Acute and persistent symptoms in children with PCR-confirmed SARS-CoV-2 infection compared to test-negative children in England: active, prospective, national surveillance

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Summary: We found a higher prevalence of acute (68% vs 40%) and on-going symptoms at 1 month (6.7% vs 4.2%) in children with PCR-confirmed COVID-19 compared to PCR-negative symptomatic controls, but mental health symptoms were high and equally prevalent in both.

Abstract

Background

Most children recover quickly after COVID-19, but some may have on-going symptoms. Follow-up studies have been limited by small sample sizes and lack of appropriate controls

Methods

We used national testing data to identify children aged 2-16 years with a SARS-CoV-2 PCR test during 01-07 January 2021 and randomly selected1,500 PCR-positive cases and 1,500 matched PCR-negative controls. Parents were asked to complete a questionnaire about the acute illness and pre-specified neurological, dermatological, sensory, respiratory, cardiovascular, gastrointestinal, mental health (including emotional and behavioural well-being) and other symptoms experienced at least five times at one month after the PCR test.

Results

Overall, 35.0% (859/2456) completed the questionnaire, including 38.0% (472/1242) cases and 32% (387/1214) controls. of whom 68% (320/472) and 40% (154/387) were symptomatic, respectively. The most prevalent acute symptoms were cough (249 /859, 29.0%), fever (236/859, 27.5%), headache (236/859, 27.4%) and fatigue (231/859, 26.9%). One month later, 21/320 (6.7%) of symptomatic cases and 6/154 (4.2%) of symptomatic controls (p=0.24) experienced on-going symptoms. Of the 65 on-going symptoms solicited, three clusters were significantly (p<0.05) more common, albeit at low prevalence, among symptomatic cases (3-7%) than symptomatic controls (0-3: neurological, sensory and emotional and behavioural wellbeing. Mental health symptoms were reported by all groups but more frequently among symptomatic cases than symptomatic controls or asymptomatic children.

Conclusions

Children with symptomatic COVID-19 had a slightly higher prevalence of on-going symptoms than symptomatic controls, and not as high as previously reported. Healthcare resources should be prioritised to support the mental health of children.

Key words: SARS-CoV-2 infection, COVID-19, transmission, long COVID, children.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus was first identified in China in December 2019 and spread rapidly across the continents, causing millions of cases and deaths worldwide [1]. In the United Kingdom, the first imported cases were identified in January 2020, with the first confirmed cases in children on 29 February 2021 [2]. COVID-19 typically presents as fever, cough or loss of smell or taste, and is usually self-limiting, although, in some, may progress to severe pneumonia, multiorgan failure and death [3-5]. Age is the most important risk factor for severe and fatal COVID-19, although other factors including ethnicity, co-morbidities and obesity are also associated with increased risk [6].

While most adults recover without sequelae, some survivors will have on-going symptoms, commonly known as long COVID or post-COVID syndrome, which may last for weeks to months after acute infection [7, 8]. So far, more than 200 on-going symptoms have been reported in adults and children [9]. The most prevalent symptoms across multiple studies include fatigue, shortness of breath and loss of smell or taste [7, 10]. In an attempt to standardise the case condition, the UK National Institute for Health and Care Excellence (NICE) has proposed two categories based on symptoms duration: *ongoing symptomatic COVID-19* in patients with symptoms persisting for 4-12 weeks after an infection consistent with COVID-19 and *post-COVID-19 syndrome*, when symptoms develop during or after an infection consistent with COVID-19, continue for >12 weeks and are not explained by an alternative diagnosis [11].

Unlike adults, children have a lower risk of severe disease, hospitalisation or death due to COVID-19 [2, 12]. Most children exposed to SARS-CoV-2 remain asymptomatic or develop mild, self-limiting upper respiratory tract symptoms which resolve within a few days [13]. There have, however, been increasing reports of long COVID in children, with one online survey indicating that 90% of children did not regain normal health up to 6-8 months after

confirmed or suspected COVID-19 [14, 15]. Many of the earlier publications, however, have been limited by a lack of laboratory-confirmed diagnosis among cases or comparison with a control group that did not have COVID-19, although more recent studies/surveys have tried to address some of these issues [13, 16-18]. This investigation aimed to determine the course of illness and on-going symptoms in children aged 2-16 years with laboratory-confirmed SARS-CoV-2 infection compared to test-negative children in England during January 2021, when the Alpha variant was prevalent.

Methods

Public Health England (PHE) receives daily electronic notification of SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) tests performed in healthcare settings and in the community through the Second-Generation Surveillance System (SGSS) [19]. SGSS data include name, date of birth, region, postcode, unique individual National Health Service (NHS) number, date of sample, reporting laboratory and test result. PHE also has access to the online Personal Demographic Service (PDS) which contains name, addresses and status (alive or dead) of all NHS-registered persons registered [20]. SGS test results for 2-16 year-olds with a SARS-CoV-2 RT-PCR taken during 01-07January 2021 in England were linked with PDS. Confirmed cases were defined as all RT-PCR positive children (n=26,820), while controls included all RT-PCR negative children who had previously never tested positive for SARS-CoV-2 (n=98,483). Using STATA® v.15.0 (StataCorp LLC, College Station, Texas), cases and controls were stratified by age in years and partial postcode in eight and 78 stratas respectively, making a total of 939 stratas. A random sample from each *strata* was taken to produce a total sample size of 1,500 cases with the same number of controls matched. On 22 February, an invitation letter was sent to cases and controls with an online link, a QR code to access the online survey developed using SnapSurvey v.11 (*see Supplementary Questionnaire),* and a paper version of the questionnaire with a stamped,

self-addressed envelope. The questionnaire was designed to be completed by the child's parent/guardian of the child and was developed following an extensive literature review of common symptoms associated with long COVID in the scientific literature and online, including those reported in adults and assessed by the study investigators to be applicable to children. The questionnaire was designed to be completed at least one month after the initial RT-PCR test. The final questionnaire requested about demographics, COVID-19 symptoms at the time of testing, household composition, confirmed cases in the household and pre-specified symptoms at the time of the RT-PCR test and at least one month later. Symptomatic cases and controls were defined as children with a positive or negative PCR test, respectively, during 01-07 January 2021 who reported any symptom at the time of the test. Asymptomatic cases and controls were defined as children who had a positive or negative PCR test, respectively, and whose parents reported no symptoms for their child at the time of the test. Elicited on-going symptoms in cases and controls were divided into neurological, dermatological, sensory, respiratory and cardiovascular, gastrointestinal, mental health (including emotional and behavioural wellbeing) and other, allowing parents to report any other symptoms not included in the questionnaire. Symptoms were defined as ongoing if experienced at least five times a month at least one month after the PCR test. Two reminders were sent to the families did not complete the questionnaire two and four weeks after the initial invitation letter. Index of multiple deprivation (IMD) was used as a proxy measure for socio-economic status and was obtained using postcodes from the Ministry of Housing, Communities & Local Government website [21].

Statistical analysis

Data were managed using Microsoft Access and analysed using Stata® 15.1 (StataCorp LLC, College Station, Texas). Categorical data are reported as frequencies and proportions and compared using the $\chi 2$ test or Fisher's exact test. Continuous data are summarised as medians with interquartile ranges and compared using the Mann Whitney U test. Data were further explored by fitting logistic regressions models for symptoms that were statistically

significant in the univariate analysis comparing symptomatic cases vs controls and asymptomatic cases vs controls, after adjusting for age, sex, ethnicity, socio-economic status and comorbidities. Results are reported as odd ratios (OR) and adjusted odd ratios (aOR) with 95% confidence intervals (CI).

Results

Of the 1,500 cases and 1,500 controls identified initially, 1,257 cases and 1,217 controls had sufficient contact information to post an invitation letter and 18 (15 cases, 3 controls) were returned because their postal address was incorrect (Figure 1). A total of 2,456 children were, therefore, invited and 35.0% (859/2456) completed the questionnaire during March (n=680) and April (n=179) 2021, including 38.0% (472/1242) laboratory-confirmed SARS-CoV-2 RT-PCR positive cases and 32% (387/1214) SARS-CoV-2 RT-PCR negative controls. Among the positive cases, 32.2% (152/472) were asymptomatic at the time of the RT-PCR test. Demographics were similar between symptomatic and asymptomatic cases and controls (**Table 1**). Symptomatic cases had mild illness and only one symptomatic case required hospitalisation. Comparison of demographic data showed no significant differences between respondents and non-respondents except older age among respondents (median age, 10 vs 6 years).

Symptoms at presentation

At the time of the RT-PCR test, the most prevalent symptoms among children who displayed any symptom included cough (29.0%, 249 /859), fever (27.5%, 236/859), headache (27.5%, 236/859) and fatigue (26.9%, 231/859) (**Table 2**). Thirteen of the eighteen elicited symptoms were significantly more prevalent among cases than controls (**Table 2**). The most common reason for testing was because the child was identified as a contact of a household case

(38.7%, 327/859), the child had COVID-19 symptoms (27.6%, 233/859) or due to another reason not specified in the survey (17.06%, 144/859), such as school testing or parental choice. More than half the symptomatic cases were tested because they were contacts of a household case (51.9%, 166/320) compared to symptomatic controls (14.3%, 22/154; p<0.001). The same was also true for asymptomatic cases (63.6%, 96/152) compared to asymptomatic controls (19.63%, 43/233; p<0.001).

On-going symptoms

One month after the RT-PCR test, a higher proportion of parents of symptomatic cases (6.73%, 21/320) reported that their child was still unwell than symptomatic controls (4.20%, 6/154; p==0.24).24). The 64 elicited on-going symptoms were categorised as follows: neurological, dermatological, sensory, respiratory, mental health, gastrointestinal and other. Of these, nine were significantly more prevalent among symptomatic cases compared to symptomatic controls **(Table 3)** and clustered into three categories (Figure 2)**.** Differences in neurological symptoms included confusion, which was only reported for symptomatic cases (5.6% [18/320] vs. 0/154; p=0.001). Differences in sensory symptoms included loss of taste (5.3% [17/320] vs 0.65% [1/154]; p=0.01), loss of smell (6.9% [22/320] vs. 0.65% [1/154]; p=0.002) and eye pain, which was only reported for symptomatic cases (2.8% [9/320] vs. 0/154; p=0.035). Differences in mental health symptoms between symptomatic cases and controls included sadness (6.9% [22/320] vs 1.3%[2/154] p=0.007), difficulty sleeping (8.8% [28/320] vs 3.3% [5/154] p=0.033), depression (4.1% [13/320] vs 0.65% [1/154]; p=0.043), mood swings (7.8% [25/320] vs 2.0% [3/154]; p=0.011) and anxiety (7.81% [25/320] vs 2.6% [4/154] p=0.025).

Logistic regression analysis was performed for the seven on-going symptoms that were significantly different between symptomatic cases and symptomatic controls in the univariate analysis. After adjusting for age, sex, ethnicity, socioeconomic status and comorbidity status,

five on-going symptoms were independently associated with symptomatic COVID-19 (**Table 4**). Logistic regression analysis was not possible for confusion and eye pain, which were only reported among cases. Neurological symptoms included confusion which was only reported for symptomatic cases. Sensory problems included loss of smell (aOR 10.2 [1.3-79.1]; p=0.026) and eye pain which was only reported for symptomatic cases. Loss of smell was also independently associated with older age-group (14-16 year: 21% [15/72] vs. 1.4% [1/73]; aOR 18.4, 95% CI: 2.35- 144.53; p=0.006). Mental health symptoms included sadness (aOR 5.3 [1.2-23.1]; p=0.026), difficulty sleeping (aOR 2.8 [1.1-7.6]; p=0.037), mood swings (aOR 3.94 [1.2-13.4]; p=0.028) and anxiety (aOR 3.0 [1.0-8.9]; p=0.049).

In the univariate analysis, none of the symptoms were significantly more prevalent among asymptomatic cases compared to asymptomatic controls. Although not statistically significant, reports of mental health symptoms were abundant among both asymptomatic cases and asymptomatic controls.

Discussion

At the time of their RT-PCR test, symptomatic children with laboratory-confirmed COVID-19 had a higher prevalence of elicited symptoms than test-negative symptomatic children, especially cough (36.2%), fatigue (35.0%) and fever (33.1%). One month later, 6.7% of symptomatic cases and 4.2% of symptomatic controls had on-going symptoms. Of the 64 elicited symptoms, nine were more common among symptomatic cases than symptomatic controls, but not among asymptomatic cases or asymptomatic controls.

Early reports of long-COVID, initially among hospitalised adults, and then among community cases with mild-to-moderate COVID-19, raised concerns about similar complications in children [15, 22, 23]. Many of the earlier studies were, however, methodologically flawed, biased towards more severe cases, often without control groups for comparison, and lacked a consensus case definition [24]. Consequently, one systematic review estimated long-

COVID prevalence of 80% (95% CI, 65-92) from 14 to 110 days post-infection another review of childhood long-COVID estimated a prevalence of 4-66% [17, 25]. More recent studies in adults, which included appropriate controls, such as SARS-CoV-2 antibody-negative adults, have provided more robust estimates for long-COVID (15% vs 3% reported ≥1 moderate-to-severe symptom lasting ≥8 months), with significant impact on work, social and home life [26].

In children, a UK Office for National Statistics (ONS) survey during March/April 2021 asked adults and parents of children whether they suffered from long-COVID, defined as any symptoms persisting after suspected COVID-19 that were not explained by another illness, and estimated a national long-COVID prevalence of 1.7%(equivalent to 1.1 million people), being higher in adults compared to 0.18% in 2-11 year-old and 0.71% in 12-16 year-olds [27]. The most common symptoms in children - which may be new onset, persistent, intermittent or relapsing – included tiredness, fatigue and headache [15, 22]. Another online survey developed by parents of children with long-COVID found that symptoms in children persisted for a mean of 8 months after initial infection, with only 10% children returning to previous levels of physical activity over the same period [15]. Among hospitalised children with COVID-19, studies in Spain and Russia also reported fatigue, sleep disturbance and sensory problems lasting for ≥6 months [28, 29], although the Spanish study included only eight¡ children and only two were confirmed by PCR-testing.

Like the earlier adult studies, the lack of controls in paediatric studies made it difficult to attribute on-going symptoms to COVID-19. A recent analysis of 258,790 children aged 5-17 years reported by an adult proxy using the online COVID Symptom Study (ZOE) app between 24 March 2020 and 22 February 2021 found that, while the median duration of illness in confirmed cases was 6 days, 4.4% (77/1,734) had persistent symptoms for ≥28 days after acute infection compared to 0.9% in the negatively- tested cohort, declining to 1.8% (25/1,379) after 8 weeks. The commonest symptoms were fatigue (84%), headache (80%) and anosmia (80%) [30].

Whilst acknowledging potential biases of the population participating in the ZOE app study (white, middleclass, female participants) and parental reporting of PCR-testing and results, a strength of this analysis was the inclusion of symptomatic but SARS-CoV-2 RT-PCR negative controls, matched 1:1 for age, gender, and week of testing. The same methodology reported significantly higher rates of persistent symptoms in adults compared to children: 13.3% lasting ≥4 weeks, 4.5% lasting ≥8 weeks and 2.3% lasting ≥12 weeks [8].

In our cohort, the reported symptoms at the time of infection and at follow-up are consistent with the reported literature for symptomatic COVID-19 in children [30, 31]. Reassuringly, the vast majority of children recovered after acute infection and, while 6.7% of symptomatic cases had on-going symptoms a month later, so did 4.2% of symptomatic controls. The difference in prevalence of on-going symptoms between symptomatic cases and symptomatic controls (2.5%) is similar to the ZOE app study for children (3.5%) but substantially different the ONS survey which reported “any symptoms ≥12 weeks after assumed date of infection” of 9.8% in 2-11 year-olds and 13.0% in 12-16 year-olds who tested positive for SARS-CoV-2 compared to 2.0% and 1.7% among test-negative controls, respectively, between April 2020 and March 2021 [27].

In our cohort, most elicited symptoms were as common among symptomatic cases as among symptomatic controls. We did, however, identify three symptom clusters among symptomatic cases, although individually these symptoms were relatively uncommon among cases. Sensory symptoms affecting taste, smell and vision had the strongest associations and were reported almost exclusively among symptomatic cases except for one symptomatic control. Similarly, too, confusion (3.8%) was only reported among symptomatic cases. These symptoms appear to be specific to COVID-19 and are well-reported in adults and children [15, 29]. Reassuringly, on-going symptoms in asymptomatic cases and control were rare.

An important finding in our cohort, however, was the high prevalence of mental health symptoms among all children, regardless of symptoms or test results, adding to global concerns about the mental health of children and adolescents, including loneliness, stress, anxiety, depression and suicide ideations [32], and the need for medical, psychological, and educational support for children, irrespective of their COVID-19 status. On-going, large-scale, population-based studies such as the CLoCK study in England [33] will provide critical information on the longer-term effects of COVID-19 and the current pandemic in adolescents.

Strengths and limitations.

One of the main strengths of this study is the random sampling of PCR-confirmed SARS-CoV-2 cases from a national dataset alongside contemporaneous, matched controls, during a period when widespread testing was available nationally. We only included cases tested in the community so that the findings were not biased towards hospitalised cases with more severe illness, which is rare in children. Another strength is the minimisation of recall bias by activating the survey within two months of the children´s PCR-test. Additionally, to improve questionnaire uptake and reduce bias against families with limited internet access, a paper version of the questionnaire was offered.

There are, however, some limitations. Despite three attempts, questionnaire completion rate was 35% and there may be some selection bias between respondents and non-respondents. Parents of children with on-going symptoms, for example, may be more likely to complete the questionnaire than those whose children recovered. Comparison of demographic data, however, found no significant differences between respondents and non-respondents except younger age among the latter (median age, 6 years), who are more likely to recover uneventfully than older children. Some children may also have been wrongly misclassified because of false-positive or false-negative PCR-tests, but this is likely to be a minority, given

that England was experiencing high case-rates because of the alpha variant. Moreover, it is possible that some controls may have been exposed to SARS-CoV-2 but remained asymptomatic or opted not to be tested. Ideally, cases and controls would have had a SARS-CoV-2 antibody test to confirm their infection status a month after the RT-PCR test. Given our sample size, too, comparisons are hampered by the sparsity of reported symptoms. For instance, our sample size had 80% power to detect a difference in proportion with symptoms of 6% vs. 1% (relative risk of around 6) and for more common symptoms, 10% vs. 3% (relative risk of around 3). The low prevalence of any of the reported symptoms among cases and controls is, however, reassuring from a clinical standing. Additionally, some questions will have been difficult for parents to answer, for example, changes in sensory symptoms in very young children, or mental health symptoms in teenagers who may not share their problems with their parents. Finally, with the emergence of the delta variant [34], it is possible that the risk and prevalence of long-COVID may be different. The CLoCK Study is uniquely placed to identify any changes between SARS-CoV-2 variants [35].

Conclusions

Children have been relatively spared by SARS-CoV-2 but have endured difficult times because of lockdowns, school closures and social isolation. Our data support more recent, well-conducted case-control studies reporting a low risk of on-going symptoms in children with confirmed COVID-19. More data are needed on the trajectory of the on-going symptoms in the medium-to-long term and on differences in the risk and outcomes of long-COVID between SARS-CoV-2 variants. In the meantime, appropriate healthcare resources must be urgently prioritised to support the mental health of children and adolescents during these difficult times.

NOTES

Acknowledgements

The authors would like to thank the Immunisation Department team at Public Health England, especially the contribution to Ruth Simmons who provided the initial data from SGSS, Rebecca Cordery, Shelui Collinson and Miranda Mindlin for their help on the design of the survey , Charlotte Ryan, Natalie Mensah and Tara Kesse-Adu for their administrative work and Ross Harris for his input in the data analysis. Applications for relevant anonymised data should be submitted to the Public Health England Office for Data Release: https://www.gov.uk/government/publications/accessing-public-health-england-data/about-the-phe-odr-and-accessing-data Public Health England (PHE) has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. This includes PHE's responsibility to monitor the safety and effectiveness of vaccines, and as such, individual patient consent is not required. PHE's Caldicott Guardian approved the collection of data by RCGP RSC to support national surveillance.

Author Contributions

SNL, ZA-C, MER, MM were responsible for conceptualization and study design/methodology. MZ and SNL contributed to the original draft and conducted the formal analysis and data validation. All authors contributed to reviewing and editing the manuscripts.

Funding

None

Conflict of interests

All authors have no conflict of interest to declare

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Table 1. Demographic characteristics among a random sample of children who tested SARS-CoV-2 PCR-positive and controls who tested PCR-negative between the 1st and he 7th of January 2021. Total N:859

	All participants **859 (100%)**	**CASES N (%)** **472 (54.95)**		**CONTROLS** **N (%)** **387 (45.05)**	
		Symptomatic **N (%) 320 (67.79)**	**Asymptomatic** **N (%) 152 (32.20)**	**Symptomatic** **N (%) 154 (39.79)**	**Asymptomatic** **N (%) 233 (60.20)**
Age (median, IQR) (859/859)	10 (6, 13)	10 (6,13)	9 (6.5,12)	8 (5,12)	12 (9,14)
Age Group (years) (859/859)					
<5	167 (19.44)	73 (22.81)	23 (15.13)	50 (32.47)	21 (9.07)
6-10	282 (32.83)	96 (30.00)	66 (47.42)	50 (32.47)	70 (30.04)
11-13	225 (26.19)	79 (24.84)	39 (25.66)	28 (18.18)	79 (33.91)
14-16	185 (21.54)	72 (22.50)	24 (15.79)	26 (16.88)	63 (27.04)
Sex (859/859)					
Female	419 (48.78)	167 (52.19)	70 (46.05)	72 (46.75)	110 (47.21)
Male	440 (51.22)	153 (47.81)	82 (53.95)	82 (53.25)	123 (52.79)
Ethnicity (859/859)					
White	643 (74.85)	246 (76.88)	101 (66.45)	119 (77.27)	177 (75.97)

Black	32 (3.73)	14 (4.38)	4 (2.63)	3 (1.95)	11 (4.72)
Asian	87 (10.13)	27 (8.44)	25 (16.45)	17 (11.04)	18 (7.73)
Mixed	65 (7.57)	24 (7.50)	15 (9.87)	10 (6.49)	16 (6.87)
Other	21 (2.44)	7 (2.19)	5 (3.29)	3 (1.95)	6 (2.58)
Prefer not to say	11 (1.28)	2 (0.63)	2 (1.32)	2 (1.30)	5 (2.15)
Region (859/859)					
North East	27 (3.14)	12 (3.75)	3 (1.97)	6 (3.90)	6 (2.58)
North West	81 (9.43)	35 (10.94)	12 (7.89)	14 (9.09)	20 (8.58)
Yorkshire and The Humber	60 (6.980	24 (7.50)	7 (4.61)	12 (7.79)	17 (7.30)
East of Midlands	47 (5.47)	19 (5.94)	7 (4.61)	10 (6.49)	11 (4.72)
West Midlands	88 (10.24)	39 (12.19)	11 (7.24)	17 (11.04)	21 (9.01)
East of England	111 (12.92)	46 (14.37)	22 (14.47)	16 (10.39)	27 (11.59)
London	200 (23.28)	52 (16.25)	47 (30.92)	38 (24.68)	64 (27.04)
South East	195 (22.70)	76 (23.75)	33 (21.71)	32 (20.78)	54 (23.18)
South West	50 (5.82)	17 (5.31)	10 (6.58)	9 (5.84)	14 (6.01)
Comorbidities (859/859)					
None	802 (93.36)	294 (91.88)	146 (96.05)	142 (92.21)	220 (94.42)
One or more	57 (6.64)	26 (8.13)	6 (3.95)	12 (7.79)	13 (5.58)
Hospitalised due to COVID-19 (859/859)					

Yes	1 (0.12)	1 (0.31)	0 (0.00)	0 (0.00)	0 (0.00)
No	858 (99.88)	319 (99.69)	154 (100.00)	154 (100.00)	233 (100.00)
Attending educational setting **(2 weeks prior to test)** (858/859)					
Yes	282 (33.22)	68 (21.38)	44 (29.93)	76 (49.67)	94 (40.69)
No	503 (59.25)	229 (72.01)	97 (65.99)	67 (43.79)	110 (47.62)
Don't know or unsure	35 (4.12)	11 (3.46)	3 (2.04)	8 (5.23)	13 (5.63)
Not applicable	29 (3.42)	10 (3.14)	3 (2.04)	2 (1.31)	14 (6.06)
Reason for testing (844/859)					
Child was unwell with symptoms of COVID-19	233 (27.61)	112 (35.00)	7 (4.64)	111 (72.08)	3 (1.37)
Contact of household case	327 (38.74)	166 (51.88)	96 (63.58)	22 (14.29)	43 (19.63)
Contact of case in education setting	38 (4.50)	5 (1.56)	5 (3.31)	8 (5.19)	20 (9.13)
Contact of case not at school and/or household	81 (9.60)	21 (6.56)	19 (12.58)	3 (1.95)	38 (17.35)
Child involved in research study	21 (2.49)	3 (0.94)	4 (2.65)	2 (1.30)	12 (5.48)
Other	144 (17.06)	13 (4.06)	20 (13.25)	8 (5.19)	103 (47.03)
Recovery after 1 month (803/859)					
On-going symptoms	30 (3.74)	21 (6.73)	3 (2.03)	6 (4.20)	0 (0.00)

Table 2. Symptoms at the time of the COVID-19 test among symptomatic childhood cases who tested SARS-CoV-2 PCR-positive and controls who tested PCR-negative

Symptoms	**Total N (%) 859 (100)**	**Case N (%) 388 (45.05)**	**Control N (%) 472 (54.95)**	**p-value***
Headache	236 (27.47)	176 (37.29)	60 (15.50)	<0.001
Cough	249 (28.99)	171 (36.23)	78 (20.16)	<0.001
Tiredness/fatigue	231 (26.86)	165 (34.96)	66 (17.05)	<0.001
Fever	236 (27.47)	156 (33.05)	80 (20.67)	<0.001
Sore throat	184 (21.42)	134 (28.39)	50 (12.92)	<0.001
Muscle aches	139 (16.18)	109 (23.09)	30 (7.75)	<0.001
Loss of appetite	133 (15.48)	95 (20.13)	38 (9.82)	<0.001
Loss of taste and or/smell	109 (12.69)	91 (19.28)	18 (4.65)	<0.001
Abdominal pain	101 (11.76)	72 (15.25)	29 (7.49)	<0.001
Diarrhoea	79 (9.20)	55 (11.65)	24 (6.20)	0.006
Shortness of breath	66 (7.68)	52 (11.02)	14 (3.62)	<0.001
Chest pain	43 (5.01)	37 (7.84)	6 (1.55)	<0.001
Swollen glands	49 (5.70)	34 (7.20)	15 (3.88)	0.036

Vomiting	43 (5.01)	32 (6.78)	11 (2.84)	0.008
Rash	34 (3.96)	27 (5.72)	7 (1.81)	0.003
Difficulty rousing	19 (2.21)	14 (2.97)	5 (1.29)	0.097
Crying	19 (2.21)	14 (2.97)	5 (1.29)	0.097
Twitching or tics	15 (1.74)	14 (2.97)	1 (0.26)	0.003

*Fisher's exact test

Table 3. Ongoing symptoms at least one month after the COVID-19 test among cases of SARS-CoV-2 PCR-positive and controls PCR-negative (N=859)

	Total N (%) 320 (37.25)	Case symptomatic N (%) 154 (17.93)	Control symptomatic N (%)	p-value	Case asymptomatic N (%) 152 (17.69)	Control asymptomatic N (%) 233 (27.12)	p-value¶
Neurological							
Tiredness	44 (5.12)	28 (8.75)	9 (5.84)	0.361	5 (3.29)	2 (0.86)	0.118
Seizures	2 (0.23)	1 (0.31)	1 (0.65)	0.545	0 (0.00)	0 (0.00)	-
Collapse	0 (0.00)						
Twitching of fingers or toes	3 (0.35)	3 (0.94)	0 (0.00)	0.554	0 (0.00)	0 (0.00)	-
Tingling or numbness in arms or legs	4 (0.47)	4 (1.25)	0 (0.00)	0.309	0 (0.00)	0 (0.00)	-

Confusion	**21 (2.44)**	**18 (5.63)**	**0 (0.00)**	**0.001**	1 (0.66)	2 (0.86)	1.0
Forgetfulness	9 (1.05)	6 (1.88)	1 (0.65)	0.436	1 (0.66)	1 (0.43)	1.0
Short-term memory loss	5 (0.58)	2 (0.63)	1 (0.65)	1	1 (0.66)	1 (0.43)	1.0
Trouble forming words	3 (0.35)	2 (0.63)	0 (0.00)	1	0 (0.00)	1 (0.43)	1.0
Headache	26 (3.03)	18 (5.63)	5 (3.25)	0.362	2 (1.32)	1 (0.43)	0.565
Hallucinations	1 (0.12)	1 (0.31)	0 (0.00)	1	0 (0.00)	0 (0.00)	-
Dizziness	14 (1.63)	10 (3.13)	3 (1.95)	0.561	1 (0.66)	0 (0.00)	0.395
Faintness	6 (0.70)	5 (1.57)	1 (0.65)	0.401	0 (0.00)	0 (0.00)	-
Vertigo	6 (0.70)	5 (1.56)	1 (0.65)	0.669	0 (0.00)	0 (0.00)	-
Difficulty swallowing	4(0.47)	2 (0.63)	2 (1.30)	0.559	0 (0.00)	0 (0.00)	-

Pins and needles	5 (0.58)	4 (1.25)	1 (0.65)	1	0 (0.00)	0 (0.00)	-
Dermatological							
Dry skin	24 (2.79)	13 (4.06)	4 (2.60)	0.599	5 (3.29)	2 (0.86)	0.118
Itchy skin	21 (2.44)	9 (2.81)	4 (2.60)	1	3 (1.97)	5 (2.15)	1.0
Bruises	3 (0.35)	1 (0.31)	0 (0.00)	1	0 (0.00)	2 (0.86)	0.521
Rashes	7 (0.81)	2 (0.63)	1 (0.65)	1	1 (0.66)	3 (1.29)	1.0
Hives	3 (0.35)	3 (0.94)	0 (0.00)	0.554	0 (0.00)	0 (0.00)	-
Swollen toes and /or fingers	7 (0.81)	2 (0.63)	3 (1.95)	0.335	0 (0.00)	2 (0.86)	0.521
Mottled feet	6 (0.70)	2 (0.63)	2 (1.30)	0.599	0 (0.00)	2 (0.86)	0.521
Sensory problems							
Loss of taste	**18**	**17 (5.31)**	**1 (0.65)**	**0.01**	0 (0.00)	0 (0.00)	-

	(2.10)						
	Total N (%)	**Case symptomatic N (%)**	**Control symptomatic N (%)**	**p-value**	**Case asymptomatic N (%)**	**Control asymptomatic N (%)**	**p-value¶**
	320 (37.25)		**154 (17.93)**		**152 (17.69)**	**233 (27.12)**	
Loss of smell	**23 (2.68)**	**22 (6.88)**	**1 (0.65)**	**0.002**	0 (0.00)	0 (0.00)	-
Loss of appetite	20 (2.33)	15 (4.69)	4 (2.60)	0.328	1 (0.66)	0 (0.00)	0.395
Flashes of light (photopsia)	3 (0.35)	3 (0.94)	0 (0.00)	0.554	0 (0.00)	0 (0.00)	-
Ringing in ears (tinnitus)	7 (0.81)	6 (1.88)	0 (0.00)	0.184	0 (0.00)	0 (0.00)	-
Blurred vision	5 (0.58)	5 (1.56)	0 (0.00)	0.179	0 (0.00)	0 (0.00)	-
Eye pain	**9 (1.05)**	**9 (2.81)**	**0 (0.00)**	**0.03**	0 (0.00)	0 (0.00)	-

				5			
Avoiding bright light (photophobia)	7 (0.81)	5 (1.56)	1 (0.65)	0.669	0 (0.00)	1 (0.43)	1
Slurred speech	1 (0.12)	1 (0.31)	0 (0.00)	1	0 (0.00)	0 (0.00)	-
Metallic taste	7 (0.81)	6 (1.88)	1 (0.65)	0.436	0 (0.00)	0 (0.00)	-
Ear pain (otalgia)	7 (0.81)	7 (2.19)	0 (0.00)	0.102	0 (0.00)	0 (0.00)	**-**
Respiratory problems							
Cough	24 (2.79)	13 (4.06)	8 (5.19)	0.635	3 (1.97)	0 (0.00)	0.061
	Total N (%)	**Case symptomatic N (%) 320 (37.25)**	**Control symptomatic N (%) 154 (17.93)**	**p-value**	**Case asymptomatic N (%) 152 (17.69)**	**Control asymptomatic N (%) 233 (27.12)**	**p-value¶**
Fits of coughing	14	10 (3.13)	3 (1.95)	0.56	1 (0.66)	0 (0.00)	0.39

	(1.63)			1			5
Coughing when lying down	17 (1.98)	12 (3.75)	4 (2.60)	0.598	1 (0.66)	0 (0.00)	0.395
Chest tightness/pain	4 (0.47)	4 (1.25)	0 (0.00)	0.309	0 (0.00)	0 (0.00)	-
Palpitations	0 (0.00)						
Shortness of breath at rest	5 (0.58)	5 (1.56)	0 (0.00)	0.179	0 (0.00)	0 (0.00)	-
Shortness of breath after activity	19 (2.21)	16 (5.00)	2 (1.30)	0.069	0 (0.00)	1 (0.43)	1
Sore throat	9 (1.05)	8 (2.50)	1 (0.65)	0.283	0 (0.00)	0 (0.00)	-
Asthma attack	0 (0.00)						
Having to sleep upright	2 (0.23)	2 (0.63)	0 (0.00)	1	0 (0.00)	0 (0.00)	-
Mental Health							
Sadness	33 (3.84)	**22 (6.88)**	**2 (1.30)**	**0.007**	5 (3.29)	4 (1.72)	0.326

Having difficulty sleeping at night or getting to sleep	44 (5.12)	**28 (8.75)**	**5 (3.25)**	**0.033**	5 (3.29)	6 (2.58)	0.758
	Total N (%)	**Case symptomatic N (%)**	**Control symptomatic N (%)**	**p-value**	**Case asymptomatic N (%)**	**Control asymptomatic N (%)**	**p-value¶**
	320 (37.25)	**154 (17.93)**			**152 (17.69)**	**233 (27.12)**	
Depression	23 (2.68)	**13 (4.06) ***	**1 (0.65)**	**0.043**	5 (3.29) *	4 (1.72) *	0.326
Mood swings	41 (4.77)	**25 (7.81)**	**3 (1.95)**	**0.011**	6 (3.95)	7 (3.00)	0.774
Anxiety	44 (5.12)	**25 (7.81)**	**4 (2.60)**	**0.025**	8 (5.26)	7 (3.00)	0.289
Gastrointestinal							
Abdominal pain	14 (1.63)	8 (2.50)	3 (1.95)	1	3 (1.97)	0 (0.00)	0.061
Nausea	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	0.39

							5
Constipation	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	0.395
Bloating	1 (0.12)	1 (0.31)	0 (0.00)	1	0 (0.00)	0 (0.00)	-
Vomiting	1 (0.12)	1 (0.66)	0 (0.00)	0.395	1 (0.66)	0 (0.00)	0.395
Diarrhoea	5 (0.58)	2 (0.63)	0 (0.00)	1	2 (1.32)	1 (0.43)	0.565
Bowel incontinence	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	0.395
Other problems							
Urinary incontinence	2(0.23)	2 (0.63)	0 (0.00)	1	0 (0.00)	0 (0.00)	-
Muscle aches	4 (0.47)	2 (0.63)	1 (0.65)	1	0 (0.00)	1 (0.43)	1
Joint pain	5 (0.58)	2 (0.63)	0 (0.00)	1	0 (0.00)	3 (1.29)	0.281
Fever	2 (0.23)	1 (0.31)	0 (0.00)	1	1 (0.66)	0 (0.00)	0.395

Back pain	3 (0.35)	1 (0.31)	1 (0.65)	0.545	0 (0.00)	1 (0.43)	1
Neck/shoulder pain	2 (0.23)	1 (0.31)	1 (0.65)	0.545	0 (0.00)	0 (0.00)	-
Hair loss	1 (0.12)	1 (0.31)	0 (0.00)	1	0 (0.00)	0 (0.00)	-

¶ Fisher's exact test *one child in that group suffered from depression prior to COVID-19 test.

Table 4. Multivariable logistic regression odds ratio (OR) and adjusted odds ratio (aOR) estimates of symptoms comparing symptomatic cases with symptomatic controls

Symptom	**Total N (%) N=474**	**OR**	**95% CI**	**p-value**	**AOR***	**95%CI**	**p-value**
Neurological							
Confusion	18 (3.81)	#	#	#	#	#	#
Sensory problems							
Loss of taste	18 (3.81)	8.58	1.13-65.11	0.038	7.5	0.97-57.78	0.053
Loss of smell	23 (4.87)	11.3	1.51-84.59	0.018	10.2	1.31-79.07	0.026
Eye pain	9 (1.91)	#	#	#	#	#	#
Mental Health							
Sadness	20 (4.24)	5.61	1.30-24.18	0.021	5.31	1.22-23.06	0.026

Depression	14 (2.97)	6.48	0.84-49.98	0.073	5.78*	0.74-45.44	0.095
Having difficulty sleeping at night or getting to sleep	33 (6.99)	2.86	1.08-7.55	0.034	2.84	1.06-7.59	0.037
Mood swings	28 (5.93)	4.27	1.27-14.35	0.019	3.94	1.16-13.40	0.028
Anxiety	29 (6.14)	3.18	1.09-9.30	0.035	2.99	1.01-8.90	0.049

*Adjusted for age, sex, ethnicity, socio-economic status and comorbiditie

Figures

Figure 1. Flow diagram of children and young people invited.

Figure 2. Venn diagram representing clustering of the most common on-going symptoms in symptomatic children at least one month after a positive SARS-CoV-2 PCR test (cases) compared to symptomatic children with a negative SARS-CoV-2 PCR test (controls).

Figure 1

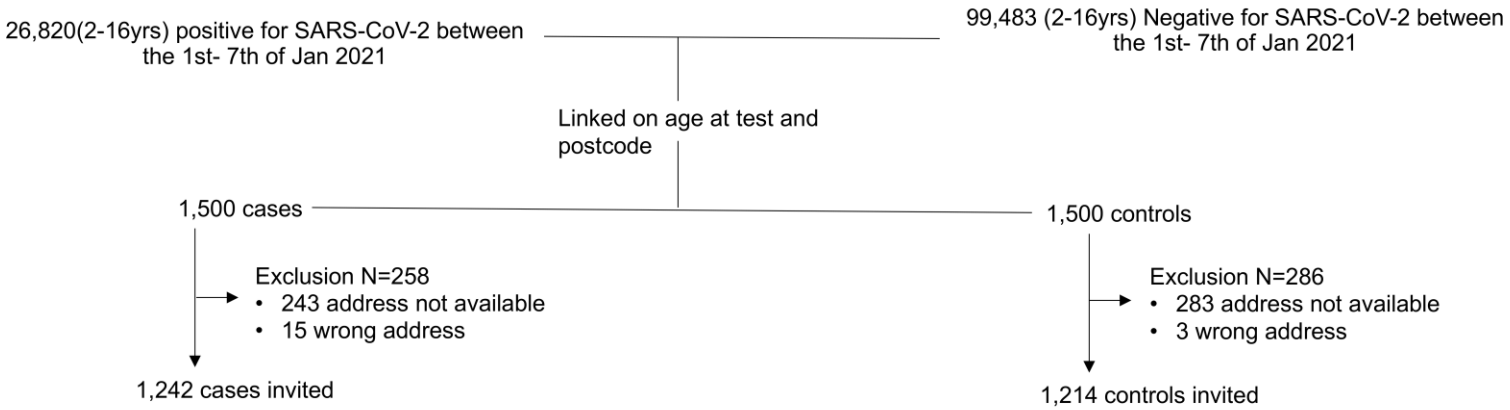
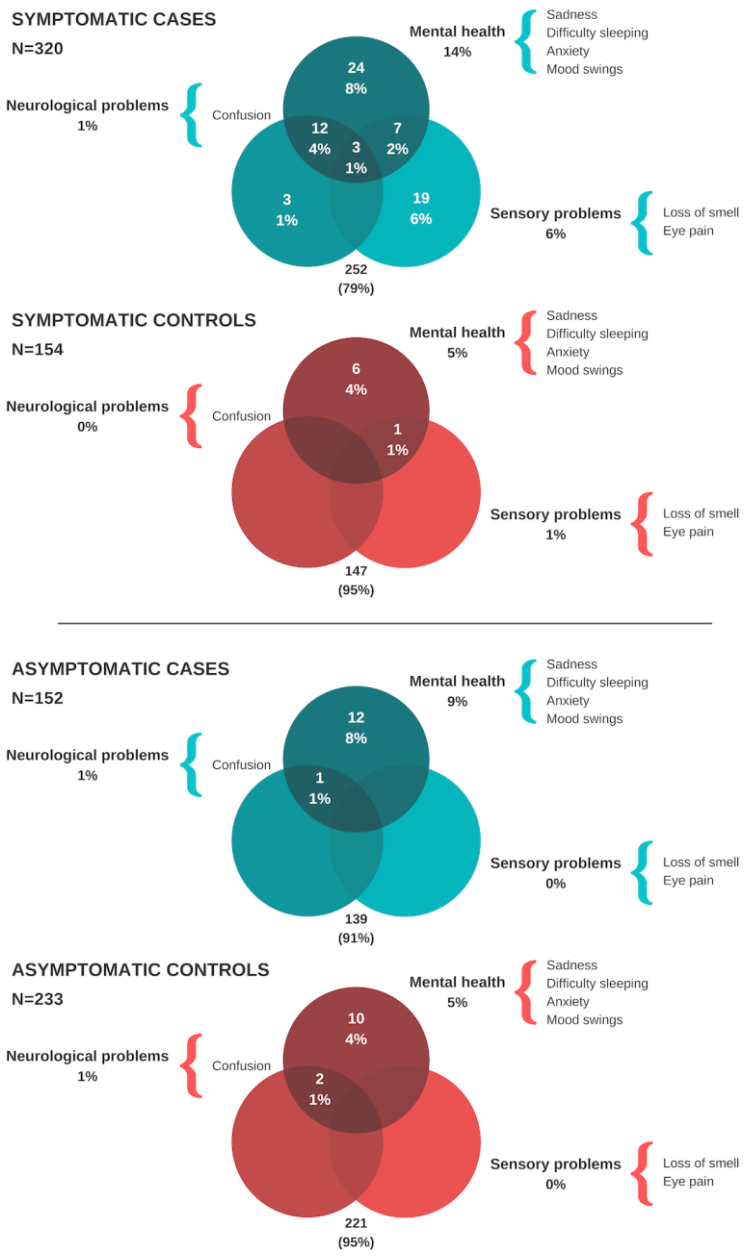

26,820(2-16yrs) positive for SARS-CoV-2 between the 1st- 7th of Jan 2021
99,483 (2-16yrs) Negative for SARS-CoV-2 between the 1st- 7th of Jan 2021
Linked on age at test and postcode
1,500 cases
1,500 controls
Exclusion N=258
• 243 address not available
• 15 wrong address
Exclusion N=286
• 283 address not available
• 3 wrong address
1,242 cases invited
1,214 controls invited

Figure 2


SYMPTOMATIC CASES
N=320
Mental health
14%
Sadness
Difficulty sleeping
Anxiety
Mood swings
Neurological problems
1%
Confusion
24
8%
12
4%
3
1%
7
2%
3
1%
19
6%
Sensory problems
6%
Loss of smell
Eye pain
252
(79%)
SYMPTOMATIC CONTROLS
N=154
Mental health
5%
Sadness
Difficulty sleeping
Anxiety
Mood swings
Neurological problems
0%
Confusion
6
4%
1
1%
Sensory problems
1%
Loss of smell
Eye pain
147
(95%)
ASYMPTOMATIC CASES
N=152
Mental health
9%
Sadness
Difficulty sleeping
Anxiety
Mood swings
Neurological problems
1%
Confusion
12
8%
1
1%
Sensory problems
0%
Loss of smell
Eye pain
139
(91%)
ASYMPTOMATIC CONTROLS
N=233
Mental health
5%
Sadness
Difficulty sleeping
Anxiety
Mood swings
Neurological problems
1%
Confusion
10
4%
2
1%
Sensory problems
0%
Loss of smell
Eye pain
221
(95%)