the questionnaire if they still had symptoms at 3 months. It should be noted that this does not mean that the prevalence of long COVID in young people is 66%. It is a percentage of the 13% who responded to the questionnaire.

After 3 months the most commonly reported symptoms amongst those who tested positive were unusual tiredness (39%), shortness of breath (23%), headache (23%), loss of taste/smell (14%) and dizziness (14%).

For those who tested negative symptoms at 3 months were: unusual tiredness (24%), other (16%), headache (14%), unusual shortness of breath (10%) and loss of smell/taste (1.4%).

For mental health there were conflicting results. Using formal measurements resulted in no difference in mental health symptoms between the matched participants, or between pre and post-pandemic levels. However, when asked a more holistic question around happiness/sadness, more reported they were unhappy. It is postulated that this could be due to more general awareness of the situation and concern for family members, rather than the focus being on concern for themselves as individuals (the objective of the formal questionnaire).

Currently there is a Delphi consensus process to produce a research definition of long COVID in children and young people, and to determine what tests are required to make a diagnosis of long COVID for research purposes.

<u>Questions from panel</u>

Q. Is there any reference to schooling in the study?

A. Currently working on data which shows the number of days of school missed.

Q. Are there any comparators with other national surveys with which to compare the 13% response rate?

Is the demographic of the population analysed representative?

A. The response rate is comparable to eg MORI polls, which are national, unsolicited surveys, but not to those which use an already captured group, such as hospital inpatients.

The response rate for the latest national ONS surveys of randomly selected households is also 13%.

Respondents were quite representative of the population. There was a high BME response. London and the North-West were under-represented. More females than males.

Q. How can we get a better grasp of prevalence?

A. This is the biggest study globally and we can state the denominator. There was a similar response rate in both matched groups. The latest national ONS surveys of randomly selected households report POPULATION prevalence levels (whereas we are describing the proportion of those who test positive who have persistent symptoms). The latest ONS **prevalence** estimates for the four-weeks ending 6 June 2021: the estimated percentage of CYP living in private household in England with self-reported long COVID of any duration is 0.51% for 12-16 years and 1.21% for 17-24 years = 31,080 11-17 year olds.

Q. Could clusters of symptoms be a way to target children who need referral?

A. The study is aiming to establish a definition for use in research. For diagnosis, if a child or young person needs referral, this should be decided by presenting symptoms, in agreement with the patient, parents and clinician, based on symptoms not a definition. If the child or young person is ill they need help, regardless of the diagnosis.

Q. Is there scope for genetic analysis? Were siblings studied to see if they are likely to have the same symptoms?

A. No, but will note this to ask about family members in the follow up study.

Q. Did you consider disutility breakdown?

A. Haven't done this but will look into it.

Q. Prevalence of chronic fatigue is 1-2%. Is there a difference?

A. There is commonality but at this stage it is preferable to keep clear water between chronic fatigue and post-COVID syndrome.

References to other work or publications to support your testimony' (if applicable):

Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.
None
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