REVIEW

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Long COVID in children and adolescents

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Purpose of review
Although acute COVID-19 has been milder in children and young people compared with adults, there is a concern that they may suffer persistent symptoms. There is a need to define the clinical phenotype, determine those most at risk, the natural course of the condition and evaluate preventive and therapeutic strategies for both mental health and physical symptoms.

Recent findings
More recent studies with control groups reported a lower prevalence of persistent symptoms in children and young people exposed to SARS-CoV-2. A systematic review and meta-analysis found that the frequency of the majority of reported persistent symptoms is similar in SARS-CoV-2 positive cases and controls. Children and young people infected with SARS-COV-2 had small but significant increases in persisting cognitive difficulties, headache and loss of smell. Factors associated with persisting, impairing symptoms include increased number of symptoms at the time of testing, female sex, older age, worse self-rated physical and mental health, and feelings of loneliness preinfection.

Summary
This review highlights the importance of a control group in studies following SARS-CoV-2 infection, the need for case definitions and research to understand the outcomes of long COVID in children and young people.

Keywords
children, long COVID, mental health, physical health, SARS-COV-2

INTRODUCTION

SARS-COV-2 is the RNA virus, which causes Coronavirus Disease 2019 (COVID-19). Ongoing symptomatic COVID-19 and post COVID-19 syndrome are referred to as long COVID, but the term post COVID-19 condition is also used as is PASC (post-acute sequelae of COVID-19) and 'long haulers' in the USA. This review was commissioned using the term long COVID and this is the term used by the public, healthcare professionals and in literature searches and systematic reviews.

There is no diagnostic test or agreed international definition of long COVID in children. The WHO has defined post-COVID-19 condition for adults: 'with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction and others, which generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time' [1].

England's National Institute for Health and Clinical Excellence has defined post-COVID-19 syndrome for adults as: 'signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed' [2].

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KEY POINTS

- There is no agreed international definition or diagnostic test for long COVID in children and young people.
- Overall, the frequency of the majority of reported persistent symptoms is similar in SARS-CoV-2 positive cases and controls.
- Small but significant risk differences have, however, been observed in CYP infected with SARS-COV-2 compared with controls, particularly for persisting cognitive difficulties, headache and loss of smell.
- A review of published studies highlights the critical importance of a control group in studies on long COVID in CYP.
- There is a pressing need for intervention studies including the impact of vaccination on both prevention and amelioration of long COVID symptoms in CYP

WHAT WE KNEW IN 2020?

Almost a year into the SARS-COV-2 pandemic, in December 2020, we submitted a grant application to NIHR/UKRI to undertake a study of long COVID in children and young people less than 18 years old (CYP). At that time, very little was known about the characteristics, risk factors, progression or outcomes of long COVID in children. Risk factors of severe COVID-19 at all ages included obesity, comorbid long-term conditions, learning and neurological disabilities, mental health problems and ethnic minority status. However, whether these would also be the CYP most at risk from long COVID was unknown. We postulated that the population of CYP likely to be most at risk of long COVID would be teenagers rather than younger children based on our previous clinical experience with other persistent postviral syndromes. We noted that the five case reports by Ludvigsson [3] with symptoms longer than 6 months had a median age 12 years and that depression, anxiety and fatigue may occur in teenagers after other viral illnesses including influenza. In adults, there was emerging evidence suggesting that long COVID was commoner in girls and with two predominant symptom groupings: one dominated by respiratory symptoms such as cough and shortness of breath, as well as fatigue and headaches, and the second being multisystemic, including the brain, gut and heart [4]. Our experience and the wider literature told us that, in both adults and CYP, a wide range of long-term conditions can increase the risk of mental ill-health after acute illness and so our study aimed to research both persisting physical and mental health problems after SARS-CoV-2 infection [5].

WHAT WE KNEW A YEAR LATER

In November 2021, we published a systematic review and meta-analysis of published studies of long COVID in children [6▪▪]. We included studies of CYP with confirmed or probable COVID-19 and who had persistent symptoms as defined by authors of the individual studies. We excluded studies wherein all participants were admitted to intensive care to increase generalizability of our findings.

The literature search was completed in July 2021 and 22 studies were eligible, including 23 141 children and young people [3,7–27]. Median duration of follow-up was 125 days (IQR 99–231). Fifteen were cohort studies, six cross-sectional studies and one included case reports. Eight studies included population-based control groups. Sample size ranged from five (the original Ludvigsson [3] study) to 6804 CYP, with a total of 23 141 participants (median, 109). Eleven studies included less than 100 participants. All studies assessed outcomes at more than 4 weeks after infection (range 28–324 days), with 15 assessing outcomes at more than 12 weeks. Across all studies, 101 symptoms were reported, with 46 symptoms reported in at least two studies and 32 symptoms reported in at least three studies. Overall, the frequency of the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and controls. This systematic review highlighted the critical importance of a control group in studies on CYP after SARS-CoV-2 infection.

CYP in the control group of the largest of the controlled studies [25] had a high rate of at least one persisting symptoms (53.3% compared with 66.5% in CYP with confirmed SARS-CoV-2 infection) 3 months after the time of SARS-COV-2 testing. For multiple persisting symptoms, 30.3% of PCR test-positive CYP and 16.2% of PCR test-negative controls had three or more symptoms, with 13.4 and 6.4%, respectively, reporting at least five symptoms. The most common symptoms among test-positive CYP were tiredness (39.0%), headache (23.2%) and shortness of breath (23.4%), and among test-negative controls were tiredness (24.4%), headache (14.2%) and other unspecified symptoms (15.8%). Although the prevalence of multiple physical symptoms was greater in CYP with confirmed SARS-COV-2 virus, their mental health, wellbeing and fatigue scores were similar to both the control group and to prepandemic norms. Notably, around 40% of both cases and controls reported feeling worried, sad or unhappy, consistent with parent-reported surveys

of mental health of CYP during the pandemic [28], highlighting the overall toll of the pandemic, school closures and social isolations on the mental health and well being of CYP, irrespective of their SARS-CoV-2 infection status.

From the meta-analysis, there were some small but significant differences in the pooled risk of some persistent symptoms between cases and controls: cognitive difficulties (3%), headache (5%), loss of smell (8%), sore throat (2%) and sore eyes (2%) but not abdominal pain, cough, fatigue, myalgia, insomnia, diarrhoea, fever, dizziness or dyspnoea. Pooled prevalence of symptoms in post-COVID participants ranged from 15% (diarrhoea) to 47% (fatigue). The older the child, the higher the prevalence of all symptoms except cough.

The lack of an agreed case definition meant that it was difficult to comment on the prevalence of long COVID in children and young people. We have used a Delphi consensus methodology to propose a research definition [29] for CYP aligned to the WHO clinical definition for adults: 'Post-COVID-19 condition occurs in CYP with a history of confirmed SARS-CoV-2 infection, with one or more persisting physical symptoms for at least 12 weeks after testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after SARS-CoV-2 infection, and may fluctuate or relapse over time'. We believe this definition is an advance that is critical to comparing future research studies, which must also include an appropriate control group.

A sensitivity analysis was used to estimate the range of frequencies for persisting symptoms attributable to SARS-COV-2 infection [25]. For UK, 1.8–14% of the 234 803 teenagers who tested positive for SARS-COV-2 between September 2020 and March 2021 would have three or more physical symptoms and 0.9–7% five or more physical symptoms attributable to the SARS-COV-2 virus.

Using a methodology involving randomly surveying households, the United Kingdom Office for National Statistics (ONS) estimated the percentage of young people in England with self-reported 'long COVID' (i.e. without a specified case definition) of any duration as 0.51% for those aged 12–16 years and 1.21% for those aged 17–24 years, equating to 31 080 teenagers aged 11–17 years across UK [30].

As the case definition of long COVID becomes more refined, along with the inclusion of appropriate control groups, prevalence estimates have been gradually revised downwards [31]. Compared with April 2021, for example, when the ONS-reported long COVID prevalence of 7.4% of primary-school aged and 8.2% of secondary school aged children, this was revised down to 3.3% [95% confidence interval (95% CI) 2.5–4.5] and 4.6% (95% CI 3.5–6.0), respectively, in September 2021. Importantly, too, in the more recent ONS analyses, a matched-control group of children had similar prevalence of 'long COVID' despite being likely to have never had COVID-19 disease [3.6% (95% CI 2.7–4.8) and 2.9% (95% CI 2.1–4.0), for primary and secondary-school aged children, respectively].

WHAT WE KNOW NOW?

At least 14 further studies reporting prolonged symptoms in CYP have been published since the 22 reviewed in the systematic review [6▪▪]. Four included a control group [32–34,35▪] and 10 were uncontrolled [36–45]. These newer studies have not changed the main messages from the original systematic review. The dominant persisting symptoms were again tiredness, headache and shortness of breath. CYP in the control group of the largest of these controlled studies [35▪] again had a high rate of persisting symptoms (33.6% compared with 43.7% in CYP with previous proven infection).

Three large Scandinavian registry studies on children provide population data. One from Norway [46▪] showed an increase in primary care use in those with COVID-19, which persisted for up to 6 months. One study from Denmark [47▪] showed that in 25–46% of children (depending on age) 'long COVID' symptoms had not resolved within 1–5 months and a second Danish study [48▪] showed that participants with SARS-CoV-2-positive tests had more long-lasting symptoms and sick leave.

The apparently high rates of reported symptoms in control groups should be interpreted against published prepandemic norms. For example, before the pandemic, 30% of 842 adolescents aged 11–15 years reported fatigue over a 4 to 6-month period [49] and a cross-sectional survey reported 19.9% of 7977 adolescents to have headache, fatigue or asthma [50].

Recently, we developed and internally validated a model to predict which teenagers are most likely to experience at least one impairing physical symptom 3 months after a positive SARS-CoV-2 PCR-test [51]. We found that a persisting, impairing symptom is more likely with increased number of symptoms at the time of testing, female sex, older age and worse self-rated physical and mental health and feelings of loneliness before their SARS-CoV-2 PCR test. Nevertheless, it is important to emphasise that the majority of CYP reporting persisting symptoms post-COVID did not have overt mental health problems pre-COVID.

CRITICISMS OF THESE STUDIES

In our systematic review [6▪▪], we wrote that the majority of the included studies were of poor quality, mostly uncontrolled and retrospective, and open to selection bias. Ten studies were assessed to have high risk of bias, six moderate and six low risk of bias. These sources of bias are also present in the more recent studies, particularly problems of not correcting for confounders, recall bias, referral bias and missing data.

However, these criticisms need to be considered in the context of doing real-world research at pace and scale in the midst of a global pandemic. Epidemiological research starts with a recognition of a new condition with initial case reports, then single-centre studies biased towards the most unwell, and subsequently larger population studies with more rigorous data collection from a more diverse and representative population, ideally with appropriate control groups for comparison.

Many of the CYP long COVID studies derived data from community-based surveys asking parents about their child's experiences or asking children themselves. This maximizes the size of the study population, can access hard to reach minorities and avoids selection bias from recruiting only CYP who seek medical attention. Such studies, however, have three aspects, which are in tension:

(1) The researchers want to ask about as many variables as possible to allow their analysis to address as many potential confounders as possible.
(2) The CYP or their proxy respondents (parents) have views on how much time they will be willing to spend providing this information. In our study, the researchers' initial draft questionnaire asked about a great deal more than the final version but took over an hour to complete. In our pilot study, the teenagers said they would only be willing to spend 20 min maximum completing the survey, despite a financial reward at nationally recommended rates.
(3) Young people can be deterred from completing surveys by being asked for information they consider confidential or intrusive. This can include questions about their parents' or siblings' health, mental health, income and so on. If the same data are asked directly from parents, that may further reduce response rates for similar reasons of concern about confidentiality around sensitive data.

Hence, it would be easy to design the perfect epidemiological study, but whether it can be done in a real world with real young people is another matter. Our response rate of 13.4% [25] was comparable to other COVID-related studies. Office for National Statistics studies had an enrolment rate 12% (July 2020–November 2021) when sampling randomly [52]. Such biases can be explored by comparing the characteristics of the respondents versus nonrespondents. Finding control groups of CYP who have never been infected will be increasingly difficult in future; vaccinated children who had no previous proven infection would be the next best alternative. Children with other proven viral infections may be an alternative control group. Historical, prepandemic data could be used for comparison where needed. These alternatives are better than no controls at all.

Moreover, all research studies which describe symptoms (whether in person, telephone or online) are, by definition, open to bias. Symptoms are the subjective description of what a person experiences. In any study of a condition without a diagnostic biomarker or confirmation by imaging or biopsy, this is an inherent feature of asking patients about their symptoms.

POTENTIAL MECHANISMS TO EXPLAIN LONG COVID IN CHILDREN

Four potential mechanisms have been postulated to explain long COVID. See Table 1 [53–58].

THE FUTURE

There are a number of priorities going forward. There is still a need for 'deep phenotyping' CYP who describe the persisting symptoms of long COVID. This has been undertaken in adults and detailed imaging, functional physiological testing, cognitive testing and measurement of biomarkers have shown persistent abnormalities in some adults suffering from long COVID [53].

Apps allowing those with persisting symptoms to self-report symptoms and severity on a regular basis (patient-reported outcome measures) have been developed for adults and could be adapted for CYP but need appropriate control groups for comparison.

The broad 'definition' of long COVID in CYP, or indeed the lack of one, brings a whole range of morbidities and severities under one heading. For example, loss of smell and taste constitutes a significant proportion of CYP with long COVID. This is not as great a concern as the more serious but rare outcomes which can leave CYP unable to function. Chronic fatigue syndrome can occur after any severe illness, often with a poor prognosis. We need better long COVID definitions of the different syndromes

Table 1. Four potential mechanisms that have been postulated to explain long COVID

1.	Damage occurs to organs during acute infection and some of the damage persists leading to long-term symptoms. For example, the 'CoverScan' study in adults showed persisting multiorgan impairment in adults [53]. Relatively small numbers of children have been admitted to intensive care with severe organ damage as a result of acute SARS-COV-2 infection. The majority of those with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 appear to be making a full recovery. Therefore, this mechanism seems unlikely to explain persisting post-COVID syndrome in children and young people.
2.	The virus persists in the body, and this leads to the persisting symptoms. This would be analogous to the mechanism of persisting or recurrent symptoms from double stranded DNA herpes viruses causing recurrent genital and labial herpes and shingles [54]. There has been a case report of biopsy proven persistence of the nucleopcapsid protein from the SARS-COV-2 RNA virus in the gut lining of a child with persisting gut symptoms [55]. In autopsies on 44 adults with COVID-19, SARS-CoV-2 was widely distributed, even among patients who died with asymptomatic to mild COVID-19 [56]. Persistent SARS-CoV-2 RNA was detected in multiple anatomic sites, including the brain, for up to 230 days following symptom onset.
3.	There is an underlying autoimmune mechanism whereby antibodies raised against the virus cross react against host tissues. This could be analogous to the mechanism of ataxia some weeks after a varicella infection due to an autoimmune inflammation of the cerebellum [57]. We are not aware of any studies supporting this mechanism in post COVID syndrome in children and young people although autoimmunity has been suggested as a factor in adults [58].
4.	Finally, perhaps none of the above biological mechanisms explain long COVID. The persistence of symptoms is unexplained as in many postviral syndromes in children.

within this condition so that we can develop appropriate referral, diagnostic and management pathways as well as better outcome studies to inform clinicians, parents and policy makers.

Finally, there is a pressing need for intervention studies. Given the multiple and varied symptoms described in over 35 studies reporting persisting post-COVID symptoms in CYP, a multicomponent intervention will be required, building on existing management of common symptoms. Studies of whether vaccination reduces the risk of long COVID in CYP who develop COVID after vaccination would be valuable.

As we continue to improve our understanding of long COVID, there is a need to support the mental health and wellbeing of CYP irrespective of their SARS-CoV-2 infection status. Although the precise number of young people who need help is difficult to ascertain, the demand is likely to exceed resources in many health systems [59,60]. For example, NHS data show that in 2021, there was the highest number of referrals to child and adolescent mental health services between April and October in 2 years. Referrals were up by 52% from 2020 to 2021, with almost 400 000 being referred [61]. YoungMinds, a charity which offers a chat line, online advice and a helpline for parents, recorded a 48% increase in demand in its services between 2019 and 2021. Papyrus, a charity dedicated to the prevention of young suicide, had a 25% increase in calls, texts and emails to its confidential HopelineUK service during the pandemic. Rapid, manualized online assistance may be necessary as a first 'port of call' for early intervention and then triage for face-to-face consultations with hard pressed services for the most severely affected.

CONCLUSION

There remains much uncertainty about the prevalence, natural history, risk factors, mechanisms and outcomes of long COVID in CYP. Nevertheless, we are much better informed now than in late 2020 when estimates of the risk of long COVID CYP ranged from 1 to 51% after SARS-CoV-2 infection. Although some CYP are severely affected and incapacitated long after the initial illness, the majority of the studies reviewed show a milder phenotype in CYP. Long COVID appears to be commoner in female teenagers and those with preexisting physical and mental health problems at the time of infection.

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Conflicts of interest

Terence Stephenson is also the Chair of the Health Research Authority for England and therefore recused

himself from the Research Ethics Application for the CLoCk Study. All other authors report no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed 4 May 2022.
2. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19 2021. https://app.magicapp.org/#/guideline/EQpzKn/section/n3vwoL. Accessed 4 May 2022.
3. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. Acta Paediatr 2021; 110:914–921.
4. Sudre CH, Murray B, Varsavsky T, *et al.* Attributes and predictors of long COVID. Nat Med 2021; 27:626–631.
5. Hysing M, Elgen I, Gillberg C, *et al.* Chronic physical illness and mental health in children. Results from a large-scale population study. J Child Psychol Psychiatry 2007; 48:785–792.
6. ■■ Behnood SA, Shafran R, Bennett SD, *et al.* Persistent symptoms following SARS-CoV-2 infection amongst children and young people: a meta-analysis of controlled and uncontrolled studies. J Infect 2022; 84:158–170.

A recent systematic review and meta-analysis including over half the studies published to date on long COVID in children and young people.

7. Blankenburg J, Wekenborg MK, Reichert J, *et al.* Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic. Sci Rep 2022; 12:2246; https://doi.org/10.1038/s41598-022-06166-y.
8. Brackel CLH, Lap CR, Buddingh EP, *et al.* Pediatric long-COVID: an overlooked phenomenon? Pediatr Pulmonol 2021; 56:2495–2502.
9. Buonsenso D, Espuny Pujol F, Munblit D, *et al.* Clinical characteristics, activity levels and mental health problems in children with long coronavirus disease: a survey of 510 children. Fut Microbiol 2022; 17:577–588.
10. Buonsenso D, Munblit D, De Rose C, *et al.* Preliminary evidence on long COVID in children. Acta Paediatr 2021; 110:2208–2211.
11. Chevinsky JR, Tao G, Lavery AM, *et al.* Late conditions diagnosed 1–4 months following an initial Coronavirus Disease 2019 (COVID-19) encounter: a matched-cohort study using inpatient and outpatient administrative data: United States, 1 March-30 June 2020. Clin Infect Dis 2021; 73(Suppl 1): S5–S16.
12. Denina M, Pruccoli G, Scolfaro C, *et al.* Sequelae of COVID-19 in hospitalized children: a 4-months follow-up. Pediatr Infect Dis J 2020; 39:e458–e459.
13. Leftin Dobkin SC, Collaco JM, McGrath-Morrow SA. Protracted respiratory findings in children post-SARS-CoV-2 infection. Pediatr Pulmonol 2021; 56:3682–3687. doi: 10.1002/ppul.25671.
14. Knoke L, Schlegtendal A, Maier C, *et al.* Pulmonary function and long-term respiratory symptoms in children and adolescents after COVID-19. Front Pediatr 2022; 10:851008. doi: 10.3389/fped.2022.851008.
15. Miller F, Nguyen V, Navaratnam AMD, *et al.* Prevalence of persistent symptoms in children during the COVID-19 pandemic: evidence from a household cohort study in England and Wales. medRxiv 2021. doi: 10.1101/2021.05.28.21257602.
16. Molteni E, Sudre CH, Canas LS, *et al.* Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. Lancet Child Adolesc Health 2021; 5:708–718.
17. Nogueira López J, Grasa C, Calvo C, García López-Hortelano M. Long-term symptoms of COVID-19 in children. Acta Paediatr 2021; 110:2282–2283.
18. Osmanov IM, Spiridonova E, Bobkova P, *et al.* Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study. Eur Respir J 2022; 59:2101341. doi: 10.1183/13993003.01341-2021.
19. Petersen MS, Kristiansen MF, Hanusson KD, *et al.* Long COVID in the Faroe Islands: a longitudinal study among nonhospitalized patients. Clin Infect Dis 2021; 73:e4058–e4063.
20. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term symptoms after SARS-CoV-2 infection in children and adolescents. JAMA 2021; 326:869–871.
21. Rusetsky Y, Meytel I, Mokoyan Z, *et al.* Smell status in children infected with SARS-CoV-2. Laryngoscope 2021; 131:E2475–E2480.
22. Sante GD, Buonsenso D, Rose CD, *et al.* Immune profile of children with postacute sequelae of SARS-CoV-2 infection (Long Covid). medRxiv 2021.
23. Say D, Crawford N, McNab S, *et al.* Postacute COVID-19 outcomes in children with mild and asymptomatic disease. Lancet Child Adolesc Health 2021; 5:e22–e23.
24. Smane L, Stars I, Pucuka Z, *et al.* Persistent clinical features in paediatric patients after SARS-CoV-2 virological recovery: a retrospective population-based cohort study from a single centre in Latvia. BMJ Paediatr Open 2020; 4:e000905-e.
25. Stephenson T, Pinto Pereira SM, Shafran R, *et al.* Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. Lancet Child Adolesc Health 2022; 6:230–239.
26. Sterky E, Olsson-Akefeldt S, Hertting O, *et al.* Persistent symptoms in Swedish children after hospitalisation due to COVID-19. Acta Paediatr 2021; 110:2578–2580.
27. Zavala M, Ireland G, Amin-Chowdhury Z, *et al.* Acute and persistent symptoms in children with PCR-confirmed SARS-CoV-2 infection compared to test-negative children in England: active, prospective, national surveillance. Clin Infect Dis 2022; 75:e191–e200. doi: 10.1093/cid/ciab991.
28. Creswell C, Shum A, Pearcey S, *et al.* Young people's mental health during the COVID-19 pandemic. Lancet Child Adolesc Health 2021; 5:535–537.
29. Stephenson T, Allin B, Nugawela MD, *et al.* Long COVID (post-COVID-19 condition) in children: a modified Delphi process. Arch Dis Child 2022; 107:674–680. doi: 10.1136/archdischild-2021-323624.
30. Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK Statistical bulletins 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/previousReleases.
31. Bhopal SS. Rapid response: long COVID in children: ONS prevalence estimates have been radically revised downwards. BMJ 2021; 374:n2356. doi: https://doi.org/10.1136/bmj.n2356.
32. Bergia M, Sanchez-Marcos E, Gonzalez-Haba B, *et al.* Comparative study shows that 1 in 7 Spanish children with COVID-19 symptoms were still experiencing issues after 12 weeks. Acta Paediatr 2022; 111:1573–1582. doi: 10.1111/apa.16368.
33. Blomberg B, Mohn KG, Brokstad KA, *et al.* Long COVID in a prospective cohort of home-isolated patients. Nat Med 2021; 27:1607–1613.
34. Matsubara D, Chang J, Kauffman HL, *et al.* Longitudinal assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated with COVID-19 infections. J Am Heart Assoc 2022; 11:e023251.
35. ■ Roessler M, Tesch F, Batram M, *et al.* Post COVID-19 in children, adolescents, and adults: results of a matched cohort study including more than 150,000 individuals with COVID-19. Plos One 2021.

A large study from Germany using routine administrative data, rather than self-reports, and including 11 950 children/adolescents and 145 184 adults with confirmed SARS-CoV-2 and matched controls.

36. Asadi-Pooya AA, Nemati H, Shahisavandi M, *et al.* Long COVID in children and adolescents. World J Pediatr 2021; 17:495–499.
37. Bottino I, Patria MF, Milani GP, *et al.* Can asymptomatic or non-severe SARS-CoV-2 infection cause medium-term pulmonary sequelae in children? Front Pediatr 2021; 9:1–5. doi: 10.3389/fped.2021.621019.
38. Capone CA, Misra N, Ganigara M, *et al.* Six month follow-up of patients with multi-system inflammatory syndrome in children. Pediatrics 2021; 148: e2021050973. doi: 10.1542/peds.2021-050973.
39. Mohiuddin Chowdhury ATM, Karim MR, Ali MA, *et al.* Clinical characteristics and the long-term postrecovery manifestations of the COVID-19 patients: a prospective multicenter cross-sectional study. Front Med (Lausanne) 2021; 8:663670.
40. Isoldi S, Mallardo S, Marcellino A, *et al.* The comprehensive clinic, laboratory, and instrumental evaluation of children with COVID-19: a 6-months prospective study. J Med Virol 2021; 93:3122–3132.
41. Kahn R, Berg S, Berntson L, *et al.* Population-based study of multisystem inflammatory syndrome associated with COVID-19 found that 36% of children had persistent symptoms. Acta Paediatr 2022; 111:354–362.
42. Matteudi T, Luciani L, Fabre A, *et al.* Clinical characteristics of paediatric COVID-19 patients followed for up to 13 months. Acta Paediatr 2021; 110:3331–3333.
43. Mei Q, Wang F, Yang Y, *et al.* Health issues and immunological assessment related to Wuhan's COVID-19 survivors: a multicenter follow-up study. Front Med (Lausanne) 2021; 8:617689.
44. Patnaik S, Jain MK, Ahmed S, *et al.* Short-term outcomes in children recovered from multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Rheumatol Int 2021; 41:1957–1962.
45. Penner J, Abdel-Mannan O, Grant K, *et al.* 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. Lancet Child Adolesc Health 2021; 5:473–482.
46. ■ Magnusson K, Skyrud KD, Suren P, *et al.* Healthcare use in 700 000 children and adolescents for six months after covid-19: before and after register based cohort study. BMJ 2022; 376:e066809.

A population study from Norway used nationwide register data to estimate the impact of Covid-19 on long-term healthcare use among 1.3 million children and adolescents.

47. Borch L, Holm M, Knudsen M, *et al.* Long COVID symptoms and duration in ■ SARS-CoV-2 positive children: a nationwide cohort study. Eur J Pediatr 2022; 181:1597–1607.
A national cohort study of 37 522 children aged 0–17 years with SARS-CoV-2 infection verified by PCR (RT-PCR) and a control group of 78 037 randomly selected children, who had not tested positive for SARS-CoV-2, from Denmark.
48. Kikkenborg Berg S, Dam Nielsen S, Nygaard U, *et al.* Long COVID symptoms ■ in SARS-CoV-2-positive adolescents and matched controls (LongCOVID-KidsDK): a national, cross-sectional study. Lancet Child Adolesc Health 2022; 6:240–248.
A Danish study including 24 315 15–18 year olds with a positive SARS-CoV-2 test and 97 257 matched controls.
49. Rimes KA, Goodman R, Hotopf M, *et al.* Incidence, prognosis, and risk factors for fatigue and chronic fatigue syndrome in adolescents: a prospective community study. Pediatrics 2007; 119:e603–e609.
50. Green H, McGinnity A, Meltzer H, *et al.* Mental health of children and young people in Great Britain, 2004: Office for National Statistics; 2005. https://files.digital.nhs.uk/publicationimport/pub06xxx/pub06116/ment-heal-chil-youn-peop-gb-2004-rep1.pdf. Accessed 4 May 2022.
51. Nugawela MD, Stephenson T, Shafran R, *et al.* Developing a model for predicting impairing physical symptoms in children 3 months after a SARS-CoV-2 PCR-test: the CLoCk Study. medRxiv 2022; Accessed 4 May 2022.
52. Office for National Statistics. Coronavirus (COVID-19) infection survey: technical data 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/COVID19infectionsurveytechnicaldata. Accessed 4 May 2022.
53. Dennis A, Wamil M, Alberts J, *et al.* Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open 2021; 11:e048391.
54. Modrow S, Dietrich F, Truyen U, Schätzl H. Viruses with a double-stranded DNA genome. In: Modrow S, Falke D, Truyen U, Schätzl H, editors. Molecular virology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013 pp. 625–873.
55. Arostegui D, Castro K, Schwarz S, *et al.* Persistent SARS-CoV-2 nucleocapsid protein presence in the intestinal epithelium of a pediatric patient 3 months after acute infection. JPGN Rep 2022; 3:e152. doi: 10.1097/PG9.0000000000000152.
56. Chertow D, Stein S, Ramelli S, *et al.* SARS-CoV-2 infection and persistence throughout the human body and brain. ResearchSquare 2021.
57. Paul R, Singhania P, Hashmi M, *et al.* Post chicken pox neurological sequelae: Three distinct presentations. J Neurosci Rural Pract 2010; 1:92–96.
58. Chang SE, Feng A, Meng W, *et al.* New-onset IgG autoantibodies in hospitalized patients with COVID-19. medRxiv 2021.
59. Bunn S, Lewis S. Children's mental health and the COVID-19 pandemic: UK Parliament 2021. https://researchbriefings.files.parliament.uk/documents/POST-PN-0653/POST-PN-0653.pdf. Accessed 4 May 2022.
60. Skripkauskaite S, Shum A, Pearcey S, *et al.* Changes in children's and young people's mental health symptoms: March 2020 to January 2021 (Report 08) 2021. https://cospaceoxford.org/wp-content/uploads/2021/02/Co-SPACE-report-08_06-09-21.pdf. Accessed 4 May 2022.
61. Beal J. Child mental health services at 'breaking point' as referrals rise: The Times; 2022. https://www.thetimes.co.uk/article/child-mental-health-services-at-breaking-point-nhs-referrals-lockdown-tphkjjzn9. Accessed 4 May 2022.