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Acute and Persistent Symptoms in Children With Polymerase Chain Reaction (PCR)–Confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Compared With Test-Negative Children in England: Active, Prospective, National Surveillance

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Background. Most children recover quickly after coronavirus disease 2019 (COVID-19), but some may have ongoing 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 1–7 January 2021 and randomly selected 1500 PCR-positive cases and 1500 matched PCR-negative controls. Parents were asked to complete a questionnaire about the acute illness and prespecified neurological, dermatological, sensory, respiratory, cardiovascular, gastrointestinal, mental health (including emotional and behavioral well-being), and other symptoms experienced ≥5 times at 1 month after the PCR test.

Results. Overall, 35.0% (859/2456) completed the questionnaire, including 38.0% (472/1242) of cases and 32% (387/1214) of 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 ($P = .24$) experienced ongoing symptoms. Of the 65 ongoing symptoms solicited, 3 clusters were significantly ($P < .05$) more common, albeit at low prevalence, among symptomatic cases (3–7%) than symptomatic controls (0–3%): neurological, sensory, and emotional and behavioral well-being. 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 ongoing symptoms than symptomatic controls, and not as high as previously reported. Healthcare resources should be prioritized to support the mental health of children.

Keywords. SARS-CoV-2 infection; COVID-19; transmission; long COVID; children.

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]. Coronavirus disease 2019 (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, comorbidities, and obesity are also associated with increased risk [6].

While most adults recover without sequelae, some survivors will have ongoing 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 ongoing 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 standardize the case condition, the UK National Institute for Health and Care Excellence (NICE) has proposed 2 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 more than 12 weeks, and are not explained by an alternative diagnosis [11].

Unlike adults, children have a lower risk of severe disease, hospitalization, or death due to COVID-19 [2, 12]. Most

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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 1 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 who 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 ongoing symptoms in children aged 2–16 years with laboratory-confirmed SARS-CoV-2 infection compared with 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 [20]. The SGS test results for 2- to 16-year-olds with a SARS-CoV-2 RT-PCR taken during 1–7 January 2021 in England were linked with the 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 version 15.0 (StataCorp LLC, College Station, TX), cases and controls were stratified by age in years and partial postcode in 8 and 78 strata, respectively, for a total of 939 strata. A random sample from each stratum was taken to produce a total sample size of 1500 cases, with the same number of matched controls. 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 version 11 (2010-2021 Snap Surveys Ltd.) version 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 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 1 month after the initial RT-PCR test. The final questionnaire requested information on demographics, COVID-19 symptoms at the time of testing, household composition, confirmed cases in the household, and prespecified symptoms at the time of the RT-PCR test and at least 1 month later. Symptomatic cases and controls were defined as children with a positive or negative PCR test, respectively, during 1–7 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 ongoing symptoms in cases and controls were divided into neurological, dermatologic, sensory, respiratory and cardiovascular, gastrointestinal, mental health (including emotional and behavioral well-being), and other, allowing parents to report any other symptoms not included in the questionnaire. Symptoms were defined as ongoing if experienced at least 5 times per month at least 1 month after the PCR test. Two reminders were sent to the families who did not complete the questionnaire 2 and 4 weeks after the initial invitation letter. An index of multiple deprivation (IMD) was used as a proxy measure for socioeconomic status and was obtained using postcodes from the Ministry of Housing, Communities and Local Government website [21].

Statistical Analysis

Data were managed using Microsoft Access and analyzed using Stata version 15.1 (StataCorp LLC). Categorical data are reported as frequencies and proportions and compared using the chi-square test or Fisher's exact test. Continuous data are summarized as medians with interquartile ranges and compared using the Mann-Whitney *U* test. Data were further explored by fitting logistic regression models for symptoms that were statistically significant in the univariate analysis and comparing symptomatic cases with controls and asymptomatic cases with controls, after adjusting for age, sex, ethnicity, socioeconomic status, and comorbidities. Results are reported as odd ratios (ORs) and adjusted ORs (aORs) with 95% confidence intervals (CIs).

RESULTS

Of the 1500 cases and 1500 controls identified initially, 1257 cases and 1217 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 2456 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 1 symptomatic case required hospitalization. Comparison of demographic data

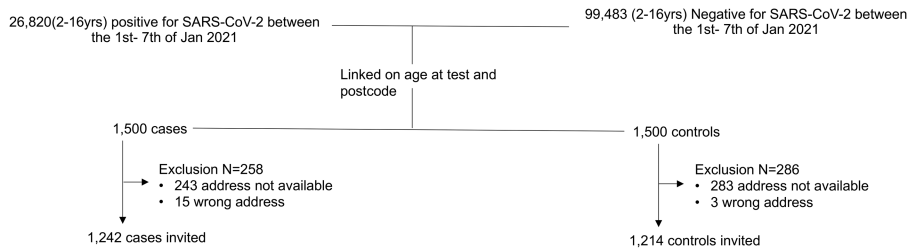

Figure 1. Flow diagram of children and young people invited to participate. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; yrs, years.

showed no significant differences between respondents and nonrespondents, except for 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 18 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 of the symptomatic cases were tested because they were contacts of a household case (51.9%, 166/320) compared with symptomatic controls (14.3%, 22/154; $P < .001$). The same was also true for asymptomatic cases (63.6%, 96/152) compared with asymptomatic controls (19.63%, 43/233; $P < .001$).

Ongoing Symptoms

One month after the RT-PCR test, a similar proportion of parents of symptomatic cases (6.73%, 21/320) reported that their child was still unwell as parents of symptomatic controls (4.20%, 6/154; $P = .24$). The 64 elicited ongoing symptoms were categorized as follows: neurological, dermatological, sensory, respiratory, mental health, gastrointestinal, and other. Of these, 9 were significantly more prevalent among symptomatic cases compared with symptomatic controls (Table 3) and were clustered into 3 categories (Figure 2). Differences in neurological symptoms included confusion, which was only reported for symptomatic cases (5.6% [18/320] vs 0/154; $P = .001$). Differences in sensory symptoms included loss of taste (5.3% [17/320] vs 0.65% [1/154]; $P = .01$), loss of smell (6.9% [22/320] vs 0.65% [1/154]; $P = .002$), and eye pain, which was only reported for symptomatic cases (2.8% [9/320] vs 0/154; $P = .035$). Differences in mental health symptoms between symptomatic cases and symptomatic controls included sadness (6.9% [22/320] vs 1.3%[2/154]; $P = .007$), difficulty sleeping (8.8% [28/320] vs 3.3% [5/154]; $P = .033$), depression (4.1% [13/320] vs 0.65% [1/154]; $P = .043$), mood swings (7.8% [25/320] vs 2.0% [3/154]; $P = .011$), and anxiety (7.81% [25/320] vs 2.6% [4/154]; $P = .025$).

Logistic regression was performed for the 7 ongoing 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, 5 ongoing 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 [95% CI: 1.3–79.1]; $P = .026$) and eye pain, which was only reported for symptomatic cases. Loss of smell was also independently associated with older age group (14–16 years: 21% [15/72] vs 1.4% [1/73]; aOR: 18.4 [95% CI: 2.35–144.53]; $P = .006$). Mental health symptoms included sadness (aOR: 5.3 [1.2–23.1]; $P = .026$), (aOR: 5.3 [95% CI: 1.2–23.1] difficulty sleeping (aOR: 2.8 [95% CI: 1.1–7.6]; $P = .037$), mood swings (aOR: 3.94 [95% CI: 1.2–13.4]; $P = .028$), and anxiety (aOR: 3.0 [95% CI: 1.0–8.9]; $P = .049$).

In the univariate analysis, none of the symptoms were significantly more prevalent among asymptomatic cases compared with 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 did test-negative symptomatic children, especially headache, cough, fatigue and fever. One month later, 6.7% of symptomatic cases and 4.2% of symptomatic controls had ongoing symptoms. Of the 64 elicited symptoms, 9 were more common among symptomatic cases than symptomatic controls, but not among asymptomatic cases compared to asymptomatic controls.

Early reports of long COVID, initially among hospitalized adults, and then among community cases with mild-to-moderate COVID-19, raised concerns about similar complications in

Table 1. Demographic Characteristics Among a Random Sample of Children Who Tested SARS-CoV-2 PCR-Positive and Controls Who Tested PCR-Negative Between 01 and 07 January 2021.

	All Participants	Cases		Controls	
	859 (100%)	472 (54.95%)		387 (45.05)	
		Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
		320 (67.79%)	152 (32.20%)	154 (39.79%)	233 (60.20%)
		n/N (%)	n/N (%)	n/N (%)	n/N (%)
Age (median, IQR)	10 (6, 13)	10 (6,13)	9 (6.5,12)	8 (5,12)	12 (9,14)
Age group (years)					
<5	167/859 (19.44)	73/320 (22.81)	23/152 (15.13)	50/154 (32.47)	21/233 (9.01)
6 to 10	282/859 (32.83)	96/320 (30.00)	66/152 (43.42)	50/154 (32.47)	70/233 (30.04)
11 to 13	225/859 (26.19)	79/320 (24.68)	39/152 (25.66)	28/154 (18.18)	79/233 (33.91)
14–16	185/859 (21.54)	72/320 (22.50)	24/152 (15.79)	26/154 (16.88)	63/233 (27.04)
Sex					
Female	419/859 (48.78)	167/320 (52.19)	70/152 (46.05)	72/154 (46.75)	110/233 (47.21)
Male	440/859 (51.22)	153/320 (47.81)	82/152 (53.95)	82/154 (53.25)	123/233 (52.79)
Ethnicity					
White	643/859 (74.85)	246/320 (76.88)	101/152 (66.45)	119/154 (77.27)	177/233 (75.97)
Black	32/859 (3.73)	14/320 (4.38)	4/152 (2.63)	3/154 (1.95)	11/233 (4.72)
Asian	87/859 (10.13)	27/320 (8.44)	25/152 (16.45)	17/154 (11.04)	18/233 (7.73)
Mixed	65/859 (7.57)	24/320 (7.50)	15/152 (9.87)	10/154 (6.49)	16/233 (6.87)
Other	21/859 (2.44)	7/320 (2.19)	5/152 (3.29)	3/154 (1.95)	6/233 (2.58)
Prefer not to say	11/859 (1.28)	2/320 (0.63)	2/152(1.32)	2/154 (1.30)	5/233 (2.15)
Region					
North East	27/859 (3.14)	12/320 (3.75)	3/152 (1.97)	6/154 (3.90)	6/233 (2.58)
North West	81/859 (9.43)	35/320 (10.94)	12/152 (7.89)	14/154 (9.09)	20/233 (8.58)
Yorkshire and Humber	60/859 (6.98)	24/320 (7.50)	7/152 (4.61)	12/154 (7.79)	17/233 (7.30)
East of Midlands	47/859 (5.47)	19/320 (5.94)	7/152 (4.61)	10/154 (6.49)	11/233 (4.72)
West Midlands	88/859 (10.24)	39/320 (12.19)	11/152 (7.24)	17/154 (11.04)	21/233 (9.01)
East of England	111/859 (12.92)	46/320 (14.38)	22/152 (14.47)	16/154 (10.39)	27/233 (11.59)
London	200/859 (23.28)	52/320 (16.25)	47/152 (30.92)	38/154 (24.68)	64/233 (27.47)
South East	195/859 (22.70)	76/320 (23.75)	33/152 (21.71)	32/154 (20.78)	54/233 (23.18)
South West	50/859 (5.82)	17/320 (5.31)	10/152 (6.58)	9/154 (5.84)	14/233 (6.01)
Comorbidities					
None	802/859 (93.36)	294/320 (91.88)	146/152 (96.05)	142/154 (92.21)	220/233 (94.42)
One or more	57/859 (6.64)	26/320 (8.13)	6/152 (3.95)	12/154 (7.79)	13/233 (5.58)
Hospitalised due to COVID-19					
Yes	1/859 (0.12)	1/320 (0.31)	0/152 (0.00)	0/154 (0.00)	0/233 (0.00)
No	858/859 (99.88)	319/320 (99.69)	152/152 (100.00)	154/154 (100.00)	233/233 (100.00)
Attending educational setting (2 weeks prior to test)					
Yes	282/849 (33.22)	68/318 (21.38)	44/147 (29.93)	76/153 (49.67)	94/231 (40.69)
No	503/849 (59.25)	229/318 (72.01)	97/147 (65.99)	67/153 (43.79)	110/231 (47.62)
Don't know or unsure	35/849 (4.12)	11/318 (3.46)	3/147 (2.04)	8/153 (5.23)	13/231 (5.63)
Not applicable	29/849 (3.42)	10/318 (3.14)	3/147 (2.04)	2/153 (1.31)	14/231 (6.06)
Reason for testing					
Child was unwell with symptoms of COVID-19	233/844 (27.61)	112/320 (35.00)	7/151 (4.64)	111/154 (72.08)	3/219 (1.37)
Contact of household case	327/844 (38.74)	166/320 (51.88)	96/151 (63.58)	22/154 (14.29)	43/219 (19.63)
Contact of case in education setting	38/844 (4.50)	5/320 (1.56)	5/151 (3.31)	8/154 (5.19)	20/219 (9.13)
Contact of case not at school and/or household	81/844 (9.60)	21/320 (6.56)	19/151 (12.58)	3/154 (1.95)	38/219 (17.35)
Child involved in research study	21/844 (2.49)	3/320 (0.94)	4/151 (2.65)	2/154 (1.30)	12/219 (5.48)
Other	144/844 (17.06)	13/320 (4.06)	20/151 (13.25)	8/154 (5.19)	103/219 (47.03)
Recovery after 1 month					
On-going symptoms	30/803 (3.74)	21/312 (6.73)	3/147 (2.03)	6/142 (4.20)	0/202 (0.00)

Data are presented as n (%) unless otherwise indicated.

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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%)	Cases (n = 388; 45.05%)	Controls (n = 472; 54.95%)	*P*[a]
Headache	236 (27.47)	176 (37.29)	60 (15.50)	<.001
Cough	249 (28.99)	171 (36.23)	78 (20.16)	<.001
Tiredness/fatigue	231 (26.86)	165 (34.96)	66 (17.05)	<.001
Fever	236 (27.47)	156 (33.05)	80 (20.67)	<.001
Sore throat	184 (21.42)	134 (28.39)	50 (12.92)	<.001
Muscle aches	139 (16.18)	109 (23.09)	30 (7.75)	<.001
Loss of appetite	133 (15.48)	95 (20.13)	38 (9.82)	<.001
Loss of taste and or/smell	109 (12.69)	91 (19.28)	18 (4.65)	<.001
Abdominal pain	101 (11.76)	72 (15.25)	29 (7.49)	<.001
Diarrhea	79 (9.20)	55 (11.65)	24 (6.20)	.006
Shortness of breath	66 (7.68)	52 (11.02)	14 (3.62)	<.001
Chest pain	43 (5.01)	37 (7.84)	6 (1.55)	<.001
Swollen glands	49 (5.70)	34 (7.20)	15 (3.88)	.036
Vomiting	43 (5.01)	32 (6.78)	11 (2.84)	.008
Rash	34 (3.96)	27 (5.72)	7 (1.81)	.003
Difficulty rousing	19 (2.21)	14 (2.97)	5 (1.29)	.097
Crying	19 (2.21)	14 (2.97)	5 (1.29)	.097
Twitching or tics	15 (1.74)	14 (2.97)	1 (0.26)	.003

Data are presented as n (%).

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Fisher's exact test.

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, 1 systematic review estimated long-COVID prevalence of 80% (95% CI: 65–92%) from 14 to 110 days postinfection; 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 a 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), which was higher in adults compared with 0.18% in 2- to 11-year-olds and 0.71% in 12- to 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% of children returning to previous levels of physical activity over the same period [15]. Among hospitalized children with COVID-19, studies in Spain and Russia also reported fatigue, sleep disturbance, and sensory problems lasting for 6 or more months [28, 29], although the Spanish study included only 8 children and only 2 were confirmed by PCR testing.

Like the earlier adult studies, the lack of controls in pediatric studies made it difficult to attribute ongoing 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% (77/1734) had persistent symptoms for 28 or more days after acute infection compared with 0.9% in the negative-test cohort, which decreased to 1.8% (25/1379) after 8 weeks. The commonest symptoms were fatigue (84%), headache (80%), and anosmia (80%) [30].

While acknowledging potential biases of the population participating in the ZOE app study (White, middle class, 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 with children , with 13.3% of adults reporting symptoms lasting 4 or more weeks, 4.5% lasting 8 or more weeks, and 2.3% lasting 12 or more 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 ongoing symptoms

Table 3. Ongoing Symptoms at Least 1 Month After the COVID-19 Test Among Cases of SARS-CoV-2 Who Were PCR-Positive and PCR-Negative Controls

		Symptomatic			Asymptomatic		
	Total (N = 859)	Cases (n = 320; 37.25%)	Controls (n = 154; 17.93%)	*P*[a]	Cases (n = 152; 17.69%)	Controls (n = 233; 27.12%)	*P*[a]
Neurological							
Tiredness	44 (5.12)	28 (8.75)	9 (5.84)	.361	5 (3.29)	2 (0.86)	.118
Seizures	2 (0.23)	1 (0.31)	1 (0.65)	.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)	.554	0 (0.00)	0 (0.00)	
Tingling or numbness in arms or legs	4 (0.47)	4 (1.25)	0 (0.00)	.309	0 (0.00)	0 (0.00)	
Confusion	21 (2.44)	18 (5.63)	0 (0.00)	.001	1 (0.66)	2 (0.86)	1.0
Forgetfulness	9 (1.05)	6 (1.88)	1 (0.65)	.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)	.362	2 (1.32)	1 (0.43)	.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)	.561	1 (0.66)	0 (0.00)	.395
Faintness	6 (0.70)	5 (1.57)	1 (0.65)	.401	0 (0.00)	0 (0.00)	
Vertigo	6 (0.70)	5 (1.56)	1 (0.65)	.669	0 (0.00)	0 (0.00)	
Difficulty swallowing	4(0.47)	2 (0.63)	2 (1.30)	.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)	.599	5 (3.29)	2 (0.86)	.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)	.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)	.554	0 (0.00)	0 (0.00)	
Swollen toes and/or fingers	7 (0.81)	2 (0.63)	3 (1.95)	.335	0 (0.00)	2 (0.86)	.521
Mottled feet	6 (0.70)	2 (0.63)	2 (1.30)	.599	0 (0.00)	2 (0.86)	.521
Sensory problems							
Loss of taste	18 (2.10)	17 (5.31)	1 (0.65)	.01	0 (0.00)	0 (0.00)	
Loss of smell	23 (2.68)	22 (6.88)	1 (0.65)	.002	0 (0.00)	0 (0.00)	
Loss of appetite	20 (2.33)	15 (4.69)	4 (2.60)	.328	1 (0.66)	0 (0.00)	.395
Flashes of light (photopsia)	3 (0.35)	3 (0.94)	0 (0.00)	.554	0 (0.00)	0 (0.00)	
Ringing in ears (tinnitus)	7 (0.81)	6 (1.88)	0 (0.00)	.184	0 (0.00)	0 (0.00)	
Blurred vision	5 (0.58)	5 (1.56)	0 (0.00)	.179	0 (0.00)	0 (0.00)	
Eye pain	9 (1.05)	9 (2.81)	0 (0.00)	.035	0 (0.00)	0 (0.00)	
Avoiding bright light (photophobia)	7 (0.81)	5 (1.56)	1 (0.65)	.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)	.436	0 (0.00)	0 (0.00)	
Ear pain (otalgia)	7 (0.81)	7 (2.19)	0 (0.00)	.102	0 (0.00)	0 (0.00)	
Respiratory problems							
Cough	24 (2.79)	13 (4.06)	8 (5.19)	.635	3 (1.97)	0 (0.00)	.061
Fits of coughing	14 (1.63)	10 (3.13)	3 (1.95)	.561	1 (0.66)	0 (0.00)	.395
Coughing when lying down	17 (1.98)	12 (3.75)	4 (2.60)	.598	1 (0.66)	0 (0.00)	.395
Chest tightness/pain	4 (0.47)	4 (1.25)	0 (0.00)	.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)	.179	0 (0.00)	0 (0.00)	
Shortness of breath after activity	19 (2.21)	16 (5.00)	2 (1.30)	.069	0 (0.00)	1 (0.43)	1
Sore throat	9 (1.05)	8 (2.50)	1 (0.65)	.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)	.007	5 (3.29)	4 (1.72)	.326
Having difficulty sleeping at night or getting to sleep	44 (5.12)	28 (8.75)	5 (3.25)	.033	5 (3.29)	6 (2.58)	.758
Depression	23 (2.68)	13 (4.06)[b]	1 (0.65)	.043	5 (3.29)[b]	4 (1.72)[b]	.326

Table 3. Continued

	Total (N = 859)	Symptomatic			Asymptomatic		
		Cases (n = 320; 37.25%)	Controls (n = 154; 17.93%)	*P*[a]	Cases (n = 152; 17.69%)	Controls (n = 233; 27.12%)	*P*[a]
Mood swings	41 (4.77)	25 (7.81)	3 (1.95)	.011	6 (3.95)	7 (3.00)	.774
Anxiety	44 (5.12)	25 (7.81)	4 (2.60)	.025	8 (5.26)	7 (3.00)	.289
Gastrointestinal							
Abdominal pain	14 (1.63)	8 (2.50)	3 (1.95)	1	3 (1.97)	0 (0.00)	.061
Nausea	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	.395
Constipation	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	.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)	.395	1 (0.66)	0 (0.00)	.395
Diarrhea	5 (0.58)	2 (0.63)	0 (0.00)	1	2 (1.32)	1 (0.43)	.565
Bowel incontinence	5 (0.58)	3 (0.94)	1 (0.65)	1	1 (0.66)	0 (0.00)	.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)	.281
Fever	2 (0.23)	1 (0.31)	0 (0.00)	1	1 (0.66)	0 (0.00)	.395
Back pain	3 (0.35)	1 (0.31)	1 (0.65)	.545	0 (0.00)	1 (0.43)	1
Neck/shoulder pain	2 (0.23)	1 (0.31)	1 (0.65)	.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)	

Data are presented as n (%).

Abbreviations: COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Fisher's exact test.

[b]One child in that group experienced depression prior to the COVID-19 test.

1 month later, so did 4.2% of symptomatic controls. The difference in prevalence of ongoing symptoms between symptomatic cases and symptomatic controls (2.5%) is similar to the ZOE app study for children (3.5%) but substantially different from the ONS survey, which reported "any symptoms ≥12 weeks after assumed date of infection" of 9.8% in 2- to 11-year-olds and 13.0% in 12- to 16-year-olds who tested positive for SARS-CoV-2 compared with 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 3 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, with the exception of 1 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, ongoing symptoms in asymptomatic cases and similar to the control group.

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. Ongoing, 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 hospitalized cases with more severe illness, which is rare in children. Another strength is the minimization of recall bias by activating the survey within 2 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 3 attempts, the questionnaire completion rate was 35% and there may be some selection bias between respondents and nonrespondents. Parents of children with ongoing 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 nonrespondents, except for younger age among the latter (median age: 6 years), who

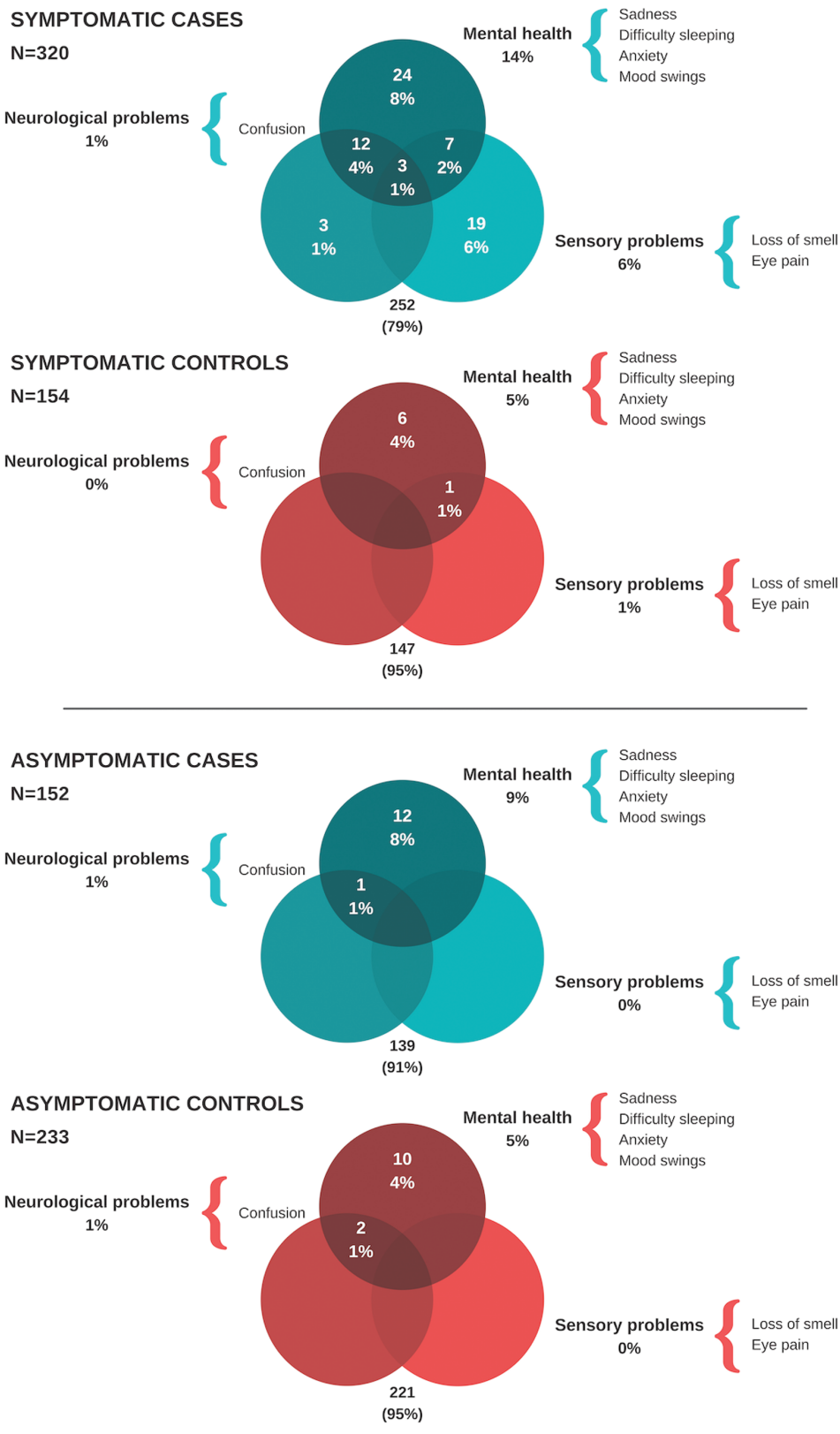

Figure 2. Venn diagram representing clustering of the most common ongoing symptoms in symptomatic and asymptomatic children at least 1 month after a positive SARS-CoV-2 PCR test (cases) compared with symptomatic and asymptomatic children with a negative SARS-CoV-2 PCR test (controls). Abbreviations: PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4. Multivariable Logistic Regression Odds Ratio and Adjusted Odds Ratio Estimates of Symptoms Comparing Symptomatic Cases With Symptomatic Controls

Symptom	Total (N = 474), n (%)	OR	95% CI	*P*	aOR[a]	95% CI	*P*
Neurological							
Confusion	18 (3.81)	…	…	…	…	…	…
Sensory problems							
Loss of taste	18 (3.81)	8.58	1.13–65.11	.038	7.5	.97–57.78	.053
Loss of smell	23 (4.87)	11.3	1.51–84.59	.018	10.2	1.31–79.07	.026
Eye pain	9 (1.91)	…	…	…	…	…	…
Mental health							
Sadness	20 (4.24)	5.61	1.30–24.18	.021	5.31	1.22–23.06	.026
Depression	14 (2.97)	6.48	.84–49.98	.073	5.78	.74–45.44	.095
Having difficulty sleeping at night or getting to sleep	33 (6.99)	2.86	1.08–7.55	.034	2.84	1.06–7.59	.037
Mood swings	28 (5.93)	4.27	1.27–14.35	.019	3.94	1.16–13.40	.028
Anxiety	29 (6.14)	3.18	1.09–9.30	.035	2.99	1.01–8.90	.049

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio

[a]Adjusted for age, sex, ethnicity, socioeconomic status, and comorbidities.

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 at the time of recruitment. Moreover, it is possible that some controls may have been exposed to SARS-CoV-2 in the past 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 1 month after the RT-PCR test. Also, given our sample size, 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% versus 1% (relative risk of ~6) and, for more common symptoms, 10% versus 3% (relative risk of ~3). The low prevalence of any of the reported symptoms among cases and controls is, however, reassuring from a clinical standpoint. 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 ongoing symptoms in children with confirmed COVID-19. More data are needed on the trajectory of the ongoing 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 prioritized to support the mental health of children and adolescents during these difficult times.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. S. N. L., Z. A.-C., and M. E. R. were responsible for conceptualization and study design/methodology. M. Z. and S. N. L. contributed to the original draft and conducted the formal analysis and data validation. All authors contributed to reviewing and editing the manuscripts.

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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