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Persistent symptoms after SARS-CoV-2 infection in children: a cross-sectional population-based serological study

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ABSTRACT

Objectives To estimate the prevalence of children and adolescents reporting persistent symptoms after SARS-CoV-2 infection.

Design A random sample of children and adolescents participated with their family members to a serological survey including a blood drawing for detecting antibodies targeting the SARS-CoV-2 nucleocapsid (N) protein and a questionnaire on COVID-19-related symptoms experienced since the beginning of the pandemic.

Setting The study took place in the canton of Geneva, Switzerland, between June and July 2021.

Participant 660 children aged between 2 and 17 years old.

Primary and secondary outcome The primary outcome was the persistence of symptoms beyond 4 weeks comparing seropositive and seronegative participants. The type of declared symptoms were also studied as well as associated risk factors.

Results Among seropositive children, the sex-adjusted and age-adjusted prevalence of symptoms lasting longer than 2 weeks was 18.3%, compared with 11.1% among seronegatives (adjusted prevalence difference (ΔaPrev)=7.2%, 95% CI: 1.5% to 13.0%). Among adolescents aged 12–17 years, we estimated the prevalence of experiencing symptoms lasting over 4 weeks to be 4.4% (ΔaPrev,95% CI: −3.8% to 13.6%), whereas no seropositive child aged 2–11 reported symptoms of this duration. The most frequently declared symptoms were fatigue, headache and loss of smell.

Conclusions We estimated the prevalence of experiencing persistent symptoms lasting over 4 weeks to be around 4% among adolescents, which represents a large absolute number, and should raise awareness and concern. We did not observe meaningful differences of persistent symptoms between seropositive and seronegative younger children, suggesting that they may be less affected than their older counterparts.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a randomly selected population-based sample of children and includes a seronegative control group.
⇒ Relying on serological tests rather than only on confirmed infections allows to have an accurate denominator for SARS-CoV-2 infections.
⇒ The study covers a large age range (6 months to 17 years) making it possible to identify age-related differences.
⇒ Serological data does not allow to clearly identify the date of infection.
⇒ The study was conducted in June–July 2021 with a design based on persistent symptoms lasting over 4 weeks, a shorter duration than the current official definition of post-COVID-19 syndrome.

INTRODUCTION

Clinically, signs and symptoms of COVID-19 lasting up to 4 weeks are defined as acute COVID-19, those lasting from 4 to 12 weeks are known as ongoing symptomatic COVID-19 (ie, ongoing COVID-19).[1] Finally, long COVID-19 or post-COVID-19 syndrome refers to experiencing long-lasting symptoms weeks to months following a SARS-CoV-2 infection.[2] It is defined by the WHO in adults as symptoms that usually appear within 3 months from the onset of COVID-19, that last for at least 2 months and cannot be explained by an alternative diagnosis in individuals with a history of probable or confirmed SARS CoV-2 infection.[3] Evidence to date indicates that 10%–30% of adults who had mild-to-severe COVID-19 experience persistent symptoms several months after infection.[4–7] Risk factors include female sex, middle age, comorbidities and the number of symptoms in the acute phase.[8] However, young and previously healthy persons are also frequently affected.[9] As such, ongoing and post-COVID-19 represent an increasing public health concern, potentially preventing affected individuals from going about their personal and professional activities, altering their quality of life and continuing to burden

the healthcare system. If substantial evidence is starting to emerge around ongoing and post-COVID-19 in adults, paediatric ongoing and post-COVID-19 has received much less attention.[2 10] A generalised definition of paediatric post-COVID-19 was recently published (February 2022) and defined as young people with a history of confirmed SARS CoV-2, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis.[11]

The pandemic has profoundly impacted directly or indirectly the lives of children and adolescents worldwide in terms of daily life and habits, mental and physical health, social behaviours and schooling.[12] Although they appear to be less susceptible to severe forms of COVID-19 compared with adults,[13] recent evidence suggests that an undetermined proportion of infected children may also experience persistent symptoms post infection, ongoing and post-COVID-19. Studies from Australia,[14] Italy,[15] England and Wales[16 17] and Switzerland[18] have reported prevalence estimates of persistent symptoms lasting more than 4 weeks ranging from 4.6%–24.0%. The most frequently reported symptoms are fatigue, insomnia, respiratory symptoms (including chest pain and tightness), nasal congestion, muscle and joint pain and difficulty concentrating, which have been reported to last from 4 weeks to 4 months.[15–17 19 20] These studies differed considerably in their methodological approaches, assessments of previous infection, sample sizes and follow-up periods, so that the actual prevalence of long-lasting symptoms among children and adolescents is still debated. Importantly, most studies were based on clinical samples of confirmed cases, while only one study[19] included data from a population-based serosurvey. If clinical samples of confirmed cases are very useful in estimating the risk of experiencing persistent symptoms once the infection is confirmed via a test, in the paediatric population where testing was generally very limited, these data do now allow to estimate the overall population prevalence of ongoing and post-COVID-19. On the contrary, population-based serological studies have the advantage of including, by definition, a representative sample of the population giving a more accurate estimation of the number of children infected (denominator). The difference between seropositive and seronegative allows the distinction of persistent symptoms due to COVID-19 from symptoms due to other viruses or to the overall pandemic context. Understanding the frequency and duration of persistent symptoms following SARS-CoV-2 infection in children using data from population-based samples is essential to guide public health strategies targeting this age group (eg, preventive measures in schools or vaccination programmes). In this study, we use a representative sample of the general population of the canton of Geneva, Switzerland, to determine the proportion of children and adolescents reporting persistent symptoms after SARS-CoV-2 infection, and comparing seropositive children and adolescents with their seronegative counterparts. We also aim to identify risk factors for experiencing persistent symptoms.

METHODS

Study population

Participants from a random sample of the general population of the state of Geneva, Switzerland, were invited to take part in a serological survey between 1 June and 7 July 2021.[21] Lists of residents were provided by the Swiss Federal Office of Statistics within the framework of the Corona Immunitas Research project.[22] As per the study protocol, randomly selected children and adolescents aged between 6 months and 17 years were invited to participate with their family members. Overall, 22.3% of the invited families participated (online supplemental figure S1). After providing written informed consent, participants provided a venous blood sample. In each family, one of the parents completed a sociodemographic online questionnaire about themselves, the household and their child(ren). For children from 2 years old, an age range considered as potentially impacted by persistent symptoms post SARS-CoV-2 infection at the time, the questionnaire included questions on COVID-19 persistent symptoms. Parent were not aware of their child(ren) serological status while answering the questionnaire.

Measures

Parents were asked if their child(ren) had experienced symptoms lasting at least 2 weeks and for each declared symptom, details on the duration (2–3 weeks, 3–4 weeks or more than 4 weeks) were collected. Parents could choose from an exhaustive list of 37 symptoms based on the literature at the time, grouped into six general categories of symptoms: fatigue, respiratory, gastrointestinal, musculoskeletal, neurological and dermatological symptoms (online supplemental table S1). Data on the impact on the child's daily activities were also collected. The impact/limitation of each selected symptom was based on the following question: 'On a scale of 1–10, to what extent is this symptom limiting the child's usual activities (attendance at school, nursery, studies, sports, games, etc)? (1 very weak limitation to 10 strong limitation)'. We subsequently created a dichotomous variable where symptoms rated six or higher were considered as having a strong limitation on the child's daily life.

Serological tests were based on commercially available immunoassays Roche Elecsys anti-SARS-CoV-2 N immunoassay, which detects immunoglobulins (IgG/A/M) targeting the virus nucleocapsid (N) protein (#09203079190, Roche-N) and has an in-house sensitivity of 99.8% (95% CI, 99.4% to 100%) and specificity of 99.1% (95% CI, 98.3% to 99.7%) (Roche Diagnostics, Rotkreuz, Switzerland). Seropositivity was defined using the manufacturer's provided cut-off index of ≥1.0.[23] The Roche N serological test identifies anti-N antibodies, which are not produced following vaccination with mRNA vaccines used in Geneva to date, such as the

Pfizer-BioNTech BNT162b2 and Moderna mRNA 1273 vaccines, and are therefore only detected if the individual was infected with SARS-CoV-2. Using this test allowed us to remove the effect of vaccination.

Parental education was categorised as primary for compulsory schooling, secondary for apprenticeship and high school and tertiary for university. Household financial status was defined as average to poor if participants chose one of the following statements about their financial situation: 'I have to be careful with my expenses and an unexpected event could put me into financial difficulty' or 'I cannot cover my needs with my income and I need external support'.

Patient and public involvement

Decision-makers, clinicians and scientists were involved in the study design. Results will be communicated to the community with reports, online interactive conferences and online posts available on the cohort online research page (https://www.specchio-covid19.ch/recherches). Participants were neither involved in the study design nor planning. However, the questionnaire used in this study included open comment fields in which participants could describe their child(ren) experiences related to the pandemic or to the study. Our group dedicated a specific email address and a hotline to help participants getting in touch with the team. Participants also receive personal answers in case of technical difficulties or any questions about the study or their serological results.

Statistical analysis

We compared the distribution of sociodemographic and COVID-19-related characteristics between children who tested positive for anti-SARS-CoV-2 antibodies and children who tested negative, overall and stratified into three age groups (2–5, 6–11 and 12–17). Participants with missing data were excluded. To estimate prevalence (95% CIs) and prevalence differences, we used marginal prediction after logistic regression, adjusting for age and sex. To calculate prevalence ratios (95% CI), we used Poisson regression with robust variance, based on the sandwich estimator.[24] To account for the fact that many children were siblings, we conducted additional analyses on the prevalence ratio estimation using mixed-effect Poisson regression with robust variance.[25] Statistical significance was defined at a level of confidence of 95% and all analyses were performed with R (V.4.0.3).

RESULTS

Our sample comprised 660 children aged 2–17 years (49.4% girls, mean age 9.3 years (SD=4.5)) from 391 households (table 1). A majority of parents (58.6%) had a tertiary education level, 7.6% had a primary education level and 22.1% reported having an average to poor financial situation. A proportion of 31.3% of children and adolescents were seropositive for anti-SARS-CoV-2 antibodies.

Overall, 13.5% of children (adjusted prevalence (aPrev)=13.3%, 95% CI: 10.4 to 16.2) were reported by their parent as having experienced at least one symptom that lasted more than 2 weeks since the beginning of the pandemic. Specifically, 18.3% (95% CI: 13.0% to 23.6%) of seropositive children had symptoms lasting more than 2 weeks versus 11.1% (95% CI: 8.2% to 14.0%), among seronegative children, with an adjusted prevalence difference (ΔPrev) of 7.2% (95% CI: 1.5% to 13.0%) (table 1). Among seropositive participants, 14.8% (95% CI: 9.9% to 19.7%) reported symptoms lasting 2–3 weeks, 1.0% (95% CI: 0.0% to 2.3%) 3–4 weeks and 2.4% (95% CI: 0.3% to 4.5%) more than 4 weeks. Among seronegative participants, the corresponding aPrev were 5.2% (95% CI 3.2% to 7.3%), 0.9% (95% CI: 0.0% to 1.8%) and 3.3% (95% CI: 1.7% to 5.0%). Moreover, for 8.6% (95% CI: 4.7% to 12.5%) of seropositive children, these persistent symptoms, all durations combined, were reported as highly limiting and resulting in a daily burden, compared with 2.9% (95% CI: 1.3% to 4.5%) among seronegatives.

The most frequently reported symptoms lasting over 2 weeks by seropositive participants were fatigue (11.6%), headache (11.1%), fever (6.2%), runny nose (6.2%), loss of smell (4.8%) and loss of taste (3.8%). Among seronegatives, the most frequently reported symptoms were fatigue (6.2%), runny nose (5.9%), cough (4.2%) and sore throat (3.1%) (online supplemental table S1 and online supplemental figure S2).

The age-adjusted and sex-adjusted prevalence of persistent symptoms varied across age groups (figure 1, online supplemental table S2) and differed by serological status. Among seropositive adolescents aged 12–17 years, 29.0% (95% CI: 19.4% to 38.7%) reported symptoms lasting over 2 weeks, while the age-adjusted and sex-adjusted prevalence was 8.9% (95% CI: 4.4% to 13.4%) among seronegative participants of the same age (age-adjusted and sex-adjusted Prevalence difference (ΔaPrev)=20.1%, 95% CI: 10.6% to 29.7%). Differences between seropositive and seronegative participants were not significant among children aged 6–11 years (ΔaPrev=−0.5%, 95% CI: −8.2% to 7.1%) and those aged 2–5 years (ΔaPrev=−0.8%, 95% CI: −13.4% to 11.6%).

Among seropositive adolescents aged 12–17 years, 5.5% (95% CI: 0.5% to 10.3%) reported experiencing symptoms lasting longer than 4 weeks, while the prevalence among seronegative was 1.1% (95% CI: 0.0% to 2.6%) with an ΔPrev in this age group of 4.4% (95% CI: −3.8% to 13.6%). No seropositive children aged 2–11 in our sample reported symptoms lasting over 4 weeks (figure 1) and prevalence differences were negative; −3.8% in 2–5 years and −4.4% in 6–11 years (online supplemental table S2).

The most frequently reported symptoms lasting over 4 weeks among seropositive adolescents were neurological symptoms (80%) (mostly headache, smell and taste loss), fatigue (60%) and respiratory symptoms (60%) (mostly cough, dripping nose and fever).

Table 1 Descriptive statistics of the study population, stratified by serological status

	All participants N=660	Seronegative N=453	Seropositive† N=207	Adjusted difference‡
Sex, N (%)				
Female	326 (49.4)	229 (50.6)	97 (46.9)	
Age (mean, SD)	9.3 (4.5)	8.9 (4.7)	10.2 (3.9)	–
Age group in years, N (%)				–
2–5	147 (22.3)	118 (26.1)	29 (14.0)	–
6–11	271 (41.1)	180 (39.7)	91 (44.0)	–
12–17	242 (36.6)	155 (34.2)	87 (42.0)	–
Parental education§, N (%)				
Tertiary	386 (58.6)	274 (60.6)	112 (54.1)	–
Secondary	223 (33.8)	145 (32.1)	78 (37.7)	–
Primary	50 (7.6)	33 (7.3)	17 (8.2)	–
Financial situation§, N (%)				
High	449 (68.1)	316 (69.8)	133 (64.3)	–
Average to poor	146 (22.1)	92 (20.3)	54 (26.1)	–
Declined to answer	65 (9.8)	45 (9.9)	20 (9.6)	–
Anti-SARS-CoV-2 testing (PCR/antigen)¶	216 (32.7)	80 (17.7)	136 (65.7)	
Hospitalisation due to COVID-19	0	0	0	
Symptoms>2 weeks				
N (%)	89 (13.5)	50 (11.0)	39 (18.8)	
aPrev (95% CI)§	13.3 (10.4 to 16.2)	11.1 (8.2 to 14.0)	18.3 (13.0 to 23.6)	7.2 (1.5 to 13.0)*
Reported symptoms				
Fatigue				
N (%)	52 (7.9)	28 (6.2)	24 (11.6)	
aPrevalence (95% CI)§	7.3 (5.1 to 9.5)	5.9 (3.7 to 8.1)	10.3 (6.1 to 14.4)	4.4 (0.2 to 9.0)*
Respiratory				
N (%)	59 (8.9)	35 (7.7)	24 (11.6)	
aPrev (95% CI)§	8.9 (6.4 to 11.3)	7.6 (5.1 to 10)	11.7 (7.3 to 16.1)	4.1 (0.0 to 9.2)
Gastrointestinal				
N (%)	41 (6.2)	22 (4.9)	19 (9.2)	
aPrev (95% CI)§	5.7 (3.8 to 7.6)	4.5 (2.6 to 6.4)	8.4 (4.6 to 12.2)	3.9 (0.3 to 8.1)
Musculoskeletal				
N (%)	19 (2.9)	7 (1.5)	12 (5.8)	
aPrev (95% CI)§	2.1 (1.2 to 3.1)	1.1 (0.2 to 2.1)	4.2 (1.4 to 7.1)	4.2 (1.4 to 7.0)*
Neurological				
N (%)	47 (7.1)	20 (4.4)	27 (13.0)	
aPrev (95% CI)§	6.1 (4.3 to 7.9)	3.8 (2.0 to 5.6)	11.0 (6.7 to 15.4)	7.2 (3.1 to 12.8)**
Dermatological				
N (%)	16 (2.4)	12 (2.6)	4 (1.9)	
aPrev (95% CI)§	2.3 (0.9 to 3.8)	2.5 (1.0 to 4.0)	1.9 (0.0 to 3.8)	–0.6 (–4.0 to 2.7)
Symptoms' duration				
2–3 weeks				
N (%)	56 (8.5)	24 (5.3)	32 (15.5)	
aPrev (95% CI)§	8.2 (6.2 to 10.3)	5.2 (3.2 to 7.3)	14.8 (9.9 to 19.7)	9.6 (4.2 to 15.1)**
3–4 weeks				

Continued

Table 1 Continued

	All participants N=660	Seronegative N=453	Seropositive† N=207	Adjusted difference‡
N (%)	8 (1.2)	5 (1.1)	3 (1.4)	
aPrev (95% CI)§	1.0 (0.1 to 1.9)	0.9 (0.0 to 1.8)	1.0 (0.0 to 2.3)	0.1 (–2.9 to 3.1)
More than 4 weeks				
N (%)	20 (3.0)	15 (3.3)	5 (2.4)	
aPrev (95% CI)§	3.0 (1.4 to 4.7)	3.3 (1.7 to 5.0)	2.4 (0.3 to 4.5)	–0.9 (–3.7 to 1.8)
Symptoms impact on daily life				
Low				
N (%)	71 (10.8)	41 (9.1)	30 (14.5)	
aPrev (95% CI)§	10.7 (8.0 to 13.3)	9.1 (6.4 to 11.7)	14.2 (9.5 to 19.0)	5.1 (–0.9 to 11.3)*
High				
N (%)	34 (5.2)	14 (3.1)	20 (9.7)	
aPrev (95% CI)§	4.7 (3.2 to 6.3)	2.9 (1.3 to 4.5)	8.6 (4.7 to 12.5)	5.7 (2.2 to 9.9)*

*P value<0.05.
†Seropositive is defined as naturally infected (Roche-N immunoassays cut-off index≥1.0).
‡Age-adjusted and sex-adjusted prevalence and prevalence differences, using marginal prediction of logistic regression and 95% CI were computed using normal approximation and truncated to 0 for the aPrev.
§Some of the children participating in the study are siblings therefore the reported parental and financial situation are presented individually.
¶The discrepancy between serological result and PCR+ might be related to test performances and errors while answering the questionnaire.
**P value<0.01.
aPrev, adjusted prevalence.

Overall, seropositive children and adolescents were 62% more likely than seronegatives to experience symptoms lasting more than 2 weeks (adjusted Prevalence Ratio (aPR)=1.62, 95% CI: 1.10 to 2.39) (table 2).

In subanalyses focusing only on seropositive children, we observed that seropositive children whose parents had a primary education level were almost three times more likely (aPR=2.97, 95% CI: 1.11 to 7.96) and those whose parents have a secondary education level two times as likely (aPR=2.10, 95% CI: 1.07 to 4.12) to experience symptoms lasting more than 2 weeks, compared with seropositive children whose parents had a tertiary education level. Similarly, parents from households with an average to poor financial status were two times as likely to declare long-lasting symptoms for their children than parents with high financial status (aPR=2.18, 95% CI 1.09 to 4.35) (table 3).

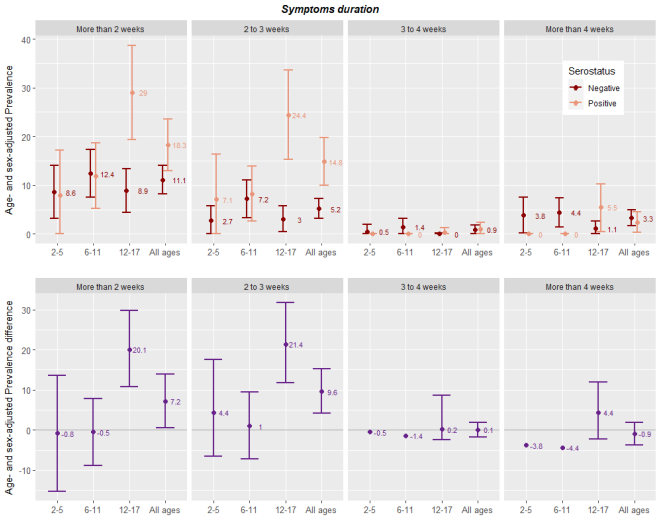

Figure 1 Age-adjusted and sex-adjusted prevalence and prevalence difference of persistent symptoms' duration, stratified by age group and serological status.

DISCUSSION

In this population-based study, 13.3% of children experienced symptoms lasting more than 2 weeks since the beginning of the COVID-19 pandemic and 3.0% experienced symptoms lasting over 4 weeks. Stratifying per age groups, the ΔPrev between seronegatives and seropositives was higher in adolescent with an estimated prevalence of 4.4% than in younger children who did not experience symptoms lasting over 4 weeks.

Many studies on persistent symptoms among children have used a duration ranging from 4 to 12 weeks, as many uncertainties existed around the characteristics of post-COVID-19 at the beginning of the pandemic. In our study, the majority of children were declared with symptoms lasting 2–4 weeks, suggesting that symptoms were mostly acute or subacute and not long-lasting. We were also able to show that a substantial share of children remained affected by symptoms lasting for over 4 weeks, which has been identified as a risk factor for developing a later post-COVID-19.[26] Most importantly, it also highlights the proportion of children who did not experience long-lasting symptoms.

Table 2 Association between persistent symptoms and serological status

Report of symptoms lasting at least 2 weeks		No (%) N=571	Yes (%) N=89	Prevalence ratio† 95% CI	Prevalence ratio‡ 95% CI
Sex	Female	285 (87.2)	42 (12.8)	1.0 (ref)	1.0 (ref)
	Male	280 (85.6)	47 (14.4)	1.11 (0.76 to 1.64)	1.14 (0.74 to 1.76)
	Diverse	8 (100.0)	0 (0.0)	Undefined	Undefined
Age (years)	2–5	132 (89.8)	15 (10.2)	1.0 (ref)	1.0 (ref)
	6–11	236 (87.1)	35 (12.9)	1.26 (0.71 to 2.23)	1.54 (0.30 to 7.83)
	12–17	203 (83.9)	39 (16.1)	1.57 (0.90 to 2.76)	1.61 (0.86 to 2.98)
Serological status	Negative	404 (89.0)	50 (11.0)	1.0 (ref)	1.0 (ref)
	Positive	169 (81.2)	39 (18.8)	1.65 (1.13 to 2.41)*§	1.62 (1.10 to 2.39)*§

*P value<0.05.
†Prevalence ratio and 95% CI are from Poisson regression with robust variance and are adjusted for age, sex or both according to independent variable.
‡Prevalence ratio and 95% CI are from Poisson regression with robust variance and random effect on the household using the GLMMadaptive package in R and are adjusted for age, sex or both according to independent variable.
§Adjusting for age and sex.
¶P value<0.01.

Cross-sectional studies on persistent symptoms after a SARS-CoV-2 infection among children[16–19 27] have reported prevalence estimates of persistent symptoms lasting more than 4 weeks ranging from 4.6% to 24.0%, with a strong heterogeneity in study design, inclusion criteria and outcomes. In our sample, we estimate the prevalence of persistent symptoms lasting more than 4 weeks, to be around 4% in adolescents aged 12–17. For younger children, we did not observe reports of long-lasting symptoms. However, it needs to be noted that our sample does not allow for enough statistical power to capture small proportions; for this a much larger sample would be needed.

Our results highlight the importance of stratifying by age groups when examining ongoing and post-COVID-19 in children, as the prevalence and characteristics likely vary between younger children and adolescents. Our findings support those of previous reports (as confirmed by Miller *et al*[17] and Behnood *et al*[27]). Adolescents appear to have an increased risk of experiencing persistent

Table 3 Association between persistent symptoms and socioeconomic indicators among seropositive children

Report of symptoms lasting at least 2 weeks, among seropositive		No (%) N=168	Yes (%) N=39	Prevalence ratio† (95% CI)	Prevalence ratio‡ (95% CI)
Sex	Female	80 (82.5)	17 (17.5)	1.0 (ref)	1.0 (ref)
	Male	85 (79.4)	22 (20.6)	1.17 (0.66 to 2.07)	1.18 (0.62 to 2.23)
	Diverse	3 (100.0)	0 (0.0)	Undefined	Undefined
Age (years)	2–5	26 (89.7)	3 (10.3)	1.0 (ref)	1.0 (ref)
	6–11	80 (87.9)	11 (12.1)	1.18 (0.35 to 3.94)	1.27 (0.36 to 3.96)
	12–17	62 (71.3)	25 (28.7)	2.84 (0.92 to 8.72)	2.84 (0.85 to 9.43)
Parental education	Tertiary	99 (88.4)	13 (11.6)	1.0 (ref)	1.0 (ref)
	Secondary	58 (74.4)	20 (25.6)	2.10 (1.11 to 3.98)*§	2.10 (1.07 to 4.12)*§
	Primary	11 (64.7)	6 (35.3)	2.98 (1.31 to 6.79)*§	2.97 (1.11 to 7.96)*§
Financial situation	High	114 (85.7)	19 (14.3)	1.0 (ref)	1.0 (ref)
	Average to poor	39 (72.2)	15 (27.8)	2.19 (1.22 to 3.09)*§	2.18 (1.09 to 4.35)*§
	Declined to answer	15 (75.0)	5 (25.0)	1.54 (0.67-3.53)§	1.55 (0.68-3.52)§

*P value<0.05.
†Prevalence ratio and 95% CI are from Poisson regression with robust variance and are adjusted for age, sex or both according to independent variable.
‡Prevalence ratio and 95% CI are from Poisson regression with random effect on the household using the GLMMadaptive package in R and are adjusted for age, sex or both according to independent variable.
§Adjusting for age and sex.
¶P value<0.01.

symptoms after the first infection phase. This is probably explained by the fact that, in general, adolescents, such as adults, are more likely to suffer from multiple symptoms during the early phase of the disease (symptomatic infection) and more likely to get a more severe form than younger children.[18] Although adolescents seem to be more frequently impacted than younger children, it must be pointed out that they remain less likely than adults to experience long-term symptoms.

Importantly, our analysis is based on a population-based sample where serological status was used to identify previous infection. Compared with clinical studies or studies of PCR-confirmed cases, this design has the advantage of including severe, mild and asymptomatic infections, thereby yielding a more accurate denominator of the proportion of children infected. The latter may also explain why our estimated prevalence of persistent symptoms is low compared with other studies.[28] It also gives a seronegative control group, which allows us to distinguish symptoms that may be due to post-COVID-19 from symptoms due to other viruses or to the pandemic context (school closures, fewer social interactions, being unable to do sports and other activities or seeing family and friends suffering from COVID-19).[29–31] Although this data comes with the limitation of not being able to identify a precise date for the infection, it provides an overall population-relevant estimate of the proportion of children affected by this condition.

In analyses restricted to seropositive children, we highlighted that children from households with a disadvantaged socioeconomic background were more likely to report symptoms lasting at least 2 weeks. These findings are not surprising as they reflect an extensive body of literature linking socioeconomic conditions to several negative health outcomes in children and adolescents.[32]

The major strength of this study is that it relies on a randomly selected population-based sample. To date, very few studies on ongoing and post-COVID-19 among children are population-based and include children from the age of 2. Previous SARS-CoV-2 infection was assessed with an objective measure, enabling us to benefit from a seronegative control group. Relying on serological tests rather than only on confirmed infections gives the advantage to get a more precise denominator for SARS-CoV-2 infections. Also, it prevents the bias of participants over-reporting persistent symptoms when knowing they have been infected.[33] Despite being a very important source of crucial information for public health planning, serological data does not allow the identification of the date of infection nor the date of onset persistent symptoms. Analyses using serological data are not intended to be conducted for estimating the individual probability of developing long-term symptoms after PCR-confirmed infections, for which another study design and a different follow-up would be necessary. Rather, serological data are useful for estimating the population prevalence of persistent symptoms after SARS-CoV-2 infection using a design that is not biased by testing attitude and practices.

Apart from the inability to yield a precise date of infection, the data has the limitation of relying on parent-reported data on questionnaires without clinical assessment. Parental point of view can be influenced by the parents' background as well as the general household environment, and be subject to recall bias.[30] Additionally, parents' awareness about their child's symptoms may be influenced by the child age. For example, adolescents tend to seek for independence and may communicate less with their parent, while younger children may be unable to adequately express symptoms. The lack of information on the temporality of seroconversion, on the duration of persistent symptoms after 4 weeks as well as symptoms' daily burden not being based on a standardised measure complicates the classification and diagnosis of ongoing and post-COVID-19. Indeed, when the study was conducted in June and July 2021, no definition on paediatric post-COVID-19 syndrome existed and we designed the study based on persistent symptoms lasting over 4 weeks. This still represents a postinfection phase and is a considerable duration for children, although it does not correspond to a definition of post-COVID-19. Finally, our sample is relatively small, with less than 10% of power to detect a difference of 1% in the prevalence of symptoms lasting more than 4 weeks between the seropositive and the seronegative sample.

CONCLUSION

Our findings revealed that a significant proportion of children aged 12–17 years have symptoms lasting over 2 weeks after SARS-COV-2 infection, as assessed by serological status before vaccination. The estimated prevalence of symptoms lasting over 4 weeks is of 4.4% in this age group, which suggests that adolescents are less likely than adults to experience long-term symptoms. This proportion represents a large absolute number of adolescents, and should raise awareness and concern in the context of unknown long-term evolution of symptoms. Children aged 2–11 years appear to experience fewer long-lasting symptoms related to SARS-CoV-2 infection. However, our power to detect small differences was limited by the sample size, and further larger studies are needed to assess the prevalence of persistent symptoms among younger children. Monitoring the evolution of ongoing and post-COVID-19 among children and adolescents is highly important as the long-term physical and mental impact of COVID-19 persistent symptoms remains unclear and adequate public health policies are needed in terms of schooling and vaccination.

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Contributors SS, RD, MN, CDM, VR, EL and IG conceptualised and designed the study, carried out the initial analyses, drafted the initial manuscript and reviewed and revised the manuscript. M-EZ, FP, CS, JL, HB and NP designed the data collection instruments, collected data, carried out the initial analyses and reviewed and revised the manuscript. AP, AGL and KMP-B contributed to the design of the study, the interpretation of data and critically reviewed the manuscript for important intellectual content. All authors have read, critically revised and approved the final version of this manuscript. SS, IG and RD are acting as guarantor.

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