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Characteristics and predictors of persistent symptoms post-COVID-19 in children and young people: a large community cross-sectional study in England

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ABSTRACT

Objective To estimate the prevalence of, and associated risk factors for, persistent symptoms post-COVID-19 among children aged 5–17 years in England.

Design Serial cross-sectional study.

Setting Rounds 10–19 (March 2021 to March 2022) of the REal-time Assessment of Community Transmission-1 study (monthly cross-sectional surveys of random samples of the population in England).

Study population Children aged 5–17 years in the community.

Predictors Age, sex, ethnicity, presence of a pre-existing health condition, index of multiple deprivation, COVID-19 vaccination status and dominant UK circulating SARS-CoV-2 variant at time of symptom onset.

Main outcome measures Prevalence of persistent symptoms, reported as those lasting ≥3 months post-COVID-19.

Results Overall, 4.4% (95% CI 3.7 to 5.1) of 3173 5–11 year-olds and 13.3% (95% CI 12.5 to 14.1) of 6886 12–17 year-olds with prior symptomatic infection reported at least one symptom lasting ≥3 months post-COVID-19, of whom 13.5% (95% CI 8.4 to 20.9) and 10.9% (95% CI 9.0 to 13.2), respectively, reported their ability to carry out day-to-day activities was reduced 'a lot' due to their symptoms. The most common symptoms among participants with persistent symptoms were persistent coughing (27.4%) and headaches (25.4%) in children aged 5–11 years and loss or change of sense of smell (52.2%) and taste (40.7%) in participants aged 12–17 years. Higher age and having a pre-existing health condition were associated with higher odds of reporting persistent symptoms.

Conclusions One in 23 5–11 year-olds and one in eight 12–17 year-olds post-COVID-19 report persistent symptoms lasting ≥3 months, of which one in nine report a large impact on performing day-to-day activities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The most common persistent symptoms post-COVID-19 reported across existing studies in children are headaches, fatigue, insomnia and anosmia. However, symptom persistence estimates in children post-COVID-19 vary substantially from 1%–51% due to heterogeneous study designs, variable follow-up periods and differing definitions.

WHAT THIS STUDY ADDS

⇒ In England at some point since the start of the pandemic until the end of March 2022, 4.4% of 5–11 year-olds and 13.3% of 12–17 year-olds with prior symptomatic infection had persistent symptoms for 3 months or more following COVID-19. Approximately one in nine of these children reported a large impact in their ability to carry out day-to-day activities due to their symptoms. The most common persistent symptoms were coughing, headaches and loss or change of sense of smell or taste.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that persistent symptoms post-COVID-19 are multiple and varied. These findings have implications for researchers, clinicians and affected families in understanding the prevalence and manifestation of long COVID in children and young people.

INTRODUCTION

Compared with adults, children and young people (CYP) are more likely to be asymptomatic or develop mild, transient symptoms following SARS-CoV-2 infection,[1] and life-threatening illness and death from COVID-19 are rare.[1] However, like adults, CYP who have been infected with SARS-CoV-2 may experience persistent, postacute symptoms, which may last for many months.[2 3] Frequently termed 'long COVID' or 'post-COVID-19 condition', recently published systematic reviews indicate that most studies have been conducted in adults.[3–7]

The most common persistent symptoms post-COVID-19 reported across existing studies in CYP are headaches, fatigue, insomnia and anosmia.[8–13] However, estimates of symptom persistence vary substantially ranging from 1% to 51%, arguably due to heterogeneous study designs, follow-up periods and definitions.[8–17] A recent meta-analysis of five controlled studies in CYP found that the frequency of the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and SARS-CoV-2 negative controls. Small but significant increases in the pooled risk difference

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were observed for loss of smell (8%), headaches (5%), cognitive difficulties (3%) and sore throat and eyes (2% each).[6]

Here, we use data from the REal-time Assessment of Community Transmission-1 (REACT-1) study to estimate the prevalence of, and associated risk factors for, persistent symptoms post-COVID-19 among CYP aged 5–17 years in England.

METHODS

Study design and participants

During each round of the REACT-1 study, a random subset of the population (over 5 years old) of England was chosen from the National Health Service (NHS) general practitioner's list and invited to participate in the study.[18] There was a round of the study approximately monthly from May 2020 to March 2022, with each round of data collection including between 15 000 and 35 000 participants aged 5–17 years. The study protocol aimed to achieve approximately equal sample sizes from each lower tier local authority (n=315).[19] Individuals who agreed to participate provided a self-administered throat and nose swab (parent/guardian administered for those aged 5–12 years old) that underwent PCR testing to determine the presence of SARS-CoV-2. In addition, participants completed an online questionnaire (parent/guardian completed by proxy for those aged 5–12 years old), which included information on demographic variables, recent symptoms, whether or not they thought that they had had COVID-19 and whether or not they had had a previous PCR test. From round 10, participants were asked about persistent symptoms related to previous COVID-19 and severity and duration of these symptoms.[18] These included a set of 30 clinically relevant symptoms potentially related to COVID-19. The questionnaires used and a table showing the sampling dates and response rates for REACT-1 are available on the study website.[20]

Data analysis

We estimated the prevalence of persistent symptoms at 3 months postsymptom onset in individuals with a history of COVID-19. We included all self-reported prior COVID-19 episodes including test confirmed and suspected but not confirmed. We only included those who reported onset of COVID-19 ≥3 months prior to the date of the survey and for whom we had complete data. We reported persistent symptoms by age, sex, ethnicity, presence of a pre-existing health condition, index of multiple deprivation (IMD),[21] COVID-19 vaccination status and dominant UK circulating SARS-CoV-2 variant at time of symptom onset. A valid COVID-19 vaccine dose was defined as a date of vaccination 14 days or more prior to COVID-19. The wild-type strain was dominant in the UK prior to December 2020. Alpha dominated between December 2020 and April 2021 followed by delta (May 2021 to mid-December 2021) and omicron (late December 2021 onwards).[22]

To estimate background prevalence of symptoms, we used data on history of any of 26 symptoms lasting 11 or more days (that were present within the 7 days prior to questionnaire completion) for children aged 5–17 years who had a negative PCR test in the REACT-1 study. The data were weighted (by sex, age, ethnicity, lower tier local authority population and IMD) to take account of the sampling design and differential response rates[18] to obtain prevalence estimates that were representative of the 5–17 year-old population of England.

We used logistic regression to quantify the associations of age, sex, ethnicity, presence of a pre-existing health condition, IMD, COVID-19 vaccination status and dominant UK circulating SARS-CoV-2 variant at time of symptom onset with persistence of symptoms at 3 months or more. ORs and 95% CIs were estimated.

Methods and results of a supplementary cluster analysis of persistent symptoms are available in online supplemental file 1.

Data were analysed using the statistical package STATA V.15.0.

RESULTS

Of 191 593 REACT-1 participants aged 5–17 years, 78 948 (41.2%) did not attempt the questionnaire. Of those (or parent/guardian) who completed the questionnaire, 111 444/112 645 (98.9%) reported whether the individual had previously had COVID-19 or not (online supplemental figure S1). Differential non-response was observed by age, sex, ethnicity and deprivation (online supplemental table S1), similar to non-response characteristics of REACT-1 overall.[23] Of participants reporting a COVID-19 episode, 10 059/22 169 (45.4%) reported a valid date of symptom onset ≥3 months before their survey date, providing our denominator population for estimates of persistent symptoms. Table 1 shows the key characteristics of these participants.

The cumulative prevalence of reported COVID-19 increased from 11.4% (5–11 years: 9.7% and 12–17 years: 13.2%) in Round 10 (March 2021) to 48.2% (5–11 years: 51.6% and 12–17 years: 46.9%) in Round 19 (March 2022). Figure 1 shows how the epidemic in CYP evolved between January 2020 and March 2022.

Prevalence of persistent symptoms

Overall, 4.4% (95% CI 3.7 to 5.1; 138/3173) of 5–11 year-olds and 13.3% (95% CI 12.5 to 14.1; 913/6886) of 12–17 year-olds symptomatic at infection had one or more persistent symptoms (from a list of 30 surveyed symptoms) for≥3 months (table 1, online supplemental figure S2). Of which, 11.2% (95% CI 9.4 to 13.3) reported their ability to carry out day-to-day activities was reduced "a lot" due to their symptoms (table 2).

Among 123 468 REACT-1 PCR-negative individuals, average weighted prevalence of any of 26 symptoms lasting 11 or more days was 2.2% (95% CI 2.1 to 2.3) and 2.6% (95% CI 2.5 to 2.7) in those aged 5–11 and 12–17 years, respectively (online supplemental figure S3).

Factors associated with persistent symptoms

Older children with prior symptomatic infection were three times more likely to report persistent symptoms compared with 5–11 year-olds with prior symptomatic infection, adjusted OR 3.4 (95% CI 2.8 to 4.0) (figure 2). Persistent symptoms post-COVID-19 were higher in those with pre-existing health conditions compared with those without (5–11 years: OR 2.6 (95% CI 1.8 to 3.9); 12–17 years: OR 2.0 (95% CI 1.7 to 2.3)) (figure 2). In 12–17 year-olds, being male, Asian ethnicity and living in more affluent areas were associated with lower odds of persistent symptoms (figure 2). Persistent symptoms in children aged 12–17 years were higher in those infected when delta (OR 1.6; 1.3–1.8) was the dominant SARS-CoV-2 variant circulating in the UK population compared with when the original wild-type strain was dominant earlier in the pandemic (figure 2). With regards to COVID-19 vaccination, persistent symptoms post-COVID-19 were lower in 12–17 year olds with at least one valid vaccine dose compared with those without (OR 0.74 (95% CI 0.52 to 1.04)) (figure 2, online supplemental table S2). However, this was not statistically significant at the 5% level.

Symptom profiles

The most common symptoms among participants with persistent symptoms were persistent coughing (27.4%; 95% CI 20.5 to

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Table 1 Numbers and proportions of participants who reported one or more symptoms (from a list of 30 surveyed symptoms) of COVID-19 at 3 months postsymptom onset, among symptomatic participants for whom we have 3-month follow-up and complete data, n=10 059

	Participants aged 5–11 years			Participants aged 12–17 years		
Category	No. reporting one or more symptoms at onset of COVID-19	No. symptomatic at 3 months	% symptomatic at 3 months	No. reporting one or more symptoms at onset of COVID-19	No. symptomatic at 3 months	% symptomatic at 3 months
All participants	3173	138	4.4 (3.7–5.1)	6886	913	13.3 (12.5–14.1)
Sex						
Male	1581	65	4.1 (3.2–5.2)	2885	216	7.5 (6.6–8.5)
Female	1592	73	4.6 (3.7–5.7)	4001	697	17.4 (16.3–18.6)
Ethnicity						
White	2588	122	4.7 (4.0–5.6)	5697	783	13.7 (12.9–14.7)
Mixed	264	9	3.4 (1.8–6.4)	360	41	11.4 (8.5–15.1)
Asian/Asian British	190	3	1.6 (0.5–4.8)	530	51	9.6 (7.4–12.4)
Black/African/Caribbean/black British	41	1	2.4 (0.3–15.7)	126	14	11.1 (6.7–17.9)
Other	35	1	2.9 (0.39–18.1)	81	16	19.8 (12.4–29.9)
IMD quintile						
1 – most deprived	310	10	3.2 (1.7–5.9)	906	144	15.9 (13.7–18.4)
2	497	26	5.2 (3.6–7.6)	1020	158	15.5 (13.4–17.8)
3	643	25	3.9 (2.6–5.7)	1367	169	12.4 (10.7–14.2)
4	744	34	4.6 (3.3–6.3)	1571	188	12.0 (10.5–13.7)
5 – least deprived	979	43	4.4 (3.3–5.9)	2022	254	12.6 (11.2–14.1)
Comorbidities						
No	2701	97	3.6 (3.0–4.4)	5085	544	10.7 (9.9–11.6)
One	412	36	8.7 (6.4–11.9)	1271	231	18.2 (16.1–20.4)
Two or more	54	5	9.3 (3.9–20.5)	513	137	26.7 (23.1–30.7)
Vaccination status at time of infection						
No	3173	138	4.4 (3.7–5.1)	6547	871	13.3 (12.5–14.1)
One dose	0	0	0	310	37	11.9 (8.8–16.0)
At least two doses	0	0	0	29	5	17.2 (7.2–35.7)
Dominant variant at time of infection						
Wild-type (before December 2020)	1722	70	4.1 (3.2–5.1)	2764	309	11.2 (10.1–12.4)
Alpha (December 2020–April 2021)	462	16	3.5 (2.1–5.6)	1032	133	12.9 (11.0–15.1)
Delta (May 2021–December 2021)	989	52	5.3 (4.0–6.8)	3090	471	15.2 (14.0–16.6)

35.6) and headaches (25.4%; 95% CI 18.6 to 33.6) in children aged 5–11 years and loss or change of sense of smell (52.2%; 95% CI 48.9 to 55.5) and taste (40.7%; 95% CI 37.5 to 44.0) in participants aged 12–17 years (figure 3, online supplemental table S3).

DISCUSSION

In this community-based study in England among children aged 5–17 years with prior COVID-19 and 3 months' observation time, the prevalence of persistent symptoms for ≥3 months (from a list of 30 clinically relevant symptoms potentially related to COVID-19) was 4.4% and 13.3% in children aged 5–11 years and 12–17 years, respectively. This compares with a background prevalence of symptoms in PCR test negative participants in REACT-1 of 2.2% and 2.6% in 5–11 and 12–17 year-olds, respectively. Our prevalence estimates of persistent symptoms in children post-COVID-19 are therefore approximately twofold and fivefold the background prevalence in children aged 5–11 and 12–17 years, respectively.

This is one of the few studies to provide prevalence estimates of persistent symptoms post-COVID-19 in 5–11 year-olds lasting ≥3 months and to report on how symptoms reduce ability to carry out day-to-day activities and what level of medical care is being accessed for these symptoms. Previous studies in England have focused on older children (CLoCk study: 11–17 years old[9 24]) or on persistent symptoms lasting >28 days (COVID Symptom Study[8]). The COVID Symptom Study found that 4.4% of UK school-aged children (aged 5–17 years) with COVID-19 still reported symptoms at 28 days.[8] The UK Office for National Statistics (ONS) estimated 7.4% of those aged 2–11 years and 8.2% of those aged 12–16 years still reported symptoms at 12 weeks.[16] The CLoCk study reported 66.5% of 11–17 year olds who tested SARS-CoV-2 positive had symptoms at 3 months, compared with 53.3% in negative controls.[9 24] These estimates are much higher than our study. There are several potential explanations for this. First, they limited their study to 11–17 year-olds, among whom persistent symptoms are higher.[6] Second, participation bias if more CLoCk non-responders had no symptoms compared with REACT-1 participants. This is possible as participants recruited to REACT-1 were not approached with the specific aim of studying persistent symptoms and were offered PCR testing that could have incentivised participation more universally. Third, CLoCk is a prospective longitudinal study, therefore subject to less recall bias. Finally, difference in study period. Our study looked across a longer timeframe during the pandemic with a mixture of the wild-type alpha and delta variants, whereas CLoCk focused on infections during a period when alpha predominated in the UK.[9] There are differences in the nature of the virus, for example, we know that alpha is more infectious and more likely to be associated with hospitalisations

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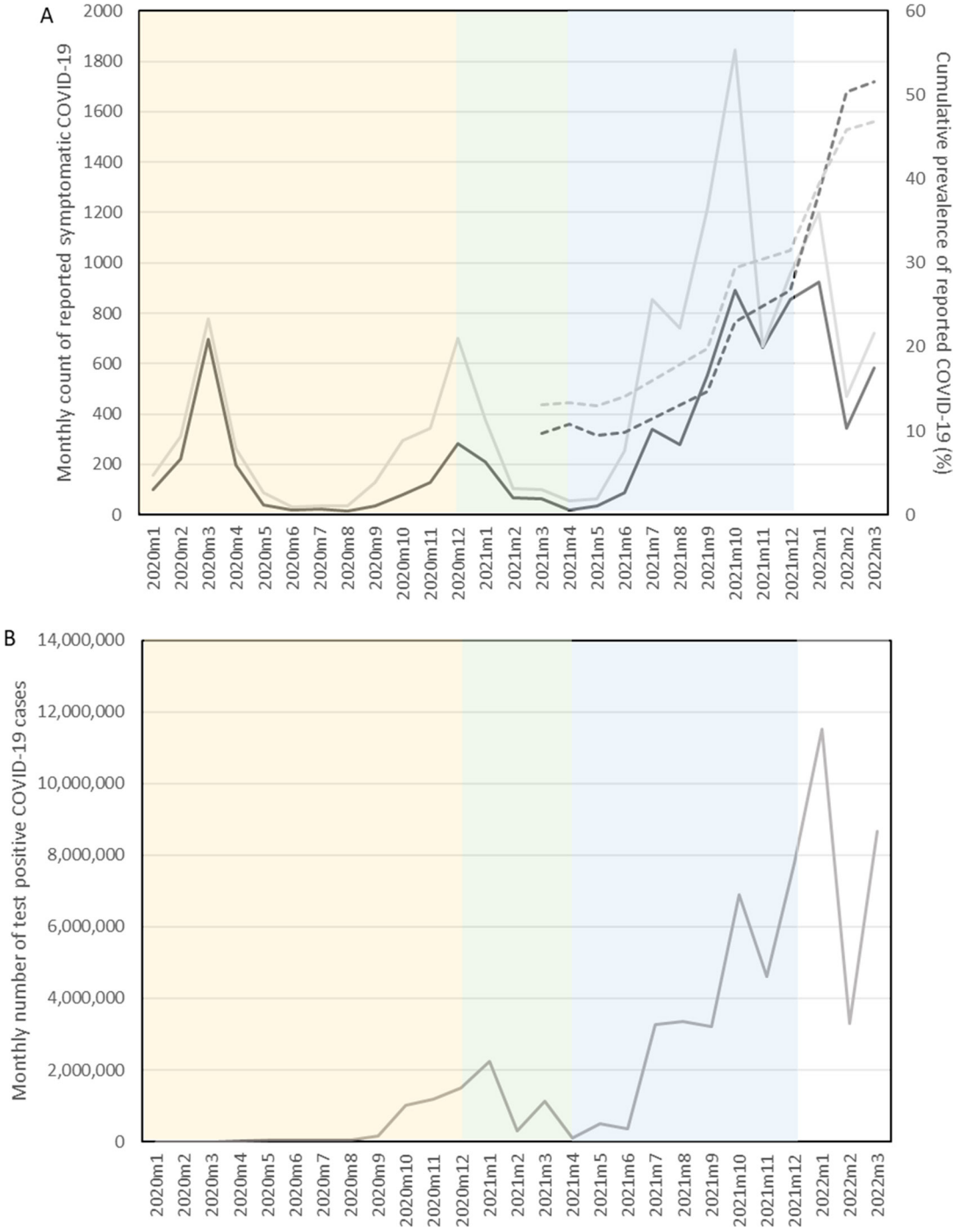


Figure 1 Reconstruction of epidemic curve from study participants with valid date of symptom onset alongside cumulative prevalence of reported COVID-19 and official case numbers for England reported by the UK Government. (A) Number of reported COVID-19 episodes by month[a] in REACT-1 (solid black line: 5–11 year-olds/sold grey line: 12–17 year-olds) (left y-axis) alongside cumulative prevalence of reported COVID-19 by month in which REACT-1 study round was completed[b] (dotted black line: 5–11 year-olds/dotted grey line: 12–17 year-olds) (right y-axis). (B) Number of test positive COVID-19 cases by month in England[c] (solid dark grey line). Data from UK Government website.[28] Shading (dominant SARS-CoV-2 variant): yellow: wild type; green: alpha; blue: delta; white: omicron. [a]n=17 585: asymptomatic individuals and symptomatic participants whose date of COVID-19 was unknown are excluded; [b]n=27 035: individuals reporting a history of COVID-19; [c]widespread testing for SARS-CoV-2 only became available in the UK from April 2020. REACT-1, REal-time Assessment of Community Transmission-1.

than the original wild-type variant.[25] This may translate into more cases of long COVID. In addition, the rate of continuing post-COVID-19 symptoms might vary between variants.

Recently, a Delphi research definition for post-COVID-19 condition in CYP has been developed, 'Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with one or more persisting physical symptoms for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time'.[26] Despite collecting information on how persistent symptoms

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Table 2 Key characteristics of persistent symptoms lasting for 3 months or more for symptomatic participants for whom we have 3-month follow-up and complete data, n=10 059

	Aged 5–11 years	Aged 12–17 years
Category	**≥3 months n=3173**	**≥3 months n=6886**
Symptom duration	**n (%; 95% CI)***	**n (%; 95% CI)***
Less than 4 weeks	2797 (88.2; 87.1 to 89.3)	5290 (76.9; 75.8 to 77.8)
4 weeks up to 2 months	183 (5.8; 5.0 to 6.6)	479 (7.0; 6.4 to 7.6)
2 months up to 3 months	52 (1.6; –1.3 to 2.1)	201 (2.9; 2.5 to 3.3)
3 months or more	138 (4.4; 3.7 to 5.1)	913 (13.3; 12.5 to 14.1)
No. of symptoms (at 3 months post-COVID-19)		
No symptoms	3035 (95.7; 94.9 to 96.3)	5973 (86.7; 85.9 to 87.5)
One	55 (1.7; 1.3 to 2.3)	311 (4.5; 4.1 to 5.0)
Two	31 (1.0; 0.7 to 1.4)	272 (4.0; 3.5 to 4.4)
Three	9 (0.3; 0.2 to 0.5)	112 (1.6; 1.4 to 2.0)
Four	14 (0.4; 0.3 to 0.7)	68 (1.0; 0.8 to 1.3)
Five or more	29 (0.9; 0.6 to 1.3)	150 (2.2; 1.9 to 2.6)
	n=138 (those with symptom duration 3 months or more)	**n=913 (those with symptom duration 3 months or more)**
Symptoms frequency	**n (%; 95% CI)***	**n (%; 95% CI)***
Every day	34 (28.6; 21.1 to 37.4)	409 (46.9; 43.6 to 50.2)
Most days	34 (28.6; 21.1 to 37.4)	269 (30.9; 27.9 to 34.0)
Come and go	51 (42.9; 34.2 to 52.0)	194 (22.3; 19.6 to 25.1)
Symptoms reduce ability to carry out day-to-day activities		
A lot	16 (13.5; 8.4 to 20.9)	95 (10.9; 9.0 to 13.2)
A little	59 (49.6; 40.6 to 58.6)	361 (41.5; 38.3 to 44.8)
Not at all	41 (34.5; 26.4 to 43.5)	363 (41.7; 38.5 to 45.0)
Don't know	3 (2.5; 0.8 to 7.6)	51 (5.9; 4.5 to 7.6)
Accessed medical help for symptoms†		
No	42 (35.3; 27.2 to 44.4)	597 (68.5; 65.3 to 71.5)
Pharmacist/by phone (GP‡/NHS 111§)	46 (33.3; 25.9 to 41.7)	204 (22.3; 19.8 to 25.2)
Visited GP/walk-in centre/ Accident and Emergency Department /hospital clinic	46 (33.3; 25.9 to 41.7)	149 (16.3; 14.1 to 18.9)
Hospital admission	8 (6.7; 3.4 to 12.9)	5 (0.6; 0.2 to 1.4)
Symptom duration in those with ≥6-month follow-up, persistent symptoms at 3 months and reported no longer having COVID-19 symptoms	**≥6 months n=68 n (%; 95% CI)***	**≥6 months n=395 n (%; 95% CI)***
3 months up to 6 months	32 (47.1; 35.3 to 59.2)	189 (47.9; 42.9 to 52.8)
6 months or more	36 (52.9; 40.8 to 64.7)	206 (52.2; 47.2 to 57.1)

*Percentages are calculated from non-missing values.
†Participants who sort more than one type of medical help counted for each type accessed.
‡GP: general practitioner, physician in primary care.
§NHS 111: a free-to-call single non-emergency number medical helpline operating in England.

impact day-to-day activities, we only had information on symptomatic SARS-CoV-2 infections. The research definition of long COVID in CYP includes all confirmed SARS-CoV-2 infection (symptomatic and asymptomatic).[26] Therefore, our estimates are likely higher and not directly comparable with studies applying this definition.

Few studies have reported on measures of association between key characteristics and persistent symptoms lasting ≥3 months in CYP. We show that increasing age and reporting a pre-existing health condition were associated with higher odds of persistent symptoms following COVID-19, consistent with other studies in children.[9 14] Persistent symptoms in children aged 12–17 years were higher in those infected during the delta period compared with the original wild-type period earlier in the pandemic. This association is temporal to a large extent as delta was circulating later in the pandemic and therefore may be confounded by the number of previous infections, information on which was not collected as part of our study. A recent case–control study conducted in the UK found a lower odds of long COVID with the omicron versus the delta variant, ranging from OR 0.2 (95% CI 0.2 to 0.3) to 0.5 (95% CI 0.4 to 0.6),[27] suggesting that the risk of long COVID may vary by variant.

Strengths and limitations

This study included data from a large random community sample, thus providing representative information on persistent COVID-19 symptoms in children with prior symptomatic infection in the community. The REACT-1 response rate in 5–17 year-olds was low (14.9%), with questionnaire response rate at 6.0%. This was lower than questionnaire response rates of the CloCK and ONS studies, with 11.2% and 12%, respectively.[24] Similar to these studies, our participants were more likely to be female, older teenagers, white ethnicity, from the southeast (less likely to be from London or the North West) and were more likely to be from the least deprived areas. In contrast to the CloCK study, our participants were broadly more similar to the England population aged 5–17 years, reflecting the random population sampling design[9 24] (online supplemental table S4).

We used information regarding presence of symptoms rather than whether participants described themselves as having 'long COVID' to reduce potential reporting bias. However, the retrospective study design introduces the possibility of recall bias. In addition, we included all self-reported prior COVID-19 episodes including test confirmed and suspected but not confirmed, which introduces the possibility of misclassification bias. When we limited the analysis to test confirmed COVID-19 episodes, the prevalence of persistent symptoms for ≥3 months was higher compared with the prevalence in suspected COVID-19 episodes (5–11 year-olds: 5.1% vs 3.7%, 12–17 year-olds: 16.0% vs 8.6%), and the magnitude and direction of associations between sociodemographic factors and persistent symptoms were similar (online supplemental tables S5 and S6). However, given the limited availability of testing early in the pandemic, it was necessary to include suspected cases. Reassuringly, our epidemic curve produced from participant reported symptom onset date closely tracked the epidemic (figure 1).

A major limitation is the lack of a SARS-CoV-2 negative control group which makes it hard to separate symptoms due to SARS-Co-V2 infection from those caused by normal life, other infections, or the pressures of a pandemic. REACT-1 was originally designed as a surveillance study to provide reliable and timely prevalence estimates of SARS-CoV-2 infection in the community to inform the immediate public health response and so we did not collect baseline information on symptom profiles at the time of symptom onset in those with a history of COVID-19, nor did we collect comparable data on participants with no history of COVID-19. Therefore, our estimates may partly reflect the large list of symptoms we surveyed, many of which are common and not specific to COVID-19. We estimated background prevalence of persistent symptoms to be 2.2% and 2.6% in 5–11 and 12–17 year-olds, respectively. These provide upper bounds for non-COVID-19 related prevalence of persistent symptoms at 3 months or more.

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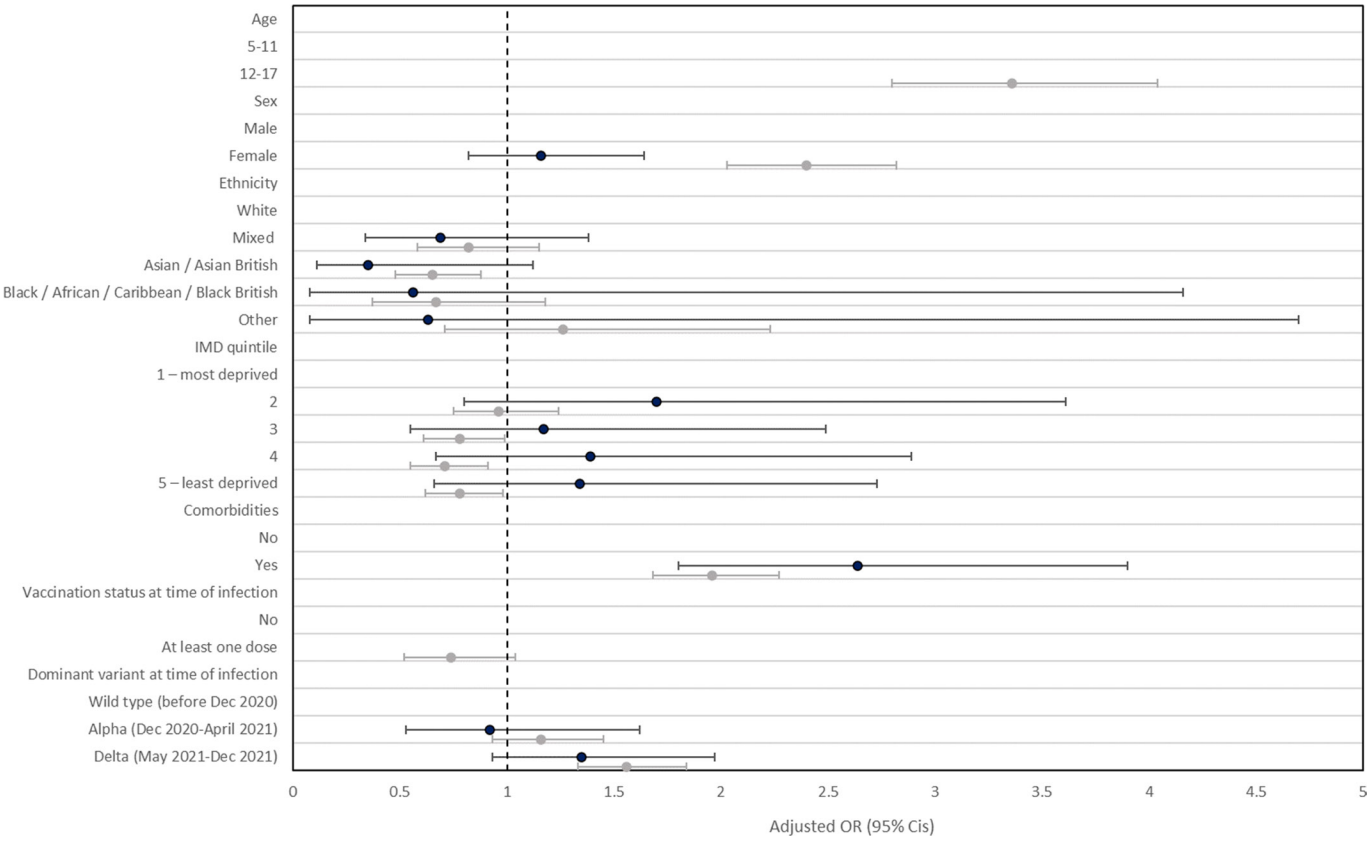


Figure 2 Logistic regression models with one or more symptoms at 3 months (y/n) as the binary outcome variable[a]. adjusted odds ratios (dot) and 95% CIs (line) presented separately for participants aged 5–11 years (black) and 12–17 years (grey), n=10 059. [a]Mutually adjusted for age, sex, ethnicity, IMD, comorbidities, vaccination status (over 12 year-olds only) and dominant variant at time of infection. No vaccination status estimate provided for children aged 5–11 years because only 5–11 year-olds with certain health conditions, or those with a weakened immune system were being offered vaccination during the study period and no participant aged 5–11 years in our study cohort reported having been vaccinated.

CONCLUSION

One in 23 children aged 5–11 years and 1 in 8 individuals aged 12–17 years have persistent symptoms lasting ≥3 months post-COVID-19. Persistent symptoms were multiple and varied with approximately one in nine children reporting a large impact in ability to carry out day-to-day activities due to their symptoms. Our study contributes to a growing evidence base regarding the

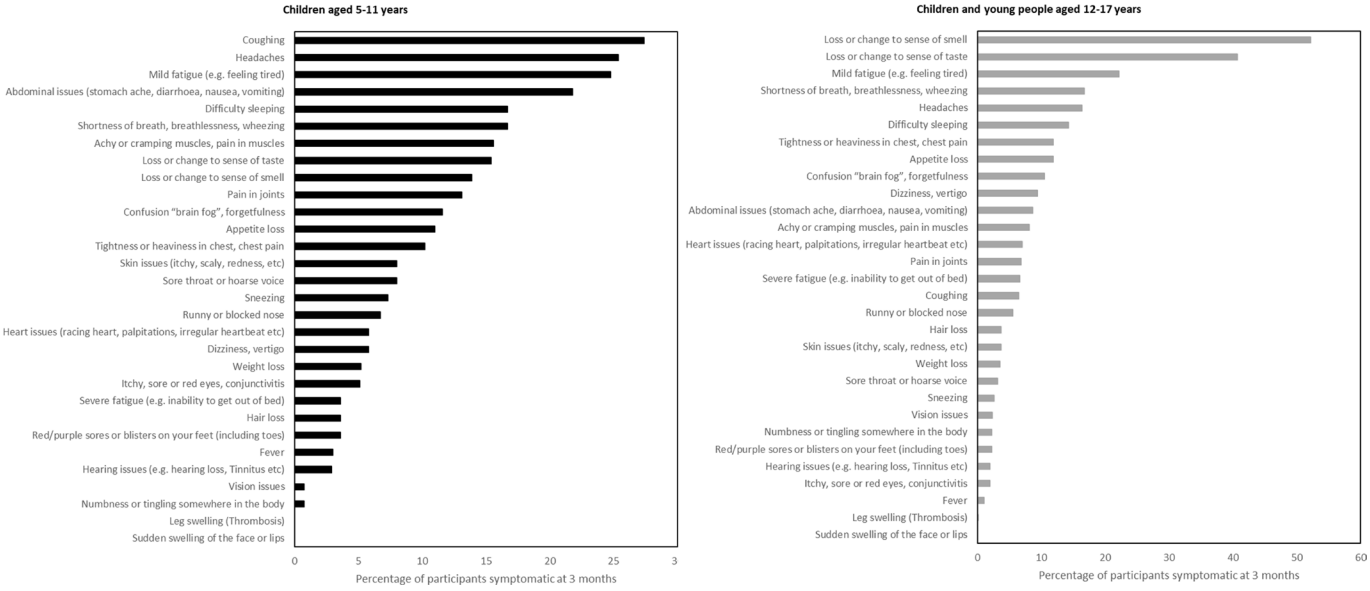


Figure 3 Percentage of individual symptoms among participants with persistent symptoms at 3 months or more post-COVID-19 onset for whom we have 3-month follow-up and complete data, n=1051.

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prevalence, risk factors and characteristics of long COVID in children.

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Supplementary File: Cluster analysis

Methods

We carried out a hierarchical cluster analysis to cluster individuals by reported symptoms at 3 months or more post COVID-19. First, an analysis using Ward's method applying squared Euclidean Distance as the distance or similarity measure was performed (1). This indicated the optimum number of clusters to work with. Second, the analysis was rerun with the selected number of clusters, which enabled every participant to be allocated to a particular cluster. Three scenarios of combinations of two, three and four clusters were used. The dendrogram of each hierarchical cluster analysis was evaluated to determine which symptom needed to be allocated to which cluster (Figure 1 & 2). The Calinski-Harabasz Index was used to select the optimal number of clusters (Table 1 & 2) (2). As sensitivity analysis, we also ran the hierarchical cluster analysis applying Jaccard Distance which unlike squared Euclidean Distance does not consider negative co-occurrence (3).

To compare the clusters by key participant characteristics (sex, ethnicity, presence of a pre-existing health condition and IMD) contingency tables and chi-squared tests (significance level: $p<0.05$) were used. To compare the clusters by age, ANOVA (significance level: $p<0.05$) was used. The prevalence of the symptoms in each constructed cluster was also estimated.

Results

Two clusters were identified in children aged 5-11 years based on symptom profiles at 3 months (Figure 1, Figure 3 & Table 1). Cluster 1 (n=90) was characterised by moderate prevalence of coughing which co-occurred with loss or change of sense of smell or taste. Cluster 2 (n=23) had a broader symptom profile with high prevalence of abdominal issues, mild fatigue, headaches, difficulty sleeping, achy or cramping muscles and joint pain (Figure 3). There was no difference in sociodemographic characteristics between the two clusters (Table 2). In children and young people aged 12-17 years, two symptom clusters were also identified (Figure 2, Figure 3 & Table 3). There was high prevalence of loss or change of sense of smell or taste in Cluster 1 (n=396). Cluster 2 (n=343) was characterised by multiple symptoms dominated by mild fatigue, headaches and shortness of breath (Figure 3). Cluster 2 contained a higher proportion of individuals who reported a pre-existing health condition (45.8% (95% CI 40.6-51.1) vs. 29.8% (95% CI 25.5-34.5) in Cluster 1; $p<0.001$) and who reported that their initial COVID-19 episode was when the wild-type strain was dominant (39.9% (95% CI 34.9-45.2) vs. 24.0% (95% CI 20.0-28.5) in Cluster 1; $p<0.001$). Conversely, Cluster 1 contained a higher proportion of individuals who reported that their initial COVID-19 episode was when the Delta strain was dominant (62.6% (95% CI 57.7-67.3) vs. 43.7% (95% CI 38.6-49.0) in Cluster 2; $p<0.001$) (Table 4).

In clustering sensitivity analysis, using hierarchical clustering with Jaccard Distance, we identified 3 and 2 clusters in children aged 5-11 and 12-17 years, respectively. For children aged 5-11 years, one cluster had a broad symptom profile dominated by abdominal issues, mild fatigue, and headache, and contained the same participants from Cluster 2 as in the main analysis (which also had a broad symptom profile with high prevalence of abdominal issues,

mild fatigue and headache), as well as some participants from Cluster 1. The other two clusters identified for this age group were small and were dominated by loss or change of sense of smell or taste in one and coughing in the other (Figure 4 & Table 5). For children aged 12-17 years, there was high prevalence of loss or change of sense of smell or taste in one cluster and a broader symptom profile in the other, which contained most of the same participants from Cluster 1 and Cluster 2 as in the main analysis, respectively (Figure 4 & Table 5).

Our identification of two symptom clusters at 3 months in both age group, albeit small numbers in each cluster particularly for younger children, suggests that long-term sequelae after COVID-19 may have distinct subgroups in children. A previous study in children aged 11-17 years using latent class analysis, found evidence of clustering in symptoms reported at 3 months, with two subgroups: one had very low prevalence of most symptoms, while the second subgroup was characterised by multiple symptoms dominated by tiredness, headache, shortness of breath and dizziness, not too dissimilar from Cluster 2 in older children in our study (4).

With regard to limitations of the clustering analysis, while this provides some insights into symptom clustering among children with persistent symptoms following COVID-19 our sample size was small, particularly for younger children. In addition, given the unpredictable emergence of new SARS-CoV-2 variants, it is unclear how stable this symptom clustering is over time.

Figure 1: Dendrogram of persistent symptom clusters among participants aged 5-11 years, N=113

Dendrograms graphically present the information concerning which observations (participants) are grouped together at various levels of (dis)similarity. At the bottom of the dendrogram, each observation is considered its own cluster. Vertical lines extend up for each observation, and at various (dis)similarity values, these lines are connected to the lines from other observations with a horizontal line. The observations continue to combine until, at the top of the dendrogram, all observations are grouped together. The height of the vertical lines and the range of the (dis)similarity axis give visual clues about the strength of the clustering. Long vertical lines indicate more distinct separation between the groups. Long vertical lines at the top of the dendrogram indicate that the groups represented by those lines are well separated from one another. Shorter lines indicate groups that are not as distinct.

We have limited our view to the top 10 branches of the dendrogram, labelled G1-10. The number of observations in each group is given below the label.

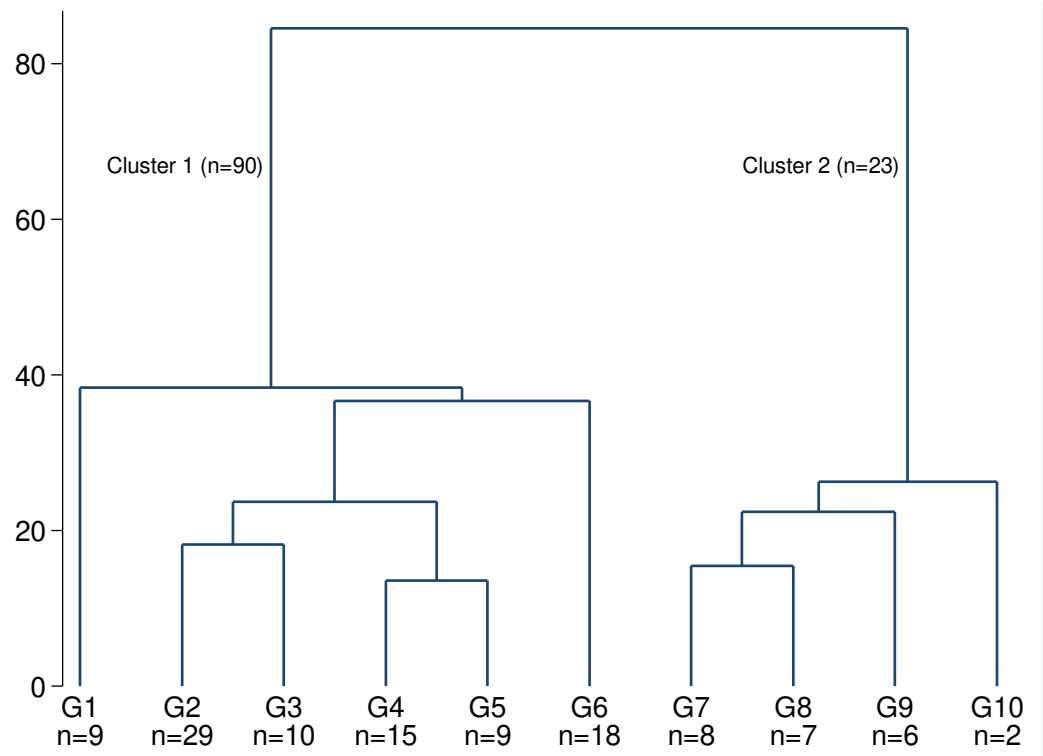


Table 1: Calinski-Harabasz Index for persistent symptom cluster analysis for participants aged 5-11 years, N=113

Calinski-Harabasz Index: Based on the idea that clusters that are 1) themselves very compact and 2) well-spaced from each other are good clusters. The index is calculated by dividing the variance of the sums of squares of the distances of individual objects to their cluster centre by the sum of squares of the distance between the cluster centers. Higher the Calinski-Harabasz Index, the better the clustering model. In this case the Calinski-Harabasz Index is maximised when the number of clusters is 2.

Number of clusters	Calinski-Harabasz Index
2	20.26
3	15.92
4	14.94
5	13.87
6	13.26
7	12.98
8	12.62
9	12.24
10	11.90
11	11.64
12	11.41
13	11.23
14	11.09
15	11.04

Table 2: Key characteristics of 3 month symptom clusters among participants aged 5-11 years with symptoms and date of symptom onset 3 months or more before survey date, N=113

For continuous variables, mean and standard deviation (SD) and analysis of variance (ANOVA) to test the difference between means. For categorical variables, column-wise within-group percentages shown in square brackets, with 95% confidence intervals in parentheses and chi-squared test to determine difference between frequencies in one or more categories.

	Category	**Cluster 1 N=90 % (95% CI)**	**Cluster 2 N=23 % (95% CI)**
Age	Mean (SD)	9.2 (1.7)	9.9 (1.3)
Sex	Male	39 [43.3 (33.4, 53.9)]	14 [60.9 (39.6, 78.7)]
	Female	51 [56.7 (46.1, 66.6)]	9 [39.1 (21.3, 60.4)]
Ethnicity	White	82 [91.1 (83.1, 95.5)]	19 [86.4 (64.2, 95.7)]
	Mixed	5 [5.6 (2.3, 12.8)]	2 [9.1 (2.2, 31.0)]
	Asian / Asian British	2 [2.2 (0.54, 8.6)]	0 [0.0 (0.0, 0.15)]
	Black / African / Caribbean / Black British	0 [0.0 (0.0, 0.04)]	1 [4.6 (0.59, 27.5)]
	Other	1 [1.1 (0.15, 7.7)]	0 [0.0 (0.0, 0.15)]
Comorbidities	No	68 [75.6 (65.5, 83.4)]	15 [65.2 (43.6, 82.0)]
	Yes	22 [24.4 (16.6, 34.5)]	8 [34.8 (18.0, 56.4)]
IMD quintile	1 – most deprived	4 [4.4 (1.7, 11.4)]	3 [13.0 (4.1, 34.5)]
	2	18 [20.0 (12.9, 29.7)]	2 [8.7 (2.1, 29.9)]
	3	14 [15.6 (9.4, 24.7)]	7 [30.4 (14.9, 52.3)]
	4	23 [25.6 (17.5, 35.7)]	6 [26.1 (11.9, 48.0)]
	5 – least deprived	31 [34.4 (25.2, 45.0)]	5 [21.7 (9.1, 43.6)]
Dominant variant at time of infection	Wild type (before Dec 2020)	42 [46.7 (36.5, 57.1)]	14 [60.9 (39.6, 78.7)]
	Alpha (Dec 2020-April 2021)	10 [11.1 (6.0, 19.6)]	2 [8.7 (2.1, 29.9)]
	Delta (May 2021-Dec 2021)	38 [42.2 (32.3, 52.8)]	7 [30.4 (14.9, 52.3)]

Figure 2: Dendrogram of persistent symptom clusters among participants aged 12-17 years, N=739

Dendrograms graphically present the information concerning which observations (participants) are grouped together at various levels of (dis)similarity. At the bottom of the dendrogram, each observation is considered its own cluster. Vertical lines extend up for each observation, and at various (dis)similarity values, these lines are connected to the lines from other observations with a horizontal line. The observations continue to combine until, at the top of the dendrogram, all observations are grouped together. The height of the vertical lines and the range of the (dis)similarity axis give visual clues about the strength of the clustering. Long vertical lines indicate more distinct separation between the groups. Long vertical lines at the top of the dendrogram indicate that the groups represented by those lines are well separated from one another. Shorter lines indicate groups that are not as distinct.

We have limited our view to the top 10 branches of the dendrogram, labelled G1-10. The number of observations in each group is given below the label.

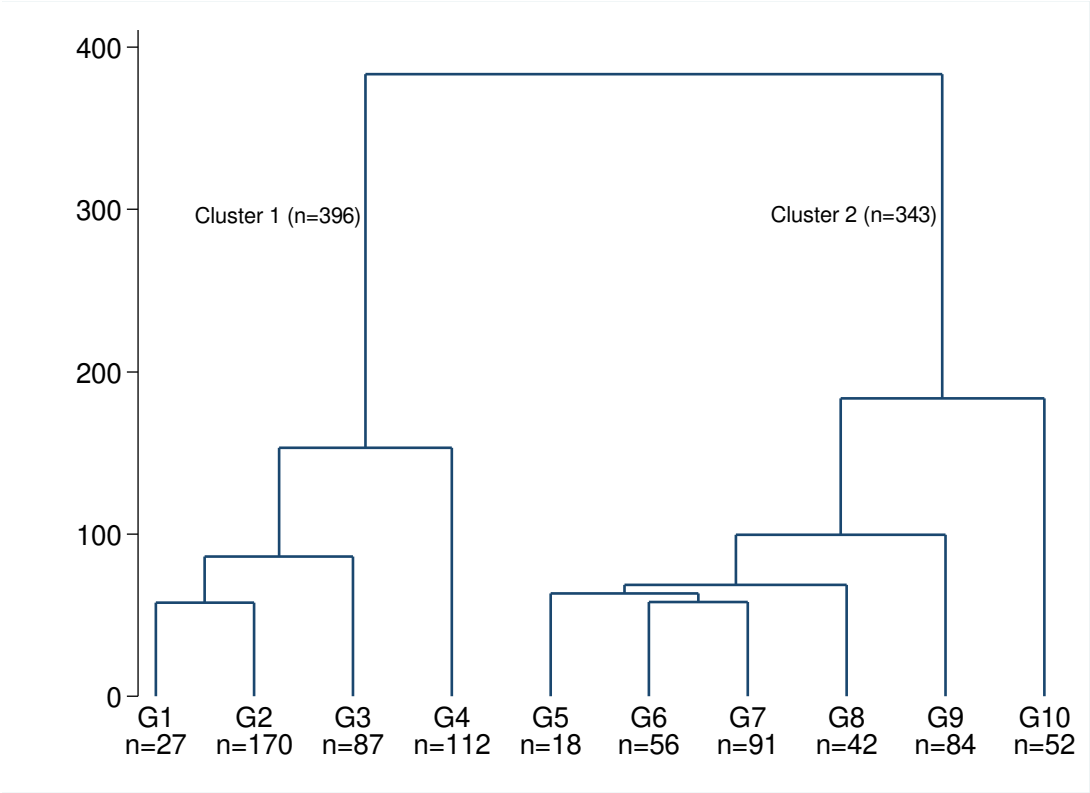


Table 3: Calinski-Harabasz Index for persistent symptom cluster analysis for participants aged 5-11 years, N=739

Calinski-Harabasz Index: Based on the idea that clusters that are 1) themselves very compact and 2) well-spaced from each other are good clusters. The index is calculated by dividing the variance of the sums of squares of the distances of individual objects to their cluster centre by the sum of squares of the distance between the cluster centers. Higher the Calinski-Harabasz Index, the better the clustering model. In this case the Calinski-Harabasz Index is maximised when the number of clusters is 2.

Number of clusters	Calinski-Harabasz Index
2	111.34
3	88.61
4	80.17
5	71.56
6	65.86
7	61.04
8	57.53
9	54.77
10	52.85
11	51.34
12	50.03
13	48.84
14	47.69
15	46.43

Table 4: Key characteristics of 3 month symptom clusters among participants aged 12-17 years with symptoms and date of symptom onset 3 months or more before survey date, N=739

For continuous variables, mean and standard deviation (SD) and analysis of variance (ANOVA) to test the difference between means. For categorical variables, column-wise within-group percentages shown in square brackets, with 95% confidence intervals in parentheses and chi-squared test to determine difference between frequencies in one or more categories. Cluster 2 contained significantly more individuals who had a pre-existing health condition (45.8% vs 29.8% in Cluster 1; p<0.001) and who had their initial COVID-19 episode when the Wild type strain was dominant (39.9% vs 24.0% in Cluster 1; p<0.001). Cluster 1 contained significantly more individuals who had their initial COVID-19 episode when the Delta strain was dominant (62.6% vs 43.7% in Cluster 2; p<0.001).

	Category	**Cluster 1 N=396 % (95% CI)**	**Cluster 2 N=343 % (95% CI)**
Age	Mean (SD)	15.0 (1.4)	15.0 (1.6)
Sex	Male	106 [26.8 (22.6, 31.4)]	78 [22.7 (18.6, 27.5)]
	Female	290 [73.2 (68.6, 77.4)]	265 [77.3 (72.5, 81.4)]
Ethnicity	White	349 [88.6 (85.0, 91.4)]	288 [84.5 (80.2, 87.9)]
	Mixed	16 [4.1 (2.5, 6.5)]	17 [5.0 (3.1, 7.9)]
	Asian / Asian British	21 [5.3 (3.5, 8.0)]	20 [5.9 (3.8, 8.9)]
	Black / African / Caribbean / Black British	5 [1.3 (0.53, 3.0)]	8 [2.4 (1.2, 4.6)]
	Other	3 [0.76 (0.24, 2.3)]	8 [2.4 (1.2, 4.6)]
Comorbidities	No	278 [70.2 (65.5, 74.5)]	186 [54.2 (48.9, 59.4)]
	Yes	118 [29.8 (25.5, 34.5)]	157 [45.8 (40.6, 51.1)]
IMD quintile	1 – most deprived	52 [13.1 (10.1, 16.8)]	53 [15.5 (12.0, 19.7)]
	2	59 [14.9 (11.7, 18.8)]	62 [18.1 (14.3, 22.5)]
	3	75 [18.9 (15.4, 23.1)]	59 [17.2 (13.6, 21.6)]
	4	97 [24.5 (20.5, 29.0)]	65 [19.0 (15.1, 23.5)]
	5 – least deprived	113 [28.5 (24.3, 33.2)]	104 [30.3 (25.7, 35.4)]
Vaccination status at time of infection	No	384 [97.0 (94.7, 98.3)]	323 [94.2 (91.1, 96.2)]
	At least one dose	12 [3.0 (1.7, 5.3)]	20 [5.8 (3.8, 8.9)]
Dominant variant at time of infection	Wild type (before Dec 2020)	95 [24.0 (20.0, 28.5)]	137 [39.9 (34.9, 45.2)]
	Alpha (Dec 2020-April 2021)	53 [13.4 (10.4, 17.1)]	56 [16.3 (12.8, 20.6)]
	Delta (May 2021-Dec 2021)	248 [62.6 (57.7, 67.3)]	150 [43.7 (38.6, 49.0)]

Figure 3: Results of clustering on symptom profile at 3 months or more post COVID-19 onset for participants aged 5-11 and 12-17 years, using hierarchical clustering. Darker red shading indicates higher symptom prevalence within the cluster. N=852

5-11 year olds			12-17 year olds	
Cluster 1 (n=90)	**Cluster 2 (n=23)**	**Symptoms at 3 months or more post COVID-19 onset**	**Cluster 1 (n=396)**	**Cluster 2 (n=343)**
6.7	82.6	Abdominal issues (stomach ache, diarrhoea, nausea, vomiting)	0.76	13.7
13.3	69.6	Mild fatigue (e.g. feeling tired)	7.3	32.1
14.4	65.2	Headaches	1	29.7
6.7	60.9	Difficulty sleeping	2	22.2
3.3	56.5	Achy or cramping muscles, pain in muscles	0.76	14.9
2.2	47.8	Pain in joints	1	12
3.3	34.8	Appetite loss	10.9	9.3
4.4	30.4	Confusion “brain fog”, forgetfulness	1	19.5
15.6	21.7	Loss or change of sense of taste	66.7	18.1
3.3	21.7	Tightness or heaviness in chest, chest pain	1.8	18.4
2.2	21.7	Weight loss	2.5	3.8
1.1	21.7	Heart issues (racing heart, palpitations, irregular heartbeat etc)	1	11.4
15.6	17.4	Loss or change of sense of smell	84.1	23.3
14.4	17.4	Shortness of breath, breathlessness, wheezing	3.3	28.9
4.4	13	Dizziness, vertigo	0.51	14.6
32.2	8.7	Coughing	1.3	10.8
7.8	8.7	Skin issues (itchy, scaly, redness, etc)	0	7.9
4.4	8.7	Itchy, sore or red eyes, conjunctivitis	0.25	2.9
2.2	8.7	Severe fatigue (e.g. inability to get out of bed)	0.51	11.1
0	8.7	Hair loss	1	6.7
10	4.4	Sneezing	0.25	5.3
7.8	4.4	Runny or blocked nose	1.5	10.5
6.7	4.4	Sore throat or hoarse voice	0.76	3.8
3.3	4.4	Fever	0.25	1.5
3.3	4.4	Hearing issues (e.g. hearing loss, Tinnitus etc)	0.51	3.2
0	4.4	Numbness or tingling somewhere in the body	1.5	2.6
4.4	0	Red/purple sores or blisters on your feet (including toes)	0.25	4.4
1.1	0	Vision issues	0	4.1
0	0	Sudden swelling of the face or lips	0	0
0	0	Leg swelling (Thrombosis)	0	0.29

Figure 4: Results of clustering (with different distance metric) on symptom profile at 3 months or more post COVID-19 onset for children aged 5-11 and 12-17 years, using the same hierarchical clustering approach as in the main analysis but replacing squared Euclidean Distance with Jaccard Distance, N=852

The plot shows cluster membership overlap between sensitivity analysis (Jaccard) and the main analysis (squared Euclidean Distance – Figure 3). For children aged 5-11 years, three clusters (Cluster S1-3) with Jaccard Distance created the best clusters according to the Calinski-Harabasz Index (Table 5). Cluster S1, with a broad symptom profile characterised by abdominal issues, mild fatigue and headache, included all the same observations from Cluster 2 from the main analysis (which also had a broad symptom profile with high prevalence of abdominal issues, mild fatigue and headache), as well as some observations from Cluster 1. Cluster S2 is a small group in which loss or change of sense of smell and taste are the predominant symptoms. Cluster 3 is a small group in which coughing is the only symptom. For children aged 12-17 years, two clusters (Cluster C1 and Cluster C2) with Jaccard Distance created the best clusters according to the Calinski-Harabasz Index (Table 5) which included most of the same observations from Cluster 1 and Cluster 2 from the main analysis, respectively. Similar to the main analysis, there was high prevalence of loss or change of sense of smell and taste in one cluster and a broader symptom profile in the other.

5-11 year olds				12-17 year olds	
Cluster S1 (n=84)	**Cluster S2 (n=17)**	**Cluster S3 (n=12)**	**Symptoms at 3 months or more post COVID-19 onset**	**Cluster C1 (n=311)**	**Cluster C2 (n=428)**
29.8	0	0	Abdominal issues (stomach ache, diarrhoea, nausea, vomiting)	0	11.7
33.3	0	0	Mild fatigue (e.g. feeling tired)	0	32.5
33.3	0	0	Headaches	0	24.8
23.8	0	0	Difficulty sleeping	0	19.6
19.1	0	0	Achy or cramping muscles, pain in muscles	0	12.6
15.5	0	0	Pain in joints	0	10.5
10.7	11.8	0	Appetite loss	0	17.5
13.1	0	0	Confusion “brain fog”, forgetfulness	0	16.6
7.1	76.5	0	Loss or change of sense of taste	64.0	29.7
9.5	0	0	Tightness or heaviness in chest, chest pain	0	16.4
7.1	5.9	0	Weight loss	0	5.4
7.1	0	0	Heart issues (racing heart, palpitations, irregular heartbeat etc)	0	10.1
7.1	70.6	0	Loss or change of sense of smell	86.5	33.6
20.2	0	0	Shortness of breath, breathlessness, wheezing	0	26.2
8.3	0	0	Dizziness, vertigo	0	12.2
22.6	0	100	Coughing	0	9.8
9.5	5.9	0	Skin issues (itchy, scaly, redness, etc)	0	6.3
6	5.9	0	Itchy, sore or red eyes, conjunctivitis	0	2.6
4.8	0	0	Severe fatigue (e.g. inability to get out of bed)	0	9.4
2.4	0	0	Hair loss	0	6.3
11.9	0	0	Sneezing	0	4.4
9.5	0	0	Runny or blocked nose	0	9.8
8.3	0	0	Sore throat or hoarse voice	0	3.7
4.8	0	0	Fever	0	1.4
4.8	0	0	Hearing issues (e.g. hearing loss, Tinnitus etc)	0	3.0
1.2	0	0	Numbness or tingling somewhere in the body	0	3.5
4.8	0	0	Red/purple sores or blisters on your feet (including toes)	0	3.7
1.2	0	0	Vision issues	0	3.3

0	0	0	Sudden swelling of the face or lips	0	0
0	0	0	Leg swelling (Thrombosis)	0	0.23

Table 5: Calinski-Harabasz Index for persistent symptom cluster analysis for participants aged 5-11 and 12-17 years, N=852

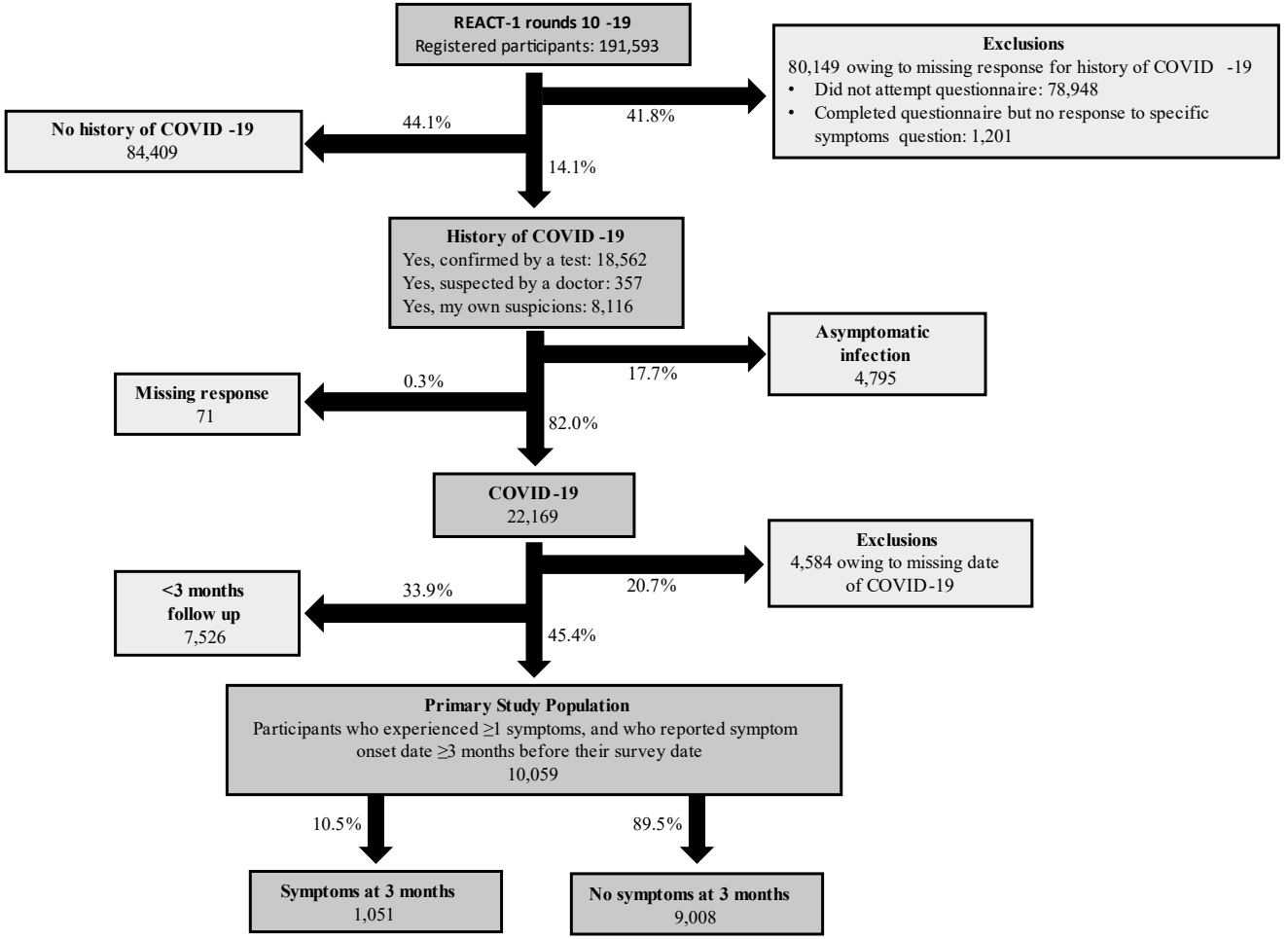
Calinski-Harabasz Index: Based on the idea that clusters that are 1) themselves very compact and 2) well-spaced from each other are good clusters. The index is calculated by dividing the variance of the sums of squares of the distances of individual objects to their cluster centre by the sum of squares of the distance between the cluster centers. Higher the Calinski-Harabasz Index, the better the clustering model. In this case the Calinski-Harabasz Index is maximised when the number of clusters is 3 and 2 for 5-11 year olds and 12-17 year olds, respectively.

Number of clusters	Calinski-Harabasz Index: 5-11 years old	Calinski-Harabasz Index: 12-17 years old
2	5.16	88.47
3	7.57	69.28
4	7.28	54.19
5	5.97	57.68
6	7.24	49.35
7	7.06	48.78
8	6.39	44.27
9	6.87	40.02
10	6.52	39.62
11	6.27	37.49
12	7.02	35.52
13	6.60	38.17
14	6.49	35.89
15	6.17	34.76

References

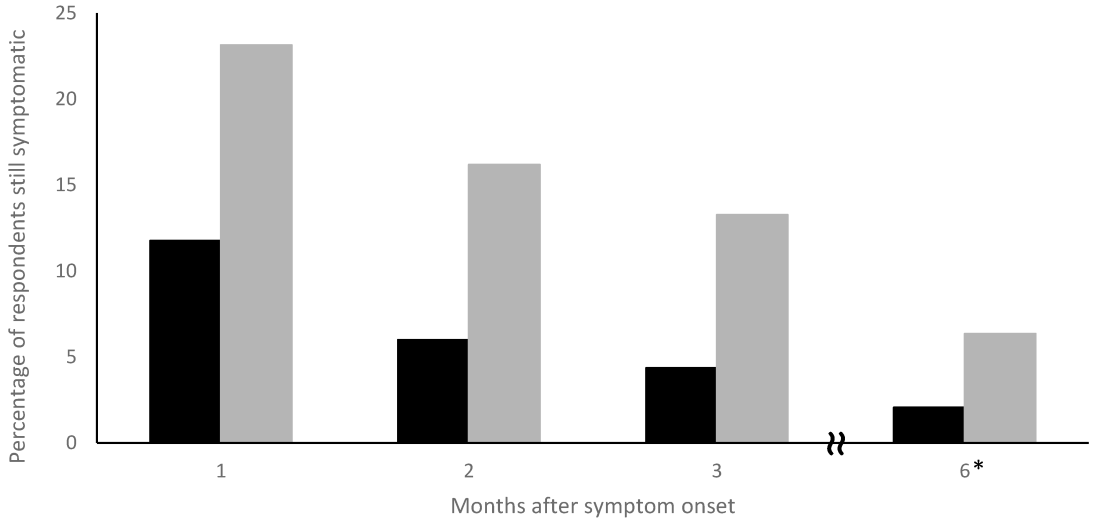
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Supplementary Figure S1. Study population flowchart



Supplementary Figure S2. Persistence of symptoms over time

Plot showing persistence of symptoms as a percentage of respondents who were symptomatic at time of infection and for whom we had 3 months follow-up and complete data, N=10,059 (*at least 6 months follow up data, N=463). Presented separately for participants aged 5-11 years (black) and 12-17 years (grey).



Supplementary Figure S3. Prevalence of symptoms persisting for 11 days or more in 123,468 PCR negative children aged 5-17 years in REACT-1.

Participants were asked about 26 separate symptoms lasting 11 days or more that were present within the 7 days of completing the questionnaire. The list of symptoms for this question was fewer than the list of 30 symptoms used for the question regarding persistent symptoms post COVID-19. Data collected between March 2021 and March 2022 (rounds 10-19). Error bars indicate 95% binomial confidence intervals of the prevalence. Average weighted prevalence of 11+ days persistent symptoms was 2.2% (95% CI 2.1–2.3) and 2.6% (95% CI 2.5–2.7) for children aged 5-11 and 12-17 years, respectively across rounds 10-19 of REACT-1.

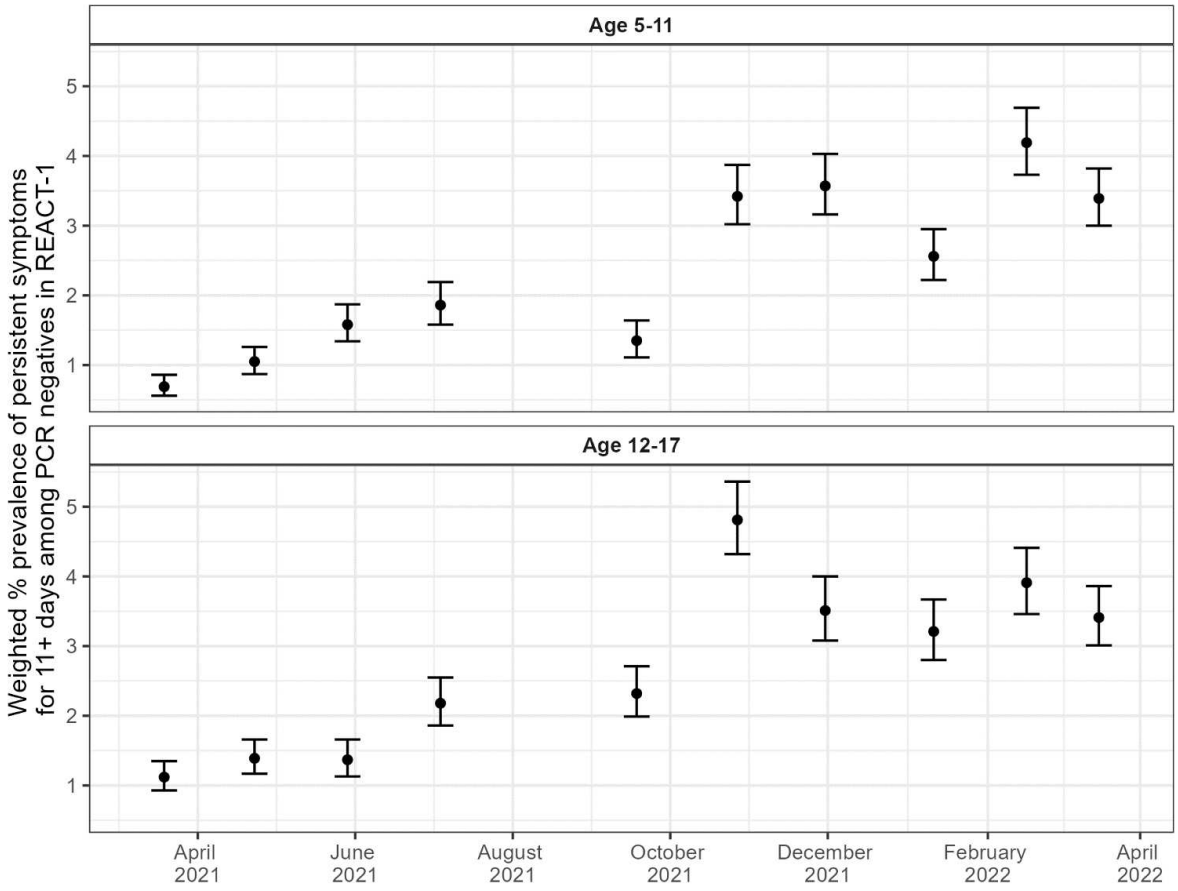


Table S1: Key characteristics of the REACT-1 study population aged 5-17 years for rounds 10-19. Numbers are reported for the full sample and by history of COVID-19 status, N=191,593

	Category	**Overall N (%; 95% CI)[a]**	**Response to history of COVID-19 N (%; 95% CI)[a]**	**Missing response to history of COVID-19 N (%; 95% CI)[a]**	**p-value [b]**
	All participants	191,593	111,444 (58.2; 57.9-58.4)	80,149 (41.8; 41.6-42.1)	
Sex	Male	91,788 (47.9; 47.7-48.1)	52,190 (46.8; 46.5-47.1)	39,598 (49.4; 49.1-49.8)	<0.001
	Female	99,805 (52.1; 51.9-52.3)	59,254 (53.2; 52.9-53.5)	40,551 (50.6; 50.2-50.9)	
Age	5-11	87,915 (45.9; 45.7-46.1)	50,438 (45.3; 45.0-45.6)	37,477 (46.8; 46.4-47.1)	<0.001
	12-17	103,678 (54.1; 53.9-54.3)	61,006 (54.7; 54.4-55.0)	42,672 (53.2; 52.9-53.6)	
Ethnicity	White	146,882 (78.4; 78.2-78.6)	88,090 (80.5; 80.3-80.7)	58,792 (75.5; 75.2-75.8)	<0.001
	Mixed	10,760 (5.7; 5.6-5.9)	6,387 (5.8; 5.7-6.0)	4,373 (5.6; 5.5-5.8)	
	Asian / Asian British	19,595 (10.5; 10.3-10.6)	10,004 (9.1; 9.0-9.3)	9,591 (12.3; 12.1-12.5)	
	Black / African / Caribbean / Black British	7,085 (3.8; 3.7-3.9)	3,435 (3.1; 3.0-3.2)	3,650 (4.7; 4.5-4.8)	
	Other	2,980 (1.6; 1.5-1.7)	1,503 (1.4; 1.3-1.4)	1,477 (1.90 1.4-1.5)	
IMD quintile	1 – most deprived	28,810 (15.0; 14.9-15.2)	14,098 (12.7; 12.5-12.8)	14,712 (18.4; 18.1-18.6)	<0.001
	2	32,572 (17.0; 16.8-17.2)	17,624 (15.8; 15.6-16.0)	14,948 (18.7; 18.4-18.9)	
	3	37,837 (19.7; 19.6-19.9)	22,181 (19.9; 19.7-20.1)	15,656 (19.5; 19.3-19.8)	
	4	41,725 (21.8; 21.6-22.0)	25,443 (22.8; 22.6-23.1)	16,282 (20.3; 20.0-20.6)	
	5 – least deprived	50,649 (26.4; 26.2-26.6)	32,098 (28.8; 28.5-29.1)	18,551 (23.2; 22.9-23.4)	
Region	North East	7,510 (3.92; 3.83-4.01)	4,146 (3.72; 3.61-3.83)	3,364 (4.20; 4.06-4.34)	<0.001
	North West	21,715 (11.3; 11.2-11.5)	12,067 (10.8; 10.6-11.0)	9,648 (12.0; 11.8-12.3)	
	Yorkshire and The Humber	16,992 (8.87; 8.74-9.00)	9,760 (8.76; 8.59-8.93)	7,232 (9.02; 8.83-9.22)	
	East Midlands	18,415 (9.61; 9.48-9.74)	10,685 (9.59; 9.42-9.76)	7,730 (9.64; 9.44-9.85)	
	West Midlands	19,746 (10.3; 10.2-10.4)	11,023 (9.89; 9.72-10.1)	8,723 (10.9; 10.7-11.1)	
	East of England	23,169 (12.1; 11.9-12.2)	13,841 (12.4; 12.2-12.6)	9,328 (11.6; 11.4-11.9)	

	London	29,765 (15.5; 15.4-15.7)	17,004 (15.3; 15.0-15.5)	12,761 (15.9; 15.7-16.2)	
	South East	35,683 (18.6; 18.5-18.8)	21,595 (19.4; 19.1-19.6)	14,088 (17.6; 17.3-17.8)	
	South West	18,598 (9.71; 9.58-9.84)	11,323 (10.2; 9.98-10.3)	7,275 (9.08; 8.88-9.28)	
Round	10	25,049 (13.1; 12.9-13.2)	15,955 (14.3; 14.1-14.5)	9,094 (11.4; 11.1-11.6)	<0.001
	11	21,625 (11.3; 11.1-11.4)	13,269 (11.9; 11.7-12.1)	8,356 (10.4; 10.2-10.6)	
	12	21,795 (11.4; 11.2-11.5)	11,432 (10.3; 10.1-10.4)	10,363 (12.9; 12.7-13.2)	
	13	19,773 (10.3; 10.2-10.5)	10,542 (9.46; 9.29-9.63)	9,231 (11.5; 11.3-11.7)	
	14	18,393 (9.60; 9.47-9.73)	10,050 (9.02; 8.85-9.19)	8,343 (10.4; 10.2-10.6)	
	15	17,496 (9.13; 9.00-9.26)	10,175 (9.13; 8.96-9.30)	7,321 (9.13; 8.94-9.34)	
	16	15,391 (8.03; 7.91-8.16)	8,805 (7.90; 7.74-8.06)	6,586 (8.22; 8.03-8.41)	
	17	16,260 (8.49; 8.36-8.61)	9,838 (8.83; 8.66-9.00)	6,422 (8.01; 7.83-8.20)	
	18	16,716 (8.72; 8.60-8.85)	9,703 (8.71; 8.54-8.87)	7,013 (8.75; 8.56-8.95)	
	19	19,095 (9.97; 9.83-10.1)	11,675 (10.5; 10.3-10.7)	7,420 (9.26; 9.06-9.46)	

[a] Percentages are calculated from non-missing values; [b] P-value calculated using Pearson's chi-squared test

Table S2: Odds ratios for persistent symptoms at 3 months among symptomatic respondents, derived from logistic regression models used in the main analysis, N=10,059 (forest plot in Figure 2).

	Participants aged 5-11 years		Participants aged 12-17 years	
Predictor	**Crude (univariate) Odds Ratio (95% CIs)**	**[a]Adjusted Odds Ratio (95% CIs)**	**Crude (univariate) Odds Ratio (95% CIs)**	**[b]Adjusted Odds Ratio (95% CIs)**
Sex				
Male	-	-	-	-
Female	1.12 (0.80-1.58)	1.16 (0.82-1.64)	2.61 (2.22-3.06) ***	2.40 (2.03-2.82)***
Ethnicity				
White	-	-	-	-
Mixed	0.71 (0.36-1.42)	0.69 (0.34-1.38)	0.81 (0.58-1.13)	0.82 (0.58-1.15)
Asian / Asian British	0.32 (0.10-1.03)	0.35 (0.11-1.12)	0.67 (0.50-0.90)**	0.65 (0.48-0.88)**
Black / African / Caribbean / Black British	0.51 (0.07-3.71)	0.56 (0.08-4.16)	0.78 (0.45-1.37)	0.67 (0.37-1.18)
Other	0.59 (0.08-4.38)	0.63 (0.08-4.70)	1.54 (0.89-2.68)	1.26 (0.71-2.23)
IMD quintile				
1 – most deprived	-	-	-	-
2	1.66 (0.79-3.48)	1.70 (0.80-3.61)	0.97 (0.76-1.24)	0.96 (0.75-1.24)
3	1.21 (0.58-2.56)	1.17 (0.55-2.49)	0.75 (0.59-0.95)*	0.78 (0.61-0.99)*
4	1.44 (0.70-2.95)	1.39 (0.67-2.89)	0.72 (0.57-0.91)**	0.71 (0.55-0.91)**
5 – least deprived	1.38 (0.68-2.78)	1.34 (0.66-2.73)	0.76 (0.61-0.95)*	0.78 (0.62-0.98)*
Comorbidities				
No	-	-	-	-
Yes	2.59 (1.77-3.78)***	2.64 (1.80-3.90)***	2.17 (1.88-2.51)***	1.96 (1.68-2.27)***
Vaccination status at time of infection				
No	-	-	-	-
At least one dose	-	-	0.92 (0.66-1.28)	0.74 (0.52-1.04)
Dominant variant at time of infection				
Wild type (before Dec 2020)	-		-	-
Alpha (Dec 2020-April 2021)	0.85 (0.49-1.47)	0.92 (0.53-1.62)	1.18 (0.95-1.46)	1.16 (0.93-1.45)
Delta (May 2021-Dec 2021)	1.31 (0.91-1.89)	1.35 (0.93-1.97)	1.43 (1.23-1.67)***	1.56 (1.33-1.84)***

[a]Mutually adjusted for sex, ethnicity, IMD, comorbidities and dominant variant at time of infection; [b]Mutually adjusted for sex, ethnicity, IMD, comorbidities and vaccination status and dominant variant at time of infection; *p<0.05, *p<0.01*; ***p<0.001

Sensitivity analysis was performed restricting the outcome to test confirmed COVID-19.

In sensitivity analysis, restricting to children and young people who reported having had COVID-19 confirmed by a test, the magnitude and direction of associations between sociodemographic factors and persistent symptoms were similar (Supplementary Table S6).

Table S3. Number and proportion of individual symptoms among participants with persistent symptoms at 3 months or more post COVID-19 onset for whom we have 3 months follow-up and complete data.

	Age 5-11	**Age 12-17**
Symptom	n (%; 95% CI)	n (%; 95% CI)
Cohort with persistent symptoms at 3 months post COVID-19 onset / Cohort who experienced ≥1 symptom at time of infection, and who reported symptom onset date ≥3 months (≥91 days) before their survey date	138/3,173 (4.4%; 3.7-5.1)	913/6,886 (13.3%; 12.5-14.1)
Loss or change of sense of smell	19 (13.9; 9.0-20.8)	470 (52.2; 48.9-55.5)
Loss or change of sense of taste	21 (15.4; 10.3-22.6)	366 (40.7; 37.5-44.0)
Fever	4 (3.0; 1.1-7.7)	9 (1.0; 0.52-1.9)
Coughing	37 (27.4; 20.5-35.6)	57 (6.4; 4.9-8.1)
Runny or blocked nose	9 (6.7; 3.5-12.4)	49 (5.5; 4.2-7.2)
Sneezing	10 (7.3; 4.0-13.1)	23 (2.6; 1.7-3.8)
Itchy, sore or red eyes, conjunctivitis	7 (5.1; 2.4-10.4)	17 (1.9; 1.2-3.0)
Vision issues	1 (0.74; 0.10-5.1)	21 (2.3; 1.5-3.5)
Sore throat or hoarse voice	11 (8.0; 4.5-14.0)	28 (3.1; 2.2-4.5)
Hearing issues (e.g. hearing loss, Tinnitus etc)	4 (2.9; 1.1-7.5)	17 (1.9; 1.2-3.0)
Skin issues (itchy, scaly, redness, etc)	11 (8.0; 4.5-13.9)	33 (3.7; 2.6-5.1)
Sudden swelling of the face or lips	0 (0.0; 0.0-0.03)	0 (0.0, 0.0-0.01)
Leg swelling (Thrombosis)	0 (0.0; 0.0-0.03)	1 (0.11; 0.02-0.78)
Red/purple sores or blisters on your feet (including toes)	5 (3.6; 1.5-8.4)	20 (2.2; 1.4-3.4)
Hair loss	5 (3.6; 1.5-8.4)	34 (3.7; 2.7-5.2)
Appetite loss	15 (11.0; 6.7-17.5)	105 (11.8; 9.8-14.0)
Weight loss	7 (5.2; 2.5-10.4)	32 (3.5; 2.5-5.0)
Abdominal issues (stomach ache, diarrhoea, nausea, vomiting)	29 (21.8; 15.6-30.0)	77 (8.6; 6.9-10.6)
Dizziness, vertigo	8 (5.8; 2.9-11.3)	84 (9.4; 7.6-11.5)
Confusion “brain fog”, forgetfulness	16 (11.6; 7.2-18.1)	92 (10.5; 8.6-12.7)
Headaches	33 (25.4; 18.6-33.6)	139 (16.3; 13.9-18.9)
Shortness of breath, breathlessness, wheezing	23 (16.7; 11.3-23.9)	149 (16.7; 14.4-19.3)
Tightness or heaviness in chest, chest pain	14 (10.2; 6.1-16.6)	106 (11.8; 9.9-14.1)
Heart issues (racing heart, palpitations, irregular heartbeat etc)	8 (5.8; 2.9-11.3)	63 (7.0; 5.5-8.8)

Difficulty sleeping	23 (16.7; 11.3-23.9)	127 (14.2; 12.0-16.6)
Mild fatigue (e.g. feeling tired)	34 (24.8; 18.3-32.8)	199 (22.1; 19.5-25.0)
Severe fatigue (e.g. inability to get out of bed)	5 (3.6; 1.5-8.4)	59 (6.6; 5.1-8.4)
Numbness or tingling somewhere in the body	1 (0.73; 0.10-5.0)	20 (2.2; 1.4-3.4)
Achy or cramping muscles, pain in muscles	21 (15.6; 10.3-22.7)	73 (8.1; 6.5-10.1)
Pain in joints	18 (13.1; 8.4-19.9)	61 (6.8; 5.3-8.6)

Table S4. Sociodemographic proportions of the REACT-1 study population aged 5-17 years for rounds 10-19 and participants included in our study compared to England population aged 5-17 years.

	England (5-17 population)[1, 2]	REACT-1 population (5-17)	Study population (5-17)
	N=8,853,841	N=191,593	N=111,444
	%	%	%
Sex			
Male	51.3	47.9	46.8
Female	48.7	52.1	53.2
Age			
5-11	55.7	45.9	45.3
12-17	44.3	54.1	54.7
Ethnicity			
White	79.2	78.4	80.5
Mixed	4.6	5.7	5.8
Asian	10.2	10.5	9.1
Black	4.6	3.8	3.1
Other	1.3	1.6	1.4
Region			
North East	4.5	3.9	3.7
North West	13.0	11.3	10.8
Yorkshire and The Humber	9.8	8.9	8.8
East Midlands	8.4	9.6	9.6
West Midlands	10.8	10.3	9.9
East of England	11.2	12.1	12.4
London	16.4	15.5	15.3
South East	16.6	18.6	19.4
South West	9.4	9.7	10.2
IMD Quintile			
1 – most deprived	19.8	15.0	12.7
2	20.9	17.0	15.8
3	20.4	19.7	19.9
4	19.7	21.8	22.8
5 – least deprived	19.1	26.4	28.8

1 Office_for_National_Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid2019 2020 [Available from: https://www.ons.gov.uk/releases/populationestimatesfortheukenglandandwalesscotlandandnorthernirelandmid2019(

2 Office_for_National_Statistics. Employee earnings in the UK: 2019 2019 [Available from: https://www.ons.gov.uk/releases/employeeearningsintheuk2019.

Table S5. Number and proportion of individual symptoms among participants with persistent symptoms at 3 months or more post COVID-19 onset for whom we have 3 months follow-up and complete data, test confirmed vs. suspected COVID-19 cases.

	Age 5-11		**Age 12-17**	
Symptom	n (%; 95% CI)		n (%; 95% CI)	
	Test confirmed COVID-19	Suspected COVID-19	Test confirmed COVID-19	Suspected COVID-19
Cohort with persistent symptoms at 3 months post COVID-19 onset / Cohort who experienced ≥1 symptom at time of infection, and who reported symptom onset date ≥3 months (≥91 days) before their survey date	71/1,382 (5.1%; 4.1-6.4)	67/1,791 (3.7%; 3.0-4.7)	692/4,313 (16.0%; 15.0-17.2)	221/2,573 (8.6%; 7.6-9.7)
Loss or change of sense of smell	15 (21.4; 13.3-32.7)	4 (6.0; 2.2-15.0)	400 (58.7; 54.9-62.3)	70 (32.1; 26.2-38.6)
Loss or change of sense of taste	17 (24.3; 15.6-35.7)	4 (6.0; 2.2-15.0)	306 (45.0; 41.3-48.8)	60 (27.4; 21.9-33.7)
Fever	2 (2.9; 0.72-11.0)	2 (3.0; 0.75-11.4)	6 (0.87; 0.39-1.9)	3 (1.4; 0.45-4.3)
Coughing	15 (21.4; 13.3-32.7)	22 (33.8; 23.4-46.2)	36 (5.3; 3.8-7.2)	21 (9.6; 6.4-14.3)
Runny or blocked nose	6 (8.6; 3.9-17.9)	3 (4.5; 1.4-13.1)	40 (5.9; 4.4-8.0)	9 (4.2; 2.2-8.0)
Sneezing	6 (8.6; 3.9-17.9)	4 (6.0; 2.2-15.0)	19 (2.8; 1.8-4.3)	4 (1.8; 0.68-4.7)
Itchy, sore or red eyes, conjunctivitis	5 (7.1; 3.0-16.1)	2 (3.0; 0.75-11.4)	11 (1.6; 0.89-2.9)	6 (2.8; 1.2-6.0)
Vision issues	1 (1.4; 0.20-9.6)	0 (0.0; 0.0-0.61)	12 (1.7; 0.99-3.0)	9 (4.1; 2.1-7.7)
Sore throat or hoarse voice	8 (11.4; 5.8-21.3)	3 (4.5; 1.4-13.1)	17 (2.5; 1.6-4.0)	11 (5.0; 2.8-8.9)
Hearing issues (e.g. hearing loss, Tinnitus etc)	1 (1.4; 0.20-9.6)	3 (4.5; 1.4-13.1)	13 (1.9; 1.1-3.2)	4 (1.8; 0.68-4.7)
Skin issues (itchy, scaly, redness, etc)	4 (5.6; 2.1-14.2)	7 (10.4; 5.0-20.4)	20 (2.9; 1.9-4.5)	13 (6.0; 3.5-10.1)
Sudden swelling of the face or lips	0 (0.0; 0.0-0.57)	0 (0.0; 0.0-0.61)	0 (0.0, 0.0-0.11)	0 (0.0, 0.0-0.31)
Leg swelling (Thrombosis)	0 (0.0; 0.0-0.57)	0 (0.0; 0.0-0.61)	0 (0.0, 0.0-0.11)	1 (0.45; 0.06-3.2)
Red/purple sores or blisters on your feet (including toes)	1 (1.4; 0.20-9.6)	4 (6.0; 2.2-15.0)	3 (0.43; 0.14-1.3)	17 (7.7; 4.8-12.0)
Hair loss	3 (4.2; 1.4-12.4)	2 (3.0; 0.75-11.4)	24 (3.5; 2.3-5.2)	10 (4.5; 2.5-8.3)
Appetite loss	8 (11.4; 5.8-21.3)	7 (10.4; 5.0-20.4)	83 (12.2; 9.9-14.8)	22 (10.4; 7.0-15.3)
Weight loss	2 (2.9; 0.72-11.0)	5 (7.5; 3.1-16.8)	23 (3.4; 2.2-5.0)	9 (4.1; 2.1-7.7)
Abdominal issues (stomach ache, diarrhoea, nausea, vomiting)	14 (20.3; 12.3-31.5)	15 (23.4; 14.6-35.4)	46 (6.7; 5.1-8.9)	31 (14.6; 10.4-20.1)
Dizziness, vertigo	4 (5.6; 2.1-14.2)	4 (6.0; 2.2-15.0)	54 (7.9; 6.1-10.2)	30 (14.2; 10.1-19.5)
Confusion “brain fog”, forgetfulness	10 (14.1; 7.7-24.3)	6 (9.0; 4.1-18.6)	71 (10.6; 8.5-13.2)	21 (9.6; 6.4-14.3)
Headaches	19 (29.7; 19.7-42.0)	14 (20.9; 12.7-32.4)	102 (15.6; 13.0-18.6)	37 (18.5; 13.7-24.5)
Shortness of breath, breathlessness, wheezing	10 (14.1; 7.7-24.3)	13 (19.4; 11.6-30.7)	104 (15.4; 12.8-18.3)	45 (20.7; 15.8-26.7)
Tightness or heaviness in chest, chest pain	3 (4.2; 1.4-12.4)	11 (16.7; 9.4-27.8)	74 (10.8; 8.7-13.4)	32 (15.0; 10.8-20.5)
Heart issues (racing heart, palpitations, irregular heartbeat etc)	3 (4.2; 1.4-12.4)	5 (7.5; 3.1-16.8)	42 (6.1; 4.5-8.1)	21 (9.6; 6.4-14.3)
Difficulty sleeping	13 (18.3; 10.9-29.1)	10 (14.9; 8.2-25.7)	85 (12.5; 10.2-15.2)	42 (19.3; 14.6-25.1)
Mild fatigue (e.g. feeling tired)	20 (28.6; 19.2-40.3)	14 (20.9; 12.7-32.4)	151 (22.1; 19.2-25.4)	48 (22.1; 17.1-28.1)
Severe fatigue (e.g. inability to get out of bed)	3 (4.2; 1.4-12.4)	2 (3.0; 0.75-11.4)	42 (6.1; 4.5-8.1)	17 (7.7; 4.8-12.0)

Numbness or tingling somewhere in the body	0 (0.0; 0.0-0.57)	1 (1.5; 0.21-10.0)	13 (1.9; 1.1-3.2)	7 (3.2; 1.5-6.6)
Achy or cramping muscles, pain in muscles	10 (14.1; 7.7-24.3)	11 (16.7; 9.4-27.8)	52 (7.6; 5.8-9.9)	21 (9.6; 6.4-14.3)
Pain in joints	8 (11.4; 5.8-21.3)	10 (14.9; 8.2-25.7)	42 (6.1; 4.5-8.1)	19 (8.9; 5.7-13.5)

Table S6: Odds ratios for persistent symptoms at 3 months among symptomatic respondents, derived from logistic regression models used in sensitivity analysis, test confirmed COVID-19 cases only (N=5,695)

	Participants aged 5-11 years		Participants aged 12-17 years	
Predictor	**Crude (univariate) Odds Ratio (95% CIs)**	**[a]Adjusted Odds Ratio (95% CIs)**	**Crude (univariate) Odds Ratio (95% CIs)**	**[b]Adjusted Odds Ratio (95% CIs)**
Sex				
Male	-	-	-	-
Female	0.97 (0.60-1.57)	0.98 (0.60-1.61)	2.85 (2.35-3.45) ***	2.63 (2.17-3.20)***
Ethnicity				
White	-	-	-	-
Mixed	0.72 (0.26-2.04)	0.71 (0.25-2.01)	0.87 (0.60-1.27)	0.86 (0.58-1.27)
Asian / Asian British	0.33 (0.08-1.36)	0.36 (0.09-1.53)	0.64 (0.46-0.89)**	0.64 (0.46-0.91)*
Black / African / Caribbean / Black British	1.00 (0.13-7.65)	1.13 (0.14-8.83)	0.97 (0.50-1.86)	0.89 (0.45-1.74)
Other	1.42 (0.18-11.09)	1.29 (0.15-10.73)	1.67 (0.89-3.15)	1.36 (0.70-2.64)
IMD quintile				
1 – most deprived	-	-	-	-
2	1.56 (0.62-3.97)	1.56 (0.60-4.11)	1.00 (0.75-1.33)	1.03 (0.76-1.39)
3	0.85 (0.32-2.27)	0.92 (0.34-2.52)	0.82 (0.62-1.09)	0.86 (0.64-1.15)
4	0.86 (0.34-2.20)	0.88 (0.34-2.31)	0.81 (0.61-1.06)	0.84 (0.63-1.12)
5 – least deprived	1.51 (0.64-3.54)	1.58 (0.65-3.82)	0.87 (0.67-1.13)	0.93 (0.71-1.23)
Comorbidities				
No	-	-	-	-
Yes	2.35 (1.36-4.07)**	2.26 (1.28-4.00)**	2.36 (1.98-2.80)***	2.09 (1.75-2.49)***
Vaccination status at time of infection				
No	-	-	-	-
At least one dose	-	-	0.73 (0.52-1.03)	0.72 (0.50-1.03)
Dominant variant at time of infection				
Wild type (before Dec 2020)	-		-	-
Alpha (Dec 2020-April 2021)	0.78 (0.34-1.77)	0.75 (0.32-1.74)	0.64 (0.48-0.85)**	0.63 (0.47-0.84)**
Delta (May 2021-Dec 2021)	0.91 (0.46-1.78)	0.82 (0.41-1.66)	0.70 (0.56-0.87)**	0.75 (0.60-0.95)*

[a]Mutually adjusted for sex, ethnicity, IMD, comorbidities and dominant variant at time of infection; [b]Mutually adjusted for sex, ethnicity, IMD, comorbidities and vaccination status and dominant variant at time of infection; *p<0.05, *p<0.01*; ***p<0.001