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.

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Research in context

Evidence before this study

This study was designed in November 2020 when there was little known about long COVID in general and long COVID in children and young people (CYP) in particular. Of the few publications, most reported data from clinical populations of CYP seeking treatment and lacked controls. Prior to our study, a search of Medline, Cochrane, medRxiv and PROSPERO did not identify any controlled, cohort studies of continuing symptoms following SARS-CoV-2 infection in non-hospitalised CYP.

Added value of this study

This is a large cohort study of CYP with PCR proven SARS-CoV-2 status, not self-reported infection. The symptoms are reported by the CYP themselves and, importantly, there is a matched test-negative group of CYP who have lived through the 'long pandemic' but never tested positive for SARS-CoV-2. The participants were recruited nationally. Physical and mental health symptoms were described rather than undefined, self-reported 'long COVID'. There was an increase in symptoms for both test-positive and test-negative CYP 15 weeks after testing. The symptom profile was similar between the two groups but with a higher prevalence for test-positives of single and, particularly, multiple symptoms at PCR-testing and 3 months later. Subsequent waves of data collection will allow prospective tracking of mental and physical health symptoms in this cohort.

Implications of all the available evidence

We provide data on the presence of 21 physical symptoms and four wellbeing scales 3 months after SARS-CoV-2 testing in 6,804 CYP. Overall, this evidence demonstrates the multiplicity and heterogeneity of 'long COVID' in children. These findings have implications for services, commissioners, researchers, clinicians and affected families as they elucidate the prevalence and manifestation of long COVID in children not accessing hospitals and inform healthcare systems on service planning.

Abstract

Background: We describe post-COVID symptomatology in a non-hospitalised, national sample of 11–17-year-old children and young people (CYP) with PCR-confirmed SARS-CoV-2 infection compared with matched test-negative CYP.

Methods: A national cohort study of SARS-CoV-2 PCR-positive CYP and age-, sex-, and geographically-matched test-negative CYP, who were tested across England during January to March 2021, were contacted to complete detailed questionnaires 3 months post-test. Baseline data at PCR testing were collected retrospectively; data 3 months later were collected prospectively.

Findings:

A total of 23,048 test-positives and 27,798 test-negatives were contacted and 6,804 CYP (3,065 test-positives, 3,739 test-negatives) completed the 3-month questionnaire (response rate, 13·4%). At PCR-testing, 35·4% of test-positives and 8·3% of test-negatives were symptomatic and 30·6% and 6·2%, respectively, had 3+ symptoms. At 3 months post-testing 66·5% of test-positives and 53·3% of test-negatives had any symptoms, whilst 30·3% and 16·2%, respectively, had 3+ symptoms. At 3 months post-testing, the most common symptoms among test-positives were tiredness, headache and shortness of breath and, among test-negatives, tiredness, headache and "other". Using these data, latent class analysis identified two classes, characterised by "few" or "multiple" symptoms. The estimated probability of being in the multiple symptom class was 29·6% (95% CI, 27·4-31·7%) for test-positives and 19·3% (17·7-21·0%) for test-negatives (risk ratio 1·53; 95% CI, 1·35-1·70). The "multiple symptoms" class was more frequent among PCR-positives, females, older CYP, and those with worse pre-test physical and mental health.

Interpretation: Test-positive CYP had similar symptoms to test-negative CYP but with higher prevalence of single and, particularly, multiple symptoms at PCR-testing and 3 months later.

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Introduction

SARS-CoV-2 in children and young people (CYP) is usually mild[1] compared to adults.[2] However, little is known about the diagnosis, prevalence, phenotype, or duration of long COVID (long haulers; post-acute COVID syndrome) in CYP.[3] The National Institute for Health and Care Excellence (NICE) definitions are:

- Acute COVID-19: symptoms <4 weeks after confirmed infection
- Ongoing symptomatic COVID-19: symptoms 4-12 weeks
- Post-COVID-19 syndrome: >12 weeks

The latter two groups are referred to as 'long COVID'[4] but "post-COVID-19 condition" (WHO) and "post-COVID-19 condition" are also used. NIHR/UKRI funded researchers continue to use long COVID because this is used by the public, healthcare professionals and in searches and systematic reviews.. Therefore, we use long COVID but are explicit that what we report are actual symptoms experienced 3 months after a SARS-CoV-2 test. Over 200 symptoms have been associated with long COVID[5,6] in individuals symptomatic or asymptomatic with acute SARS-CoV-2 and as persistent or intermittent symptoms.[5,6] Adolescents may have a higher risk[1] but it is unclear which long COVID symptoms are related to the viral infection or the effects of lockdown, school closures and social isolation.

A July 2021 literature review of long COVID in CYP identified 21 relevant publications (Supplementary Table 1). These studies included 16,243 CYP <20 years old with 28–324-day follow-up; median follow-up 125 days (25^{th}, 75^{th} centiles: 99, 231). Fourteen (67%) were cohort studies, six (29%) cross-sectional studies and one was a case report. Seven of the 21 studies included population-based control groups. Nine (43%) recruited from a mix of hospitalised and non-hospitalised CYP, eight (38%) recruited from non-hospitalised CYP and four (19%) recruited hospitalised CYP post-discharge. The most common symptoms at 3 months were fatigue, insomnia, anosmia, and headaches.

The reported rate of long COVID in CYP was 1-51%, with smaller studies reporting higher rates. Additionally, a UK survey of self-reported long COVID reported a prevalence of 0·16% for 2-11 years, 0·65% for 12-16 years, and 1·22% for 17-24 years.[7]

The CLoCk study is a national, matched longitudinal cohort study of CYP in England,[8] describing the clinical phenotype and rate of post-COVID physical and mental health problems in CYP with laboratory-confirmed SARS-CoV-2 compared to test-negative CYP. This paper presents the descriptive results from the study 3 months after PCR-testing.

Methods

Design

A cohort study of SARS-CoV-2 PCR-positive CYP aged 11-17 years matched on month of test, age, sex, and geographical area to SARS-CoV-2 test-negative CYP from the Public Health England (PHE) database. PHE receives results of all SARS-CoV-2 PCR tests in England from healthcare (Pillar 1 tests) and community (Pillar 2 tests) settings, irrespective of reason (screened for school attendance; contact; symptomatic). Only NHS number, name, age, sex and postcode are recorded. PHE can access the electronic Patient Demographic Service (PDS), containing name, postal address and vital status (alive/dead) of all NHS patients.

Participants

The CLoCk study collects data on >19,000 CYP at 6, 12 and 24 months after a SARS-CoV-2 PCR test taken September 2020-March 2021.[8] Only the sub-sample of almost 7,000 CYP (from 23,048 test-positives and 27,798 test-negatives invited to participate) tested January-March 2021 (Figure 1) could also report, without recall bias, symptoms ~3 months post-test. Baseline data at PCR testing were collected retrospectively; data 3 months later were collected prospectively.

Sample size calculations

The original study design calculation was that 5,000 participants (2,500 test-positives, 2,500 test-negatives) would have 80% power to detect a ≥4% difference in symptom frequency at 5% significance, if test-negative participants had a 34% symptom prevalence (based on available data at the time),[9] accounting for attrition and possible lower baseline symptom prevalence. A difference of 4% was thought to be clinically relevant and realistic. To achieve these numbers, accounting for potentially differential response rates in test-positives and negatives, we planned to invite twice as many negatives than positives while matching the distribution of age, sex, region and month of testing of the positives. As interest in studying multiple symptoms and in identifying risk factors for long COVID developed, and evidence that long COVID was less common in CYP increased, we realised a larger study was needed. For these reasons, we invited all test-positives and, when numbers allowed, twice the number of test-negatives (except those tested in December 2020 due to funding constraints).[8]

Data collection

CYP tested January-March 2021 were contacted 3 months after testing by letter with reminders 2- and 4-weeks later. Those who consented completed an online questionnaire about their physical and mental health at the time of their PCR test ("baseline") and at the time of completing the questionnaire although symptoms could have waxed and waned over the intervening 3 months; a carer could assist younger CYP and CYP with special educational needs or disability. The completed questionnaires were returned at a median time of 14·9 weeks after testing [IQR, 13·1, 18·9]. A total of 63 test-negative CYP reported having had a previous positive SARS-CoV-2 test (prior to testing) and were excluded. Of the test-positives, 49 went to hospital with 26 staying overnight.

Measures

The questionnaire included demographics, elements of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric COVID-19 questionnaire,[10] and the recent Mental Health of Children and Young people in England surveys.[11] Designed with ISARIC Paediatric Working Group as a harmonised data collection tool to facilitate international comparisons, it included 21 physical symptoms (mostly assessed as present/absent, see Supplementary Document).

The Index of Multiple Deprivation (IMD), derived from the CYP's lower super output area (a small local area level based geographic hierarchy), was used as a proxy for socio-economic status. We used IMD quintiles from most (quintile 1) to least (quintile 5) deprived.

CYP rated their physical and mental health before their SARS-CoV-2 test in two separate questions using a five-category Likert scale; for analysis, we recoded these variables into three categories (very poor/poor, ok and good/very good). To assess mental health and wellbeing, the Strengths and Difficulties Questionnaire (SDQ)[12] 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).[13] A higher SDQ total difficulties score indicates more problems; a higher SWEMWBS score indicates better mental well-being. Quality of life/functioning was measured via the EQ-5D-Y[14] and fatigue was measured by the 11-item Chalder Fatigue Questionnaire (CFQ).[15]

Statistical methods

To assess the representativeness of our study participants, we compared their demographic characteristics (sex, age, region of residence, and IMD) 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

stratified by SARS-CoV-2 test status. As the prevalence of long COVID may vary by age,[1,7] we stratified the analyses into two age-groups that reflected key education stages (11-14y vs. 15-17y).

We used latent class analysis to assess separately whether and how (i) baseline and (ii) 3-month physical symptoms clustered among CYP.[16] We analysed the data jointly by test status but separately by time and allowed for differential model parametrization by SARS-CoV-2 test status. The number of classes was selected by comparing the Akaike and 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.

This is a descriptive study. Significance tests should be avoided in descriptive tables (STROBE);[17] hence we do not report p-values for comparisons by SARS-CoV-2 test status at baseline. However, we do report p-values for crude (unadjusted) comparisons of symptoms by SARS-CoV-2 test status at 3-months post-test (accounting for multiple testing using Bonferroni correction) and also report estimates of latent class prevalence by SARS-CoV-2 test status, as well as their ratio, with confidence intervals computed using the delta method.[18] To assess the impact of potential response bias, we re-weighted all symptom frequencies according to the age, sex, region, IMD and SARS-CoV-2 test status of the responders so that analyses align with the characteristics of the target population. All analyses used STATA v16.0.

Role of the funding source

The Department of Health and Social Care, as the National Institute for Health Research (NIHR), and UK Research & Innovation (UKRI) awarded grant COVLT0022 but were not involved in study design, data collection, analysis or writing.

Results

The completed questionnaires were returned at a median time of 14·9 weeks after testing [25th and 75th centiles: 13·1, 18·9].

Study representativeness

A total of 6,804 CYP tested January-March 2021 completed the 3-month questionnaire (response rate 13.4% (6,804/50,846), Table 1). Overall, there was little difference in demographic characteristics between test-positive and test-negative participants, reflecting the matched-cohort study design (Table 2).

Physical symptoms and profile: baseline and 3-month post-test

At the time of testing, 35·4% (n=1,084) of test-positives and 8·3% (n=309) of test-negatives reported having had any symptoms whilst 30·6% (n=936) of test-positives and 6·2% (n=231) of test-negatives had at least 3 symptoms and 23.7% (n=726) versus 3.8% (n=143) at least 5 symptoms. As differences between test-positives and test negatives become more striking for multiple symptoms than for a single symptom, we use 3+ and 5+ symptoms for illustrative purposes. Table 3 gives comprehensive data on 1, 2, 3, 4 and 5+ symptoms. 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 cough. The prevalence of symptoms varied by SARS-CoV-2 status (e.g., headaches were reported by 26·3% (n=806) of test-positives compared to 4·8% (n=178) of test-negatives). Of note, pre-existing morbidity and problems (e.g., asthma) were broadly similar in SARS-CoV-2 positive and negative participants (Supplementary Table 2). Three months' post-test, the presence of physical symptoms had increased in both groups; 66·5% (n=2,038) of test-positives and 53·3% (n=1,993) of test-negatives had any symptoms whilst 30·3% (n=928) of test-positives and 16·2% (n=603) of test-negatives, respectively, had at least 3 symptoms (and 13.4% (n=411) vs. 6.4% (n=238) at least 5 symptoms;

Table 4). 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 test-positives, 39·0% (n=1,196) and 23·2% (n=710) versus 24·4% (n=911) and 14·2% (n=530) among test-negatives, respectively. Prevalence was higher for 15–17-year-olds than 11–14-year-olds; for example, 44.9% (n=818) of 15–17-year-old test-positives reported being tired compared to 30.4% (n=378) of 11–14-year-old test-positives. When we reweighted the percentage of reported symptoms at baseline and at 3 months post-test, broadly similar patterns were observed to those reported above (Supplementary Table 3). When we compared reasons for testing, the majority of test-negatives were identified via school surveillance (71.1% (n=2,658) versus 25.9% (n=793) among positives; Supplementary Table 4). With the exception of age, no systematic differences were observed in demographic characteristics across reasons for testing (Supplementary Table 5).

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 SWEMWBS) between test-positives and negatives. The SDQ median (25th, 75th centile) was 9 (5,14) for both test-positive and test-negative 11–14-year-olds and 12 (7,16) for test-positives and test-negative 15–17-year-olds. SWEMWBS scores did not vary by age and were similar among test-positives (Mean=21·5, SD=4·3) and test-negatives (Mean=21·4, SD=4·3). Fatigue showed no substantial differences between positives (Mean=13·3, SD=5·2) and negatives (Mean=12·5, SD=5·1), with slightly greater values in older participants. For 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, and younger ones to be more worried/sad (Supplementary Figure 1). Strikingly, overall 40% of both positives and negatives

felt worried, sad or unhappy on the single item of the EQ-5D-Y (39.2% (n=1,467) of negatives and 40.8% (n=1,251) of positives).

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

At baseline, there was no evidence of clustering of physical symptoms for either test-positive or test-negative participants. In contrast, there was evidence of clustering of physical symptoms reported at 3 months, with two sub-groups emerging for both test-positive and test-negative CYP (Supplementary Figures 2 and 3, Supplementary Table 6). In each, the largest subgroup (class 1) had very low prevalence of most physical symptoms, while the second subgroup (class 2) was characterised in both test-positives and test-negatives by multiple symptoms dominated by tiredness, headache, shortness of breath and dizziness. We 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% CI, 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 the "multiple" symptoms class 2 at 3 months were more likely to be female, older and have very poor/poor baseline physical and mental health (Supplementary Table 7). At 3 months, they were more likely to have problems with all 5 items on the EQ-5D-Y scale and in general also had higher SDQ (total difficulties and each subscale) and CFS scores, and lower SWEMWBS scores (Supplementary Table 8).

Discussion

Without a definition of long COVID, we elected not to ask about self-reported long COVID. This study describes child-reported symptoms during their acute illness and 3 months after PCR-proven

SARS-CoV-2 infection, with a PCR-negative comparison group and standardised mental health, well-being and fatigue instruments.

Important findings are, first, three months after the SARS-CoV-2 test, the presence of physical symptoms was higher than at the time of testing, emphasising the importance of having a comparison group to interpret the findings. Although 64·6% (n=1.981) of test-positives reported no symptoms at time of testing (compared to 91·7% (n=3,430) of test-negatives), only 33·5% (n=1,027) of test-positives (and 46·7% (n=1,746) of test-negatives) reported no symptoms at 3 months. This could be due to self-selection; recall bias for symptoms at the time of testing; returning to school from March 2021 following national lockdown from January 2021 with exposure to other infections.

Second, symptoms reported at time of testing did not distinguish test-positives (sore throat, headache, tiredness and loss of smell) and test-negatives (sore throat, headache, fever and cough), potentially because national testing was primarily targeted for those with fever, new onset cough and loss of taste or smell. However, the two groups could be separated according to the number of symptoms at three months, when 30·3% (n=928) of test-positives and 16·2% (n=603) of test-negatives had 3+ symptoms. Consideration of number of symptoms is particularly important given that 53·3% (n=1,993) of the test-negatives had at least one symptom 3 months post-test. These figures should be interpreted against published pre-pandemic norms: 30% of 11-15 year-olds reported fatigue over a 4-6-month pre-pandemic period;[19] a cross-sectional survey of CYP reported 19.9% of adolescents to have headache, fatigue or asthma.[20]

Third, for both test-positives and test-negatives, those assigned to the latent class with "multiple symptoms" at three months were more likely to be female, older and have poorer physical and mental health before COVID-19, suggesting that pre-existing physical and mental health difficulties may influence symptoms at 3 months. Unsurprisingly, regardless of test status, those with multiple physical symptoms at 3 months post-test, concurrently had poorer mental health, reflecting the close relationship between physical and mental health.

Fourth, whilst the prevalence of physical symptoms differed between test-positives and test-negatives, their mental health, wellbeing and fatigue scores were similar. However, a large proportion (~40%) in both groups reported feeling worried, sad or unhappy, consistent with parent-reported surveys of mental health of CYP during the pandemic.[21,22] The findings emphasise the importance of incorporating a comparator matched cohort of test-negative CYP who also experienced a pandemic, school closures and social isolation. Our findings suggest that any definition of long COVID should consider multiple symptoms that impact functioning and recognise different clusters of symptoms.[23]

Finally, given the multiple symptoms at 3 months, a multi-component intervention will be required, building on existing management of symptoms such as chronic fatigue and headaches.[24] The commonest symptoms at 3 months among test-positives of tiredness, headache, shortness of breath, dizziness and anosmia are consistent with other CYP studies,[1,7] which also identified higher symptom prevalence in girls, teenagers and children with long-term conditions.[1]

We show that mental and physical health symptoms are related. Stress may manifest as somatic symptoms,[25] and persisting physical symptoms may be associated with depression and anxiety. Family approaches to continuing symptoms are key,[26] as is the negative impact of protracted medical investigations and treatments.[25]

This study has limitations, including the cross-sectional nature of this initial questionnaire 3 months post-test. The questionnaire will be resent at 6-, 12- and 24-months post-test. Although the study design is prospective, the data on symptoms at PCR-testing were retrospective and hence prone to recall bias. Some symptoms may have been present before SARS-COV-2 infection.

CYP did not report the severity of symptoms and although the number of symptoms could serve as a proxy of overall illness severity, a single severe symptom might be more disabling than several mild symptoms. The EQ-5D-Y is one indicator of severity because it assesses the impact on daily living.

It is possible that some cases may have been misdiagnosed as SARS-CoV-2 negative and vice versa. False negatives may be attributable to the timing of the PCR, swab technique and assay sensitivity. False positives PCR's are rare.

We could not recruit or match on ethnicity, medical history or testing location (as not recorded in PHE Database at testing) but subsequent self-reported ethnicity was very similar in test-positives and negatives (Table 2) and geographical address served as a proxy for socio-economic status; both potentially important variables in long COVID.[27] We did not assess physical symptom severity at the time of testing or 3 months post-test. We used established scales to measure mental health,[12] well-being,[13,14] and fatigue,[15] but acknowledge the limitations of self-reporting and floor/ceiling effects.

Our response rate was 13·4% (n=6,804), comparable to other COVID-related studies. ONS studies had an enrolment rate 12% (July 2020-November 2021) when sampling randomly.[28] The REACT 2 study had a 30% response rate for adults randomly selected from NHS patient lists despite being offered a free antibody test delivered to their home.[29] We cannot deduce how representative the 6,804 respondents were of the 23,048 positives and 27,798 negatives we approached, other than in terms of age, sex, region and IMD quintiles because only NHS number, name, age, sex and postcode were recorded in the PHE database. We can consider a 'sensitivity analysis' of two scenarios. Between 1st September 2020 and 31st March 2021, 234,803 11–17-year-olds tested positive for SARS-CoV-2. If our 13% of respondents are representative of all test-positive 11–17-year-olds, then across England, 70,441 CYP would have 3+ physical symptoms >3 months after a positive test and 30,524 would have 5+ physical symptoms. How many of these are attributable to SARS-CoV-2 infection over and above the background symptom levels in teenagers who tested negative? The excess is 32,872 (1 in 7 or 14% of 234,803) with 3+ physical symptoms and 16,436 (1 in 14 or 7%) with 5+ physical symptoms.

The ONS estimated the percentage of CYP in England with self-reported long COVID of any duration as 0.51% for 12-16 years and 1.21% for 17-24 years, equating to 31,080 11-17-year-olds across

England.[7] Despite differences in definitions and methodology, this is very similar to our figure of 32,872 11–17-year-olds (1 in 7 or 14% of 234,803) with 3+ persisting physical symptoms attributable to SARS-CoV-2.

However, if our 13% of responders are entirely unrepresentative and the 87% non-responders had completely recovered, then 9,157 of the 234,803 11–17-year-olds who tested positive for SARS-CoV-2 would have 3+ physical symptoms >3 months after a positive test and 3,968 would have 5+ symptoms physical symptoms. The number attributable to SARS-CoV-2 infection over and above the background symptom levels in test-negative teenagers is 4,273 (1 in 50 or 1.8% of 234,803) with 3+ physical symptoms and 2,137 with 5+ physical symptoms (1 in 100 or 0.9% of 234,803).

Both scenarios indicate the additional risk of multiple symptoms >3 months after a SARS-CoV-2 positive test is much less than the 51% feared (Supplementary Table 1).

Another limitation is that we did not assess whether symptoms were intermittent or continuous for the entire 3 months. Finally, the experiences of CYP were likely to vary depending on whether they were in lockdown or attending school at the time. At the time of their PCR-testing, schools were closed, while, at 3 months after testing, schools had reopened albeit with social distancing, repeated testing and restriction of activities.

Our findings reflect a period when the Alpha variant was predominant in the UK. The rate of continuing post-COVID symptoms may change with different variants.

In summary, our research demonstrates (1) the importance of having a test-negative comparison group to interpret findings, (2) it is essential to consider multiple symptoms in the phenotype of long COVID, (3) mental and physical health symptoms should both be considered, (4) PCR-proven SARS-CoV-2 positive CYP had a higher frequency of any symptoms and multiple physical symptoms 3 months post-test than test-negatives.

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Olivia Swann and Elizabeth Whittaker designed the elements of the ISARIC Paediatric COVID-19 follow-up questionnaire which were incorporated into the online questionnaire used in this study to which all the CLoCk Consortium members contributed.

All members of the CLoCk Consortium made contributions to the conception or design of the work; were involved in drafting both the funding application and this manuscript; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of interests

Terence Stephenson is Chair of the Health Research Authority and therefore recused himself from the Research Ethics Application.

Trudie Chalder is a member of the NICE committee for Long COVID. She has written self-help books on chronic fatigue and has conducted workshops on chronic fatigue and post infectious syndromes.

All remaining authors have no conflicts of interest.

Data sharing statement: Data is not publicly available. All requests for data will be reviewed by the Children & young people with Long Covid (CLoCk) study team, to verify whether the request is subject to any intellectual property or confidentiality obligations. Requests for access to the participant-level data from this study can be submitted via email to Clock@phe.gov.uk with detailed proposals for approval. A signed data access agreement with the CLoCK team is required before

accessing shared data. Code is not made available as we have not used custom code or algorithms central to our conclusions.

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Table 1. Response rate of participants who completed the 3-month questionnaire by sex, age, area of residence and Index of Multiple Deprivation at time of testing, overall and stratified by SARS-CoV-2 status.

SARS-CoV-2 Status			Target Population N	Study Participants N	Study Participants *% of Target Population*
Overall			**50,846**	**6,804**	***13·4***
Negative	**All**		27,798	3,739	*13·5*
	Sex	Female	15,120	2,352	*15·6*
		Male	12,678	1,387	*10·9*
	Age *(y)*	11-14	12,689	1,609	*12.7*
		15-17	15,109	2,130	*14.1*
	Region	East Midlands	2,132	340	*15·9*
		East of England	4,278	630	*14·7*
		London	5,356	629	*11·7*
		North East	925	122	*13·2*
		North West	3,816	426	*11·2*
		South East	4,262	620	*14·5*
		South West	1,554	293	*18·9*
		West Midlands	3,414	431	*12·6*
		Yorkshire and the Humber	2,061	248	*12·0*
	Index of Multiple Deprivation				
		Quintile 1 (most deprived)	8,097	756	*9.3*
		Quintile 2	6,300	740	*11.7*
		Quintile 3	4,978	733	*14.7*
		Quintile 4	4,439	718	*16.2*
		Quintile 5 (least deprived)	3,984	792	*19.9*
Positive	**All**		23,048	3,065	*13·3*
	Sex	Female	12,412	1,945	*15·7*
		Male	10,636	1,120	*10·5*
	Age *(y)*	11-14	10,651	1,244	*11.7*
		15-17	12,397	1,821	*14·7*
	Region	East Midlands	1,815	297	*16·4*
		East of England	3,392	466	*13·7*
		London	4,412	510	*11·6*
		North East	819	111	*13·6*
		North West	3,235	371	*11·5*
		South East	3,496	483	*13·8*
		South West	1,238	238	*19·2*
		West Midlands	2,854	373	*13·1*
		Yorkshire and the Humber	1,787	216	*12·1*
	Index of Multiple Deprivation				
		Quintile 1 (most deprived)	6,732	643	*9.6*
		Quintile 2	5,198	633	*12.2*
		Quintile 3	4,159	571	*13.7*
		Quintile 4	3,679	593	*16.1*
		Quintile 5 (least deprived)	3,280	625	*19.1*

Table 2. Frequencies (and percentages) of participants who completed the 3-month questionnaire by sex, age, ethnicity, area of residence and Index of Multiple Deprivation at time of testing, overall and stratified by SARS-CoV-2 status.

	All participants		SARS-CoV-2 Negative		SARS-CoV-2 Positive	
	N	%	N	%	N	%
All	6,804	*100·0*	3,739	*100·0*	3,065	*100·0*
Female	4,297	*63·2*	2,352	*62·9*	1,945	*63·5*
Age (years)						
11-14	2,853	*41.9*	1,609	*43.0*	1,244	*40.6*
15-17	3,951	*58.1*	2,130	*57.0*	1,821	*59.4*
Ethnicity						
White	5,035	*74·0*	2,804	*75·0*	2,231	*72·8*
Asian/Asian British	1,011	*14·9*	520	*13·9*	491	*16·0*
Mixed	342	*5·0*	195	*5·2*	147	*4·8*
Black/African/Caribbean	249	*3·7*	140	*3·7*	109	*3·6*
Other	115	*1·7*	55	*1·5*	60	*2·0*
Unknown	52	*0·8*	25	*0·7*	27	*0·9*
Region						
East Midlands	637	9·4	340	9·1	297	9·7
East of England	1,096	16·1	630	16·9	466	15·2
London	1,139	16·7	629	16·8	510	16·6
North East	233	3·4	122	3·3	111	3·6
North West	797	11·7	426	11·4	371	12·1
South East	1,103	16·2	620	16·6	483	15·8
South West	531	7·8	293	7·8	238	7·8
West Midlands	804	11·8	431	11·5	373	12·2
Yorkshire and the Humber	464	6·8	248	6·6	216	7·1
Index of Multiple Deprivation						
Quintile 1 (most deprived)	1,399	20.6	756	20.2	643	21.0
Quintile 2	1,373	20.2	740	19.8	633	20.7
Quintile 3	1,304	19.2	733	19.6	571	18.6
Quintile 4	1,311	19.3	718	19.2	593	19.4
Quintile 5 (least deprived)	1,417	20.8	792	21.2	625	20.4

Table 3. Number and percentage of reported symptom(s) at the time of test and physical and mental health before test, by SARS-CoV-2 status, overall and stratified by age-group.

	All participants				Age: 11-14				Age: 15-17			
	SARS-CoV-2 Negative		SARS-CoV-2 Positive		SARS-CoV-2 Negative		SARS-CoV-2 Positive		SARS-CoV-2 Negative		SARS-CoV-2 Positive	
	N	%	N	%	N	%	N	%	N	%	N	%
At time of test												
All	3,739	*100·0*	3,065	*100·0*	1,609	*100·0*	1,244	*100·0*	2,130	*100·0*	1,821	*100·0*
No reported symptoms	3,430	*91·7*	1,981	*64·6*	1,450	*90.1*	830	*66.7*	1,980	*93·0*	1,151	*63.2*
1 symptom	35	*0.9*	60	*2.0*	22	*1.4*	32	*2.6*	13	*0·6*	28	*1.5*
2 symptoms	43	*1.2*	88	*2.9*	29	*1.8*	45	*3.6*	14	*0·7*	43	*2.4*
3 symptoms	52	*1.4*	101	*3.3*	29	*1.8*	50	*4.0*	23	*1·1*	51	*2.8*
4 symptoms	36	*1.0*	109	*3.6*	15	*0.9*	56	*4.5*	21	*1·0*	53	*2.9*
5+ symptoms	143	*3·8*	726	*23·7*	64	*4.0*	231	*18.6*	79	*3.7*	495	*27.2*
Specific symptoms												
Fever	148	*4·0*	548	*17·9*	76	*4·7*	195	*15·7*	72	*3·4*	353	*19·4*
Chills	91	*2·4*	461	*15·0*	40	*2·5*	154	*12·4*	51	*2·4*	307	*16·9*
Persistent cough	143	*3·8*	476	*15·5*	67	*4.2*	149	*12·0*	76	*3·6*	327	*18·0*
Tiredness	125	*3·3*	696	*22·7*	57	*3·5*	233	*18·7*	68	*3·2*	463	*25.4*
Shortness of breath	56	*1·5*	354	*11·6*	19	*1·2*	83	*6·7*	37	*1·7*	271	*14·9*
Loss of smell	55	*1·5*	631	*20·6*	24	*1·5*	210	*16.9*	31	*1·5*	421	*23·1*
Unusually hoarse voice	41	*1·1*	145	*4·7*	16	*1·0*	42	*3·4*	25	*1·2*	103	*5·7*
Unusual chest pain	57	*1·5*	280	*9·1*	13	*0.8*	71	*5·7*	44	*2·1*	209	*11·5*
Unusual abdominal pain	44	*1·2*	138	*4·5*	21	*1·3*	55	*4·4*	23	*1·1*	83	*4·6*
Diarrhoea	41	*1·1*	166	*5·4*	20	*1·2*	52	*4·2*	21	*1·0*	114	*6·3*
Headaches	178	*4·8*	806	*26·3*	86	*5·3*	306	*24·6*	92	*4·3*	500	*27·5*
Confusion, disorientation or drowsiness	29	*0·8*	225	*7·3*	9	*0·6*	53	*4·3*	20	*0.9*	172	*9·5*
Unusual eye-soreness	30	*0·8*	185	*6·0*	13	*0·8*	56	*4·5*	17	*0·8*	129	*7·1*
Skipping meals	67	*1·8*	360	*11·8*	23	*1·4*	103	*8.3*	44	*2·1*	257	*14·1*
Dizziness or light-headedness	86	*2·3*	462	*15·1*	33	*2·1*	133	*10·7*	53	*2·5*	329	*18·1*
Sore throat	200	*5·4*	687	*22·4*	98	*6.1*	241	*19·4*	102	*4·8*	446	*24·5*
Unusual strong muscle pains	45	*1·2*	338	*11·0*	17	*1·1*	99	*8·0*	28	*1·3*	239	*13·1*
Earache or ringing in ears	41	*1·1*	155	*5·1*	11	*0·7*	44	*3·5*	30	*1·4*	111	*6·1*

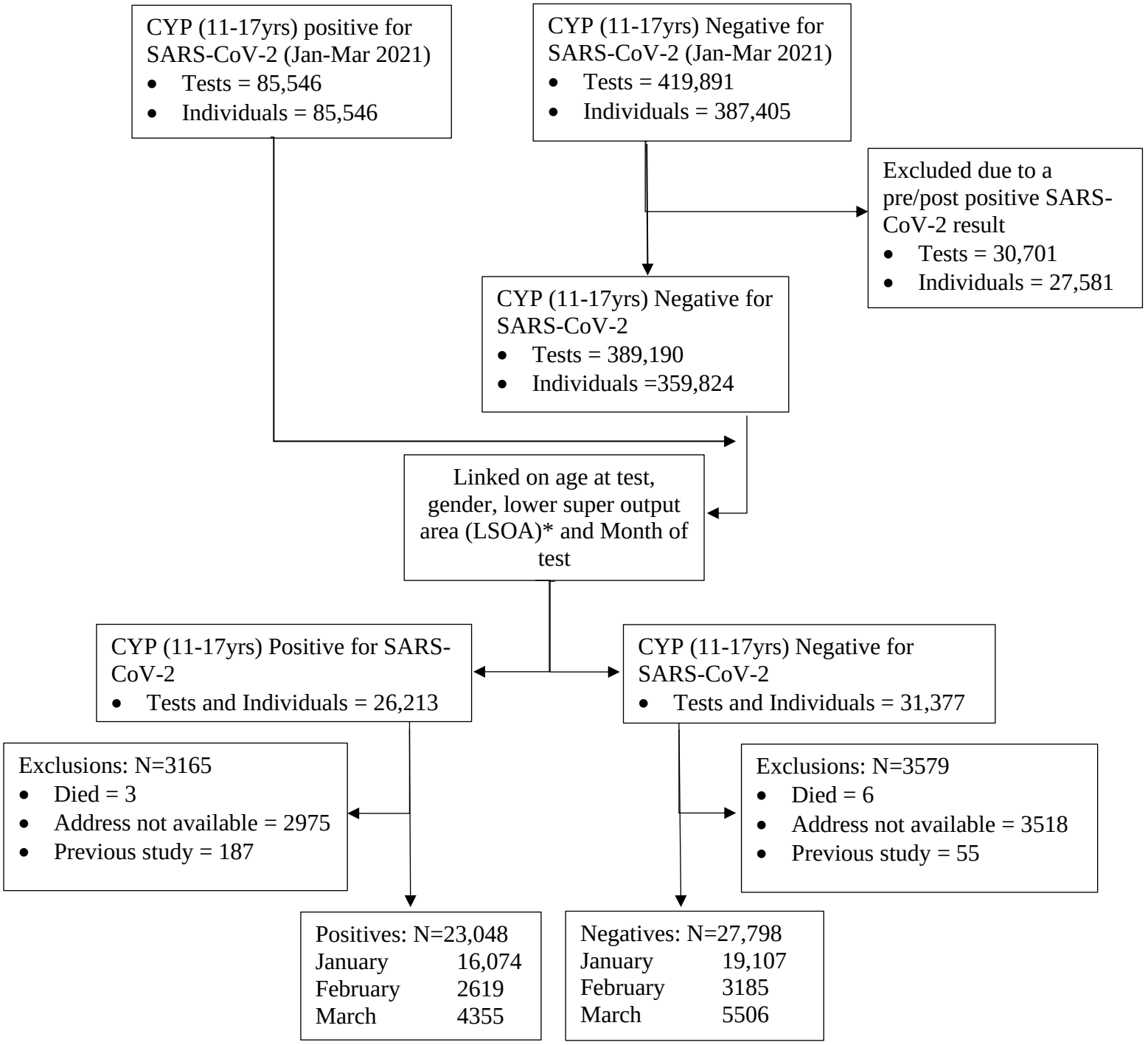
Raised welts on skin or swelling	7	*0·2*	35	*1·1*	3	*0·2*	14	*1·1*	4	*0·2*	21	*1·2*
Red/purple sores/blisters on feet	9	*0·2*	21	*0·7*	5	*0·3*	7	*0·6*	4	*0·2*	14	*0·8*
Other	17	*0·5*	73	*2·4*	13	*0·8*	29	*2·3*	4	*0·2*	44	*2·4*
Before test												
Previous physical health												
Very poor/poor	81	*2.2*	66	*2.2*	22	*1.4*	14	*1.1*	59	*2.8*	52	*2.9*
Ok	800	*21.4*	670	*21.9*	281	*17.5*	223	*17.9*	519	*24.4*	447	*24.6*
Good/ very good	2,858	*76.4*	2,329	*76.0*	1,306	*81.2*	1,007	*81.0*	1,552	*72.9*	1,322	*72.6*
Previous mental health												
Very poor/poor	362	*9.7*	279	*9.1*	84	*5.2*	60	*4.8*	278	*13.1*	219	*12.0*
Ok	1065	*28.5*	901	*29.4*	341	*21.2*	265	*21.3*	724	*34.0*	636	*34.9*
Good/ very good	2312	*61.8*	1885	*61.5*	1,184	*73.6*	919	*73.9*	1,128	*53.0*	966	*53.1*

Table 4. Number and percentage of reported symptom(s) at the 3 months questionnaire by SARS-CoV-2 status, overall and stratified by age-group.

	All participants					Age: 11-14					Age: 15-17				
	SARS-CoV-2 Negative		SARS-CoV-2 Positive			SARS-CoV-2 Negative		SARS-CoV-2 Positive			SARS-CoV-2 Negative		SARS-CoV-2 Positive		
	N	%	N	%		N	%	N	%		N	%	N	%	
At time of 3-month questionnaire															
All	3,739	*100·0*	3,065	*100·0*		1,609	*100·0*	1,244	*100·0*		2,130	*100·0*	1,821	*100·0*	
No reported symptoms	1,746	*46.7*	1,027	*33.5*		845	*52.5*	492	*39.6*		901	*42.3*	535	*29·4*	
1 symptom	1,019	*27.3*	671	*21.9*		436	*27.1*	293	*23.6*		583	*27.4*	378	*20.8*	
2 symptoms	371	*9.9*	439	*14.3*		123	*7.6*	167	*13.4*		248	*11.6*	272	*14.9*	
3 symptoms	228	*6.1*	300	*9.8*		68	*4.2*	91	*7.3*		160	*7.5*	209	*11.5*	
4 symptoms	137	*3.7*	217	*7.1*		51	*3.2*	70	*5.6*		86	*4.0*	147	*8.1*	
5+ symptoms	238	*6·4*	411	*13·4*	**	86	*5·3*	131	*10·5*	**	152	*7·1*	280	*15·4*	**
Specific symptoms															
Fever	55	*1·5*	50	*1·6*		18	*1·1*	9	*0·7*		37	*1·7*	41	*2·3*	
Chills	192	*5·1*	269	*8·8*	**	88	*5·5*	96	*7.7*		104	*4·9*	173	*9·5*	**
Persistent cough	98	*2·6*	98	*3·2*		41	*2·6*	35	*2·8*		57	*2·7*	63	*3·5*	
Tiredness	911	*24·4*	1,196	*39·0*	**	277	*17.2*	378	*30·4*	**	634	*29·8*	818	*44.9*	**
Shortness of breath	388	*10·4*	717	*23·4*	**	135	*8·4*	202	*16·2*	**	253	*11·9*	515	*28·3*	**
Loss of smell	51	*1·4*	414	*13·5*	**	12	*0·8*	145	*11·7*	**	39	*1·8*	269	*14·8*	**
Unusually hoarse voice	46	*1·2*	56	*1·8*		20	*1·2*	21	*1·7*		26	*1·2*	35	*1·9*	
Unusual chest pain	129	*3·5*	216	*7·1*	**	46	*2.9*	61	*4·9*		83	*3·9*	155	*8·5*	**
Unusual abdominal pain	107	*2·9*	119	*3·9*		33	*2·1*	43	*3·5*		74	*3·5*	76	*4·2*	
Diarrhoea	80	*2·1*	92	*3·0*		29	*1·8*	35	*2.8*		51	*2·4*	57	*3·1*	
Headaches	530	*14·2*	710	*23·2*	**	174	*10·8*	258	*20·7*	**	356	*16·7*	452	*24·8*	**
Confusion, disorientation or drowsiness	123	*3·3*	198	*6·5*	**	43	*2.7*	61	*4·9*		80	*3·8*	137	*7·5*	**
Unusual eye-soreness	134	*3·6*	182	*5·9*	**	49	*3·1*	55	*4·4*		85	*4·0*	127	*7·0*	**
Skipping meals	275	*7·4*	296	*9·7*	*	91	*5·7*	84	*6·8*		184	*8·6*	212	*11·6*	
Dizziness or light-headedness	314	*8·4*	419	*13·7*	**	104	*6·5*	123	*9·9*		210	*9·9*	296	*16·3*	**
Sore throat	281	*7·5*	291	*9·5*		107	*6·7*	129	*10·4*	*	174	*8·2*	162	*8·9*	
Unusual strong muscle pains	83	*2·2*	165	*5·4*	**	29	*1·8*	56	*4·5*	**	54	*2·5*	109	*6·0*	**
Earache or ringing in ears	165	*4·4*	191	*6·2*		71	*4·4*	72	*5·8*		94	*4·4*	119	*6·5*	
Raised welts on skin or swelling	32	*0·9*	48	*1·6*		15	*0·9*	22	*1·8*		17	*0·8*	26	*1·4*	
Red/purple sores/blisters on feet	40	*1·1*	35	*1·1*		17	*1·1*	14	*1·1*		23	*1·1*	21	*1·2*	
Other	590	*15·8*	335	*10·9*	**	280	*17·4*	145	*11·7*	**	310	*14·6*	190	*10·4*	**

*p-value <0.05 **p-value<0.01 from Pearson's chi-squared test for the difference between SARS-CoV-2 negative and positive participants in terms of number of reported symptoms (0, 1, 2, 3, 4, 5+) and each specific symptom, after correction for multiple testing using Bonferroni adjustment.

Figure 1. Flowchart of young people invited to participate in the Study.



*lower super output areas are a standardised geographic hierarchy designed to improve the reporting of small area statistics in England and Wales. For more details see: https://datadictionary.nhs.uk/nhs_business_definitions/lower_layer_super_output_area.html