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Long COVID symptoms in SARS-CoV-2-positive adolescents and matched controls (LongCOVIDKidsDK): a national, cross-sectional study

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Summary

Background Many adolescents have been affected by the COVID-19 pandemic either directly by being infected with the virus or indirectly by lockdowns and restrictions influencing normal living. We aimed to investigate health, including symptoms of long COVID, in adolescents (aged 15–18 years) who tested positive for SARS-CoV-2 compared with a control group.

Methods LongCOVIDKidsDK was a national, cross-sectional study carried out in Denmark, which included SARS-CoV-2-positive adolescents and matched controls. All Danish adolescents aged 15–18 years with a positive SARS-CoV-2 test during the period Jan 1, 2020, to July 12, 2021, and a control group matched (1:4) by age and sex were sent a survey from July 20, 2021. Participants had until Sept 15, 2021, to respond. Symptoms associated with COVID-19, school attendance, and health-related quality of life were investigated using ancillary questions and validated questionnaires (Paediatric Quality of Life Inventory [PedsQL] and Children's Somatic Symptoms Inventory-24 [CSSI-24]). Statistical analyses included descriptive statistics and logistic regression. This study is registered at ClinicalTrials.gov, NCT04786353.

Findings 24 315 adolescents with a positive SARS-CoV-2 test (case group) and 97 257 matched controls were invited to participate. 3013 matched controls were excluded because of suspected SARS-CoV-2 infection. 6630 (27·3%) responded in the case group and 21 640 (22·3%) responded and were eligible to participate in the control group. Across both groups, median age was 17·6 years (IQR 16·4–18·5), 16 277 (57·6%) of 28 270 responders were female, and 11 993 (42·4%) were male. Participants in the case group had greater odds of having at least one long COVID symptom lasting at least 2 months compared with the control group (3159 [61·9%] *vs* 12 340 [57·0%], odds ratio 1·22 [95% CI 1·15–1·30]; p<0·0001). Participants in the case group reported significantly lower symptom scores (ie, less somatic distress) on the CSSI-24 than in the control group: mean 10·7 (SD 11·4, median 7·0 [IQR 2·0–15·0]) versus 11·9 (10·6, 9·0 [4·0–17·0]; p<0·0001). Participants in the case group had better quality of life scores on the PedsQL than in the control group: physical functioning mean score 88·7 (SD 13·9, median 93·8 [IQR 84·4–100·0]) versus 86·5 (14·3, 90·6 [81·3–96·9]; p<0·0001); emotional functioning 77·1 (20·3, 80·0 [65·0–95·0]) versus 71·7 (21·4, 75·0 [60·0–90·0]; p<0·0001); social functioning 93·1 (12·5, 100·0 [90·0–100·0]) versus 88·4 (16·2, 95·0 [80·0–100·0]; p<0·0001); and school functioning 66·9 (22·5, 65·0 [60·0–85·0]) versus 62·9 (22·1, 65·0 [50·0–80·0]; p<0·0001). More participants in the case group than in the control group reported 16 or more sick days (1205 [18·2%] *vs* 2518 [11·6%]; p<0·0001) and 16 or more days of school absence (695 [10·5%] *vs* 1777 [8·2%]; p<0·0001).

Interpretation Participants with SARS-CoV-2-positive tests had more long-lasting symptoms and sick leave, whereas participants in the control group had more short-lasting symptoms and worse quality of life. Knowledge of long COVID in adolescents is important to guide clinical recognition and management of this condition.

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Introduction

Children and adolescents with SARS-CoV-2 infection are generally considered to have a lower risk of hospitalisation and low mortality rates compared with adults.[1,2] International awareness has been raised about persistent symptoms following SARS-CoV-2 infection, such as fatigue, headaches, and shortness of breath lasting for several months (long COVID).[3,4] In October, 2021, WHO defined long COVID as persistent or fluctuating symptoms with an impact on everyday functioning following SARS-CoV-2 infection for at least 2 months that cannot be explained by an alternative diagnosis in adults;[5] however, a definition has not yet been specified for children or adolescents. Several studies have investigated symptoms of long COVID among adults,[6–9] but only a few studies have addressed long COVID in children and adolescents. A recent review identified 14 such studies,[10] but only five of these included a control group, with a total of only 5270 cases and 12 588 controls.[11–15] Of these five studies, three found that persistent SARS-CoV-2-related symptoms

Research in context

Evidence before this study

We searched PubMed in January, 2021, before designing this study, to identify studies investigating long COVID in children and adolescents. The search terms used were "child" OR "children" OR "adolescent" AND "COVID-19" AND "symptoms" OR "long COVID". We found one case description from Sweden of five children. We also searched Google and social media and found one study from Italy including 75 children who had COVID-19 with no control group (preprint before peer review) and a webpage (longcovidkids.org) reporting data from a survey—Child Long COVID Symptoms Survey 1. Furthermore, we searched ClinicalTrials.gov for ongoing studies in the COVID-19 database. We found no Danish studies registered and no national survey studies with matched controls.

Added value of this study

This national study investigated long-term symptoms and quality of life in adolescents with PCR-confirmed SARS-CoV-2 compared with age and sex matched controls. This study has the longest follow-up time of more than 12 months and is the largest to date, including 6630 responders in the case group and 21 640 eligible responders in the control group. Long COVID is reported according to the new definition from WHO (symptoms lasting more than 8 weeks). Furthermore, the study reports on the duration and intensity of each symptom. The study includes findings on psychological wellbeing, social wellbeing, and school absence during the pandemic. We found that adolescents in the case group had higher odds of having long-lasting central COVID-19 symptoms but had better quality of life scores and fewer short-lasting symptoms compared with the control group. The case group had more sick days and more school absences than the control group.

Implications of all the available evidence

Early in the COVID-19 pandemic, studies without control groups reported long COVID to be highly prevalent. However, recent studies including control groups have reported symptoms to also be highly prevalent among controls. Results from this LongCOVIDKidsDK study combined with findings in other recent studies including a control group suggest that persisting symptoms are more prevalent in adolescents after a SARS-CoV-2 infection than in controls. Knowledge of long COVID in adolescents is important to guide clinical recognition and management of this condition, as well as inform decisions about vaccine strategies. Findings on psychological and social challenges among adolescents in both groups suggest that these areas need attention, especially during periods of lockdown and school closures where social relations are restricted.

were more prevalent in children and adolescents following SARS-CoV-2 infection (cases) compared with controls,[13–15] and two studies found no differences between cases and controls.[11,12] The longest follow-up time was 12 weeks, and two studies did not have laboratory-confirmed SARS-CoV-2.[16,17] Long-term symptoms after a viral infection are a known phenomenon in children and adolescents—eg, persistent coughing after a respiratory syncytial virus infection in infants and toddlers,[18] and persistent fatigue, headaches, and abdominal pain after Epstein-Barr virus infection.[19] Thus, long COVID in adolescents would not be unexpected.

Another perspective on the health of adolescents during the pandemic is the effect of pandemic living conditions such as physical distancing and lockdowns of schools and society. Children and adolescents are reported to have more anxiety and depression than before the pandemic,[20] and more so during lockdowns.[21] However, evidence about the extent is conflicting.[22,23]

Our aim was to investigate health, including symptoms of long COVID, in adolescents (aged 15–18 years) who tested positive for SARS-CoV-2 compared with a control group. The objectives were to explore (1) the prevalence of symptoms lasting more than 2 months; (2) the duration and intensity of symptoms; (3) quality of life; and (4) psychological and social outcomes in adolescents testing positive for SARS-CoV-2 compared with matched controls who never had a SARS-CoV-2-positive test. Finally, we aimed to explore new symptoms that developed after the positive SARS-CoV-2 test and were not known before the test.

We hypothesised that SARS-CoV-2 infection could affect the prevalence, intensity, and duration of long-lasting symptoms, psychological and social outcomes, school absence, and sick leave from school.

Methods

Study design and participants

The LongCOVIDKidsDK study was a national, cross-sectional study carried out in Denmark. We administered a survey to all adolescents (aged 15–18 years) in Denmark who tested positive for SARS-CoV-2 and to matched controls who had not tested positive.

All 24 315 Danish adolescents aged 15–18 years with a positive SARS-CoV-2 test in the period Jan 1, 2020, to July 12, 2021, (case group) were identified from the Danish COVID-19 database, which has complete national coverage of all Danish individuals with a positive SARS-CoV-2 test. On July 12, 2021, this constituted 9% of Danish individuals aged 15–18 years. A group of controls without a positive SARS-CoV-2 test, matched 1:4 (n=97 257) by sex and age at the time of the case's positive test was identified from the Danish Civil Registration System.[19] Thus, the control group consisted of both adolescents with one or more negative tests during the pandemic and adolescents who were never tested.

Questionnaires were administered through e-Boks (a Nordic secure digital post-box that is used by public

authorities to communicate with Danish citizens) to be answered in REDCap (a secure web application for online surveys)[24] from July 20 to Sept 15, 2021, with one initial invitation and two reminders.[25] Cases were asked about comorbidities before the SARS-CoV-2 positive test and controls were asked about previous comorbidity with no index date.

Controls who reported that they suspected having been infected by SARS-CoV-2 at some point during the pandemic but who did not have access to a test at the time were excluded. Controls who were infected in the time between extraction of population from the register (July 12, 2021) and survey invitation were asked not to respond.

This study was approved by the data protection agency (P-2021-195). Access to register data was granted by The Danish Health Data Authority (FSEID 00005625 and 00005757). No further ethical approval is granted for surveys in Denmark. Informed consent was provided by submitting the answered electronic questionnaire.

Variables

The Children's Somatic Symptoms Inventory-24 (CSSI-24) is a 24-item generic questionnaire, developed to identify the presence of various somatic symptoms in children. The items are scored on a 5-point Likert scale from 0 (not at all) to 4 (a lot) and converted into a single summary score covering the past 2 weeks. A higher sum score indicates greater somatic distress.[26]

The 23-item generic questionnaire, Pediatric Quality of Life (PedsQL), covers four dimensions of health-related quality of life in children aged 15–18 years. The PedsQL offers a total summary score and subscores covering physical functioning, emotional functioning, social functioning, and school functioning experienced over the past month. The PedsQL scale ranges from 0 to 100, with higher scores indicating better health.[27]

See Online for appendix

In addition to the CSSI-24 and the PedsQL, the 23 most common long COVID symptoms identified from the Long COVID Kids Rapid Survey January 2021 were included in the questionnaire we administered.[28] Questions about height and bodyweight to calculate body-mass index as well as questions about sick leave and absence from school, were also included.

Data sources and management

Adolescents who had tested positive for SARS-CoV-2 were asked to report all symptoms since infection, including answering questions about intensity and duration of symptoms. Participants were asked whether the symptoms were present before SARS-CoV-2 infection and whether they believed the symptom to be related to the infection. Long COVID symptoms must not have been known before infection. To identify adolescents in the case group with new symptoms that might be related to COVID-19, a nested population was established (long COVID group). This consisted of participants from the case group with at least one new-onset symptom not known before the positive SARS-CoV-2 test that was present 8 weeks after the positive test.

The control group was asked about the same symptoms and to rate their intensity and duration. Using statistical software, the control group was divided into four random groups of equal size. These four groups were asked to report on the 23 long COVID symptoms going back 3, 6, 9, or 12 months to match the varying recall times in the case group.

23 common long COVID symptoms were prespecified and identified from the Long COVID Kids Rapid Survey, January, 2021.[28] The symptoms were stomach aches, chest pain, headache, fatigue, pain in muscles or joints, sore throat, dizziness, rashes, mood swings, nausea, fever, loss of appetite, trouble breathing, dark circles under the eyes, palpitations, trouble remembering or concentrating, cold hands or feet, cough, chapped lips, dizziness when standing, light sensitivity, discoloured fingers or toes, and extreme paleness. When comparing the 23 common long COVID symptoms among the case group and control group, we used the criteria of symptoms lasting 2 months or more to comply with the WHO definition of long COVID.[5] Participants were not asked about interruptions in the duration of symptoms but about intensity—eg "sometimes" or "always" during the reported period.

In Denmark, schools were open from March 11, 2020, to June, 2021, with varying periods of closing. Accessibility to SARS-CoV-2 testing moved from being by medical reference in the first months of 2020 to easily accessible walk-in centres from May, 2020. Our data were obtained during a period when Denmark was not in lockdown but was in the middle of the post-COVID-19-lockdown respiratory syncytial virus epidemic (appendix p 10).

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables are presented as mean (SD) and median (IQR).

Logistic regression was used to calculate odds ratios (ORs) and corresponding 95% CIs for the outcomes reporting at least one symptom lasting 2 months and for reporting each of the 23 symptoms lasting 2 months in the case group and control group. Analyses were adjusted for age and sex. Differences in prevalence and means between the case group and control group were tested using two-sided c^2 test for categorical variables and *t* tests or the independent non-parametric Wilcoxon Signed Rank test for continuous variables not normally distributed. These tests applied for testing differences in CSSI-24 scores and PedsQL scores, as well as differences in sick leave and psychological and social symptoms between the case and control groups. Analyses were prespecified.

For CSSI-24 scores and PedsQL scores, the standardised difference between the means was assessed using

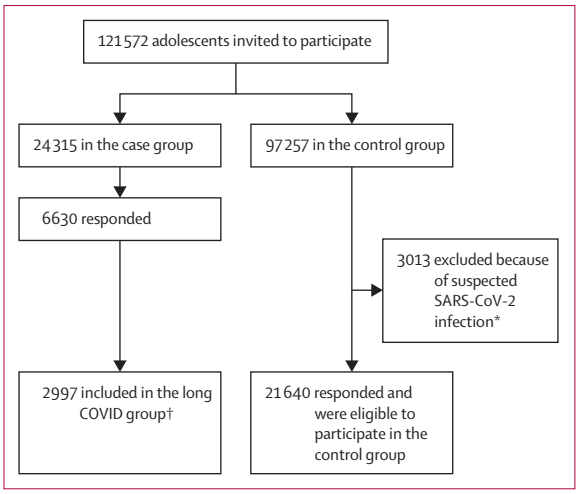

Figure 1: **Study profile**
*Suspected SARS-CoV-2 infection was defined as controls who reported that they suspected having been infected by SARS-CoV-2 but who did not have access to a test at the time. †The long COVID group consisted of cases with at least one new-onset symptom not known before the positive SARS-CoV-2 result and present 8 weeks after the positive test.

Hedges' *g*. An effect size of 0·2 is considered a small difference, 0·5 represents a medium difference, and 0·8 a large difference.[29]

To adjust for multiple testing, the Bonferroni correction method was used. The significance level was set at less than 0·05 and 41 tests were done. Therefore, we considered a p value of 0·001 to be statistically significant.

We did a post-hoc power calculation for the proportion of cases and controls with at least one symptom lasting 2 months: with 6630 cases compared with 21 640 controls and α=0·001, the power was 100%. We used the post-hoc power calculator to calculate power based on the actual difference found.

Missing data was not an issue in the dataset, as all questions had to be answered to submit the survey.

For results with fewer than five individuals, absolute values are shown as 1–4 and percentages are masked due to data protection rules from the Danish data authorities.

All analyses were done using SAS version 9.4 M5. This study is registered at ClinicalTrials.gov, NCT04786353.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
24 315 adolescents were invited to participate in the case group and 97 257 were invited to participate in the control group (figure 1). 3013 adolescents invited to the control group were excluded because of suspected SARS-CoV-2. 6630 (27·3%) responded in the case group and 21 640 (22·3%) responded and were eligible to participate in the control group (figure 1; table 1). Non-responders and responders were similar in age (non-responders median 17·4 years [IQR 16·3–18·5]; responders median 17·6 years [16·4–18·5]) and more non-responders were male (489 621 [54·2%]) than female (41 335 [45·8%]). 2997 participants from the case group were included in the long COVID subgroup (figure 1).

Among responders, participants in the case group and the control group were similar in age and sex distribution when responding to the questionnaire (table 1). All participants in the case group were a maximum of 18 years old at the time of the positive SARS-CoV-2 test.

	Case group (n=6630)	Control group (n=21 640)	Long COVID group* (n=2997)
Age, years	17·6 (16·5–18·6)	17·5 (16·4–18·5)	17·7 (16·5–18·6)
Sex			
Female	3873 (58·4%)	12 404 (57·3%)	2072 (69·1%)
Male	2757 (41·6%)	9236 (42·7%)	925 (30·9%)
Body-mass index			
<18·5	759 (11·4%)	3030 (14·0%)	351 (11·7%)
18·5–24·9	4870 (73·5%)	15 120 (70·0%)	2173 (72·5%)
≥25·0	756 (11·4%)	2482 (11·5%)	348 (11·6%)
≥30·0	177 (2·7%)	668 (3·1%)	92 (3·1%)
≥35·0	62 (0·9%)	315 (1·5%)	31 (1·0%)
Pre-existing comorbidity†‡			
Allergy	1248 (18·8%)	4950 (22·9%)	653 (21·8%)
OCD, anxiety, or depression	365 (5·5%)	2057 (9·5%)	241 (8·0%)
Asthma	507 (7·7%)	1602 (7·4%)	286 (9·5%)
Eczema	371 (5·6%)	1344 (6·2%)	23 (0·8%)
ADHD or ADS	176 (2·7%)	931 (4·3%)	84 (2·8%)
Autism	108 (1·6%)	807 (3·7%)	51 (1·7%)
Hyper-mobility	124 (1·9%)	670 (3·1%)	72 (2·4%)
Tics	66 (1·0%)	381 (1·8%)	36 (1·2%)
Epstein-Barr virus	166 (2·5%)	107 (0·5%)	74 (2·5%)
Arthritis	26 (0·4%)	105 (0·5%)	29 (1·0%)
Myalgic encephalomyelitis or CFS	23 (0·3%)	25 (0·1%)	17 (0·6%)
Human papillomavirus	1–4	10 (<0·1%)	1–4
Time since positive SARS-CoV-2 test			
≤1 month	366 (5·5%)	NA	NA
>1 to 3 months	1158 (17·5%)	NA	461 (15·4%)
4 to 6 months	856 (12·9%)	NA	394 (13·1%)
7 to 9 months	3165 (47·7%)	NA	1598 (53·3%)
10 to 12 months	843 (12·7%)	NA	433 (14·4%)
>12 months	242 (3·7%)	NA	111 (3·7%)
Self-reported acute SARS-CoV-2 severity			
No symptoms	2241 (33·8%)	NA	663 (22·1%)
Mild symptom burden	3795 (57·2%)	NA	1897 (63·3%)
Severe symptom burden	594 (9·0%)	NA	437 (14·6%)

Data are median (IQR) or n (%). ADHD=attention-deficit hyperactivity disorder. ADS=attention-deficit syndrome. CFS=chronic fatigue syndrome. OCD=obsessive compulsive disorder. NA=not applicable. *The long COVID group was defined as participants in the case group reporting at least one new-onset symptom not known before the positive SARS-CoV-2 test and present 8 weeks after the positive test. †The case group were asked about comorbidity before SARS-CoV-2 infection; the control group were asked about present comorbidity. ‡For results with fewer than five individuals per cell, numbers are presented as 1–4 and percentages are masked due to data protection rules from the Danish data authorities.

Table 1: **Demographic and clinical profile of adolescents who tested positive for SARS-CoV-2, matched controls, and the long COVID subgroup**

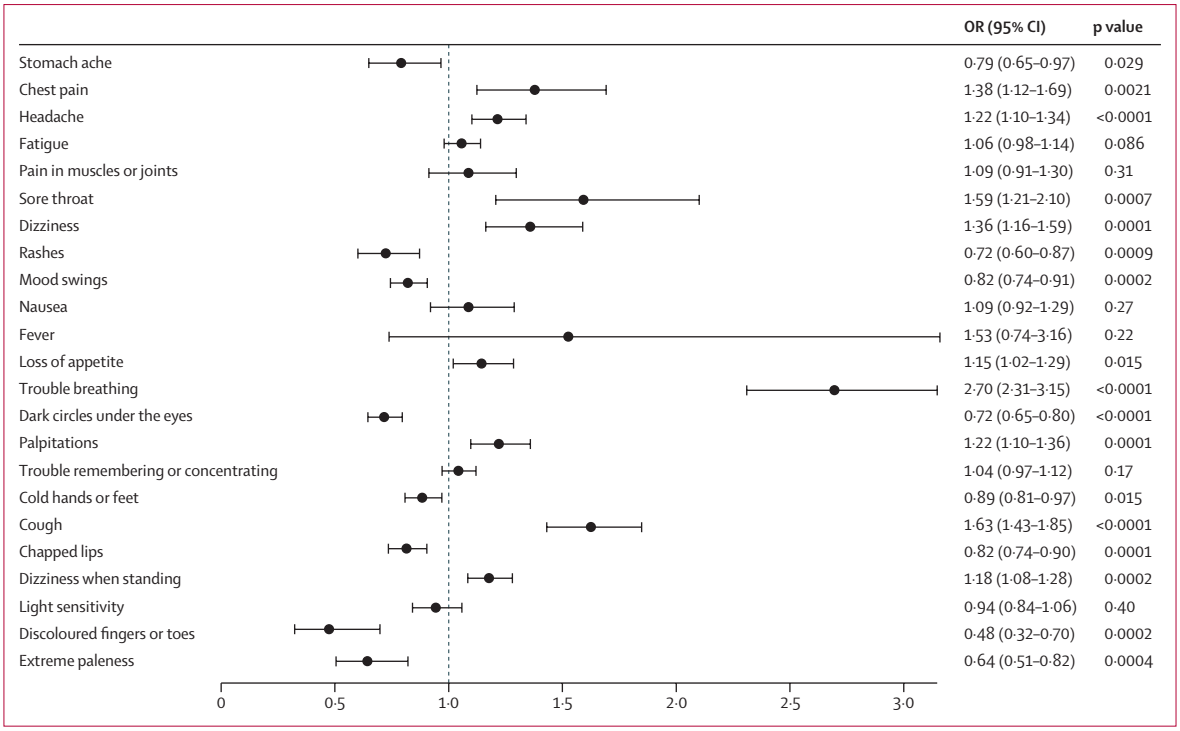

Figure 2: **Forest plot of symptoms lasting at least 2 months in the case group, with the control group as reference**
OR=odds ratio.

16 277 (57·6%) of 28 270 responders were female and 11 993 (42·4%) were male. Demographics and clinical characteristics of the responders are shown in table 1.

The long COVID group was similar in age, but with a greater proportion of female participants than the total SARS-CoV-2-positive group and a smaller proportion of participants with an asymptomatic SARS-CoV-2 infection in the acute phase (table 1).

3159 (61·9%) participants in the case group had at least one symptom lasting more than 2 months (irrespective of whether symptoms were present before the SARS-CoV-2-positive test), compared with 12 340 (57·0%) in the control group (OR 1·22 [95% CI 1·15–1·30]; p<0·0001). The ORs for each symptom are shown in figure 2 and the absolute values and proportions of participants with each symptom at all timepoints are shown in the appendix (pp 3–5). In both groups, more female participants than male participants had symptoms lasting more than 2 months (2118 [71·7%] *vs* 1041 [48·4%]; OR 2·70 [95% CI 2·40–3·03]; p<0·0001 in the case group and 8282 [66·8%] *vs* 4058 [43·9%]; OR 2·56 [2·42–2·70]; p<0·0001 in the control group).

On the CSSI-24 (with 2 week recall), participants in the case group reported significantly lower symptom scores than participants in the control group (mean 10·7 [SD 11·4], median 7·0 [IQR 2·0–15·0] *vs* 11·9 [10·6], 9·0 [4·0–17·0]; p<0·0001, Hedges' *g* 0·11; table 2). On the PedsQL (with 4 week recall), participants in the case group reported significantly better quality of life on physical functioning (mean 88·7 [SD 13·9], median 93·8 [IQR 84·4–100·0] *vs* 86·5 [14·3], 90·6 [81·3–96·9]; p<0·0001, *g* 0·16), emotional functioning (77·1 [20·3], 80·0 [65·0–95·0] *vs* 71·7 [21·4], 75·0 [60·0–90·0]; p<0·0001, *g* 0·26), social functioning (93·1 [12·5], 100·0 [90·0–100·0] *vs* 88·4 [16·2], 95·0 [80·0–100·0]; p<0·0001, *g* 0·31), and school functioning (66·9 [22·5], 65·0 [60·0–85·0] *vs* 62·9 [22·1], 65·0 [50·0–80·0]; p<0·0001, *g* 0·18; table 2). Results for the CSSI-24 and PedsQL scores by time since positive SARS-CoV-2 test were similar to the overall results (table 2).

For the psychological and social outcomes of the PedsQL, significantly fewer participants in the case group than in the control group often felt scared or worried (appendix p 6). Significantly more participants in the control group had trouble sleeping than in the case group (appendix p 6). Significantly more participants in the control group sometimes experienced a lack of friendship and sometimes being teased than in the case group (appendix p 6).

More participants in the case group than in the control group reported 16 or more sick days (1205 [18·2%] *vs* 2518 [11·6%]; p<0·0001) and 16 or more days of school absence (695 [10·5%] *vs* 1777 [8·2%]; p<0·0001; appendix p 7).

The mean CSSI-24 score for the long COVID group was 15·5 (SD 12·6, median 12·0 [IQR 6·9–21·0]) and the mean PedsQL scores were 83·1 (SD 15·6, median 87·5 [IQR 75·0–93·8]) for physical functioning, 69·6 (21·4,

	1 month since positive SARS-CoV-2 test (n=366)	Up to 3 months since positive SARS-CoV-2 test (n=1158)	Up to 6 months since positive SARS-CoV-2 test (n=856)	Up to 9 months since positive SARS-CoV-2 test (n=3165)	Up to 12 months since positive SARS-CoV-2 test (n=843)	More than 12 months since positive SARS-CoV-2 test (n=242)	Total case group (n=6630)	Control group (n=21 640)
CSSI-24 score								
Mean (SD)	11·2 (11·6)	10·1 (10·7)	11·0 (11·8)	10·4 (10·9)	11·2 (12·6)	13·4 (14·4)	10·7 (11·4)	11·9 (10·6)
Median (IQR)	8·0 (3·0–16·0)	7·0 (2·0–14·0)	8·0 (2·0–15·5)	7·0 (2·0–15·0)	7·0 (2·0–16·0)	9·0 (3·0–20·0)	7·0 (2·0–15·0)	9·0 (4·0–17·0)
PedsQL score								
Physical functioning								
Mean (SD)	88·4 (14·6)	89·7 (12·6)	88·0 (14·9)	88·9 (13·6)	88·3 (14·8)	86·0 (16·5)	88·7 (13·9)	86·5 (14·3)
Median (IQR)	93·8 (84·4–100·0)	93·8 (84·4–100·0)	93·8 (81·4–100·0)	93·8 (84·4–100·0)	93·8 (81·3–100·0)	93·8 (78·1–100·0)	93·8 (84·4–100·0)	90·6 (81·3–96·9)
Emotional functioning								
Mean (SD)	78·6 (19·4)	78·2 (19·9)	77·8 (20·5)	76·4 (20·1)	77·6 (20·9)	75·2 (23·4)	77·1 (20·3)	71·7 (21·4)
Median (IQR)	80·0 (65·0–95·0)	80·0 (65·0–95·0)	80·0 (65·0–95·0)	80·0 (65·0–95·0)	80·0 (65·0–95·0)	80·0 (60·0–100·0)	80·0 (65·0–95·0)	75·0 (60·0–90·0)
Social functioning								
Mean (SD)	93·4 (12·2)	94·7 (11·0)	92·1 (13·9)	92·8 (12·5)	93·4 (12·5)	92·0 (14·8)	93·1 (12·5)	88·4 (16·2)
Median (IQR)	100·0 (90·0–100·0)	100·0 (95·0–100·0)	100·0 (90·0–100·0)	100·0 (90·0–100·0)	100·0 (90·0–100·0)	100·0 (90·0–100·0)	100·0 (90·0–100·0)	95·0 (80·0–100·0)
School functioning								
Mean (SD)	69·6 (21·3)	68·5 (21·6)	67·0 (22·3)	66·6 (22·7)	65·1 (23·1)	65·2 (24·2)	66·9 (22·6)	62·9 (22·1)
Median (IQR)	70·0 (55·0–85·0)	70·0 (55·0–85·0)	70·0 (50·0–85·0)	65·0 (50·0–85·0)	65·0 (50·0–85·0)	65·0 (50·0–80·0)	65·0 (60·0–85·0)	65·0 (50·0–80·0)

In CSSI-24, the 24 items are scored on a 5-point Likert scale from 0 (not at all) to 4 (a lot) and converted into a single summary score covering the past 2 weeks, with a higher sum score indicating greater somatic distress. PedsQL includes 23 items covering four dimensions of health-related quality of life, with a higher score indicating better quality of life; the highest possible score is 100. CSSI-24=Children's Somatic Symptoms Inventory-24. PedsQL=Pediatric Quality of Life.

Table 2: **Symptom burden and health-related quality of life in the case group, by time since positive test, and in the control group**

70·0 [55·0–85·0]) for emotional functioning, 91·1 (14·0, 100·0 [85·0–100·0]) for social functioning, and 59·9 (22·4, 60·0 [45·0–75·0]) for school functioning. Sick days and school absences in the long COVID group are shown in the appendix (p 7).

4353 (65·7%) participants in the case group reported at least one new symptom present after 4 weeks from the SARS-CoV-2 positive test and not known before infection, with a mean of 3·5 (SD 2·9, median 3·0 [IQR 1·0–5·0]) new symptoms out of 23 possible symptoms in the questionnaire. 6264 participants in the case group responded to questions about long COVID symptoms, of whom 2997 (47·8%) had long COVID and 2419 (38·6%) suspected that the new symptom was related to COVID-19. 50 (20·7%) of 242 reported at least one new symptom lasting 12 months following SARS-CoV-2 infection. Participants in the case group had mean 1·3 (SD 2·3, median 0·0 [IQR 0·0–2·0]) long COVID symptoms not known before the positive SARS-CoV-2 test and present 8 weeks after the positive test.

Participants in the case group who reported severe acute COVID-19 symptoms had mean 3·3 (SD 3·5, median 2·0 [IQR 0·0–5·0]) long COVID symptoms, participants with mild acute symptoms had mean 1·4 (2·2, 0·0 [0·0–2·0]) long COVID symptoms, and participants who reported no acute symptoms had mean 0·7 (1·5, 0·0 [0·0–2·0]) long COVID symptoms.

The most frequent symptoms in the long COVID group were headache, fatigue, loss of appetite, trouble breathing, and trouble remembering or concentrating (table 3). The long COVID group reported a decreasing number of symptoms over time (table 3).

Discussion

In this study, we investigated symptoms and quality of life in the Danish adolescent population between 15–18 years old who were SARS-CoV-2 positive, and in a sex and age matched control group. Compared with the control group, participants in the case group had greater odds of having long-lasting central COVID-19 symptoms but had better quality of life scores and fewer short-lasting symptoms. Participants in the case group had more sick days and more school absences than in the control group.

A central strength of this study is access to the Danish registers, including all SARS-CoV-2 PCR test results for the total Danish population and the Danish Civil Registration System offering matching for survey purposes of national interest. Furthermore, a national secure digital post-box reaches all citizens without the delays that would be caused by postal mail, and with a direct link to the survey. The study also has several limitations. The number of symptoms suggested to be related to COVID-19 is very long.[10] We included symptoms from two validated questionnaires[26,27] and added 23 symptoms as reported in the literature, plus data on diseases that the participants had at baseline that could have affected the outcomes.[28] The list of symptoms we used is not complete, and we do not know if all relevant symptoms are assessed. Our response rates were in the 23–27% range, which is slightly less than for

other, non-COVID-19 studies including adolescents in general,[30,31] yet much higher than in recent studies investigating COVID-19 symptoms in adolescents (less than 14%).[10,13,15] Non-response bias might be present because more non-responders were male than female. Sampling bias is unlikely due to similar response rates between the two groups. Participants in the case group and the control group were not sent the same questionnaire because participants in the case group were asked to report on acute symptoms and if symptoms were perceived to be new and related to COVID-19. Furthermore, those in the case group were asked to report on comorbidities before their SARS-CoV-2-positive test and those in the control group were asked to report on previous comorbidity with no index date. This difference caused some systemic response error. The retrospective recall up to 12 months might have caused recall bias. Most data are subjective; however, that is the nature of symptoms such as headache, anxiety, and fatigue. The case-only reporting is important to investigate new symptoms not known before the SARS-CoV-2-positive test; however, data should be interpreted with caution due to the absence of meaningful controls.

	At least 2 months (n=5978)	At least 3 months (n=5106)	At least 6 months (n=4250)	At least 9 months (n=1085)	At least 12 months (n=242)
Stomach ache					
Almost never or sometimes	106 (1·8%)	82 (1·6%)	42 (1·0%)	8 (0·7%)	1–4
Often or almost always	66 (1·1%)	55 (1·1%)	29 (0·7%)	1–4	0
Chest pain					
Almost never or sometimes	206 (3·4%)	155 (3·0%)	94 (2·2%)	17 (1·6%)	4 (1·7%)
Often or almost always	85 (1·4%)	70 (1·4%)	43 (1·0%)	10 (0·9%)	1–4
Headache					
Almost never or sometimes	288 (4·8%)	219 (4·3%)	136 (3·2%)	25 (2·3%)	1–4
Often or almost always	259 (4·3%)	212 (4·2%)	141 (3·3%)	28 (2·6%)	5 (2·1%)
Fatigue					
Almost never or sometimes	409 (6·8%)	315 (6·2%)	209 (4·9%)	36 (3·3%)	1–4
Often or almost always	661 (11·1%)	547 (10·7%)	380 (8·9%)	81 (7·5%)	8 (3·3%)
Pain in muscles or joints					
Almost never or sometimes	233 (3·9%)	168 (3·3%)	99 (2·3%)	19 (1·8%)	1–4
Often or almost always	102 (1·7%)	89 (1·7%)	59 (1·4%)	14 (1·3%)	1–4
Sore throat					
Almost never or sometimes	134 (2·2%)	101 (2·0%)	63 (1·5%)	9 (0·8%)	1–4
Often or almost always	49 (0·8%)	37 (0·7%)	22 (0·5%)	5 (0·5%)	0
Dizziness					
Almost never or sometimes	254 (4·2%)	200 (3·9%)	110 (2·6%)	21 (1·9%)	1–4
Often or almost always	122 (2·0%)	97 (1·9%)	60 (1·4%)	13 (1·2%)	1–4
Rashes					
Almost never or sometimes	58 (1·0%)	40 (0·8%)	18 (0·4%)	1–4	0
Often or almost always	41 (0·7%)	34 (0·7%)	19 (0·4%)	5 (0·5%)	0
Mood swings					
Almost never or sometimes	146 (2·4%)	111 (2·2%)	60 (1·4%)	13 (1·2%)	1–4
Often or almost always	144 (2·4%)	121 (2·4%)	82 (1·9%)	13 (1·2%)	1–4
Nausea					
Almost never or sometimes	176 (2·9%)	131 (2·6%)	69 (1·6%)	12 (1·1%)	0
Often or almost always	110 (1·8%)	81 (1·6%)	48 (1·1%)	14 (1·3%)	1–4
Fever					
Almost never or sometimes	41 (0·7%)	32 (0·6%)	21 (0·5%)	1–4	0
Often or almost always	5 (0·1%)	1–4	1–4	0	0
Loss of appetite					
Almost never or sometimes	313 (5·2%)	228 (4·5%)	135 (3·2%)	19 (1·8%)	1–4
Often or almost always	298 (5·0%)	230 (4·5%)	137 (3·2%)	24 (2·2%)	0
Trouble breathing					
Almost never or sometimes	309 (5·2%)	254 (5·0%)	154 (3·6%)	26 (2·4%)	6 (2·5%)
Often or almost always	219 (3·7%)	183 (3·6%)	122 (2·9%)	27 (2·5%)	1–4
Dark circles under the eyes					
Almost never or sometimes	92 (1·5%)	76 (1·5%)	45 (1·1%)	9 (0·8%)	0
Often or almost always	113 (1·9%)	91 (1·8%)	66 (1·6%)	13 (1·2%)	1–4

(Table 3 continues on next page)

Overall, participants in the case group had fewer pre-existing comorbidities than in the control group. In general, participants in the case group had a higher number of symptoms lasting a long time than in the control group—eg chest pain, trouble breathing, cough, headaches, sore throat, and dizziness. These could be long-lasting symptoms of COVID-19. Three[13–15] of five previous studies of long COVID in adolescents that included a control group found a difference in persistent symptoms, with more symptoms in the case group, whereas two studies[11,12] reported no difference between the groups. The studies reporting no difference in persistent symptoms had shorter follow-up times of 1·5 to 3 months, had smaller sample sizes, and included different symptoms (eg, sleep disturbance and myalgia or arthralgia) and methods than the studies that did report a difference between the groups. Surprisingly, in our study, compared with the case group, participants in the control group generally reported worse outcomes in the validated generic questionnaires for symptoms, psychological outcomes, and quality of life with 2–4 weeks recall time. However, the differences might not be clinically relevant even though they were statistically significant as only for emotional and social outcomes were small, clinically significant effect sizes found. In the control group, we also found more reporting of rashes, mood swings, dark circles under the eyes, and chapped lips, compared with the case group. One possible explanation of the difference in these symptoms might be the demographic and clinical profiles at baseline, with more comorbidity among the control group. It could also be that the control group had greater fear of COVID-19 and more restricted everyday life due to protecting themselves from the virus. Also, our validated questionnaires have 2–4 weeks recall, meaning that many participants in the case group went a long time since infection and could be free of symptoms.

Pandemic symptoms (ie, health symptoms caused by poor thriving due to lockdowns and social restrictions) have been suggested[10] and might be caused by poor thriving due to lockdown and social restrictions.[10,32] Long

COVID symptoms might be difficult to identify in surveys due to possible pandemic symptoms such as difficulty sleeping, anxiety, depression,[22] respiratory syncytial virus, and vaccine side-effects. Furthermore, the symptoms are common ailments that many people have every year. Thus, potential differences between the groups in intensity and duration of these symptoms might have been masked.

Denmark is one of the countries testing the most, with a mean of almost ten PCR tests per person from the beginning of the pandemic up to when the survey was administered, and as many antigen tests. However, some adolescents might have had undetected, asymptomatic SARS-CoV-2 infection and, therefore, the reported mean differences in symptoms between our case and control groups could be greater than those experienced by the average individual contracting a SARS-CoV-2 infection.

Differences in sick days and school absences were, not surprisingly, found between the two groups. School absence could partly be due to quarantine restrictions, whereas sick days were reported as days feeling too ill to go out. The findings inform on the burden of COVID-19 from health, family, and societal economic perspectives as sick days can affect parental work as well as children's learning and social wellbeing.

2997 (47·8%) of 6264 participants in the case group reported at least one new symptom present 8 weeks after infection and not known before then. Previous smaller studies have reported varied prevalence of symptoms of 4–66%[10] depending on factors such as the number and type of symptoms included. The most prevalent symptoms in our study were headache, loss of appetite, and fatigue. Previous literature has verified these findings with varying prevalence;[10] however, difficulty breathing was not reported previously. The number and severity of symptoms decreased over time, which was also detected previously; however, this study provides more robust evidence of this decrease. It should be noted that new-onset symptoms might also have been experienced in the control group, but the absence of a natural index event in the control group make a complete comparison very difficult.

Compared with male participants, female participants had more symptoms among both the case and control groups. A similar result was found by Molteni and colleagues.[13] Female adolescents generally have a larger burden of complaints and report more symptoms and disease.[33,34] During the COVID-19 pandemic, both female and male adolescents reported more anxiety, depression, and less life satisfaction than before the pandemic; however, this was more pronounced in female participants.[35]

In assessing generalisability, the circumstances of societal pandemic handling might have influenced health outcomes in adolescents. Furthermore, adolescent body-mass index and psychological health might differ between countries.

	At least 2 months (n=5978)	At least 3 months (n=5106)	At least 6 months (n=4250)	At least 9 months (n=1085)	At least 12 months (n=242)
(Continued from previous page)					
Palpitations					
Almost never or sometimes	197 (3·3%)	157 (3·1%)	99 (2·3%)	18 (1·7%)	1–4
Often or almost always	82 (1·4%)	69 (1·4%)	49 (1·2%)	13 (1·2%)	1–4
Trouble remembering or concentrating					
Almost never or sometimes	339 (5·7%)	270 (5·3%)	160 (3·8%)	36 (3·3%)	6 (2·5%)
Often or almost always	335 (5·6%)	300 (5·9%)	221 (5·2%)	53 (4·9%)	8 (3·3%)
Cold hands or feet					
Almost never or sometimes	67 (1·1%)	51 (1·0%)	33 (0·8%)	1–4	0
Often or almost always	61 (1·0%)	56 (1·1%)	38 (0·9%)	12 (1·1%)	1–4
Cough					
Almost never or sometimes	145 (2·4%)	99 (1·9%)	60 (1·4%)	7 (0·6%)	1–4
Often or almost always	72 (1·2%)	52 (1·0%)	35 (0·8%)	1–4	1–4
Chapped lips					
Almost never or sometimes	58 (1·0%)	42 (0·8%)	18 (0·4%)	1–4	0
Often or almost always	92 (1·5%)	80 (1·6%)	53 (1·2%)	11 (1·0%)	1–4
Dizziness when standing					
Almost never or sometimes	204 (3·4%)	162 (3·2%)	106 (2·5%)	23 (2·1%)	5 (2·1%)
Often or almost always	160 (2·7%)	135 (2·6%)	93 (2·2%)	20 (1·8%)	1–4
Light sensitivity					
Almost never or sometimes	123 (2·1%)	93 (1·8%)	56 (1·3%)	5 (0·5%)	1–4
Often or almost always	62 (1·0%)	52 (1·0%)	33 (0·8%)	11 (1·0%)	1–4
Discoloured fingers or toes					
Almost never or sometimes	7 (0·1%)	1–4	1–4	1–4	0
Often or almost always	7 (0·1%)	7 (0·1%)	5 (0·1%)	1–4	0
Extreme paleness					
Almost never or sometimes	25 (0·4%)	16 (0·3%)	9 (0·2%)	1–4	1–4
Often or almost always	10 (0·2%)	8 (0·2%)	6 (0·1%)	1–4	0

Cases are included in the specific time periods if they had sufficient follow-up time since a positive SARS-CoV-2 test. For results with fewer than five individuals per cell, numbers are presented as 1–4 and percentages are masked due to data protection rules from the Danish data authorities.

Table 3: **Duration of long COVID-19 symptoms within the case group**

Differences were found between the groups, with participants with a positive SARS-CoV-2 test having more long-lasting symptoms and sick leave and participants in the control group having more short-lasting symptoms and worse quality of life. Further research should study post-COVID-19 diagnoses, prescribed drugs, and health-care use.

Contributors

SKB conceptualised the study with input from all co-authors. SKB, SDN, UN, and HB are the co-senior authors. SKB and AVC have directly assessed and verified the underlying data. AVC did the statistical analysis. SKB wrote the first draft. All authors provided critical scholarly feedback on the manuscript. All coauthors approved the final version of the manuscript and were responsible for the decision to submit for publication. All authors had access to the underlying data. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

SDN received a research grant from Novo Nordisk Foundation, a travel grant from Gilead, and is on the advisory board for Gilead, GSK, and MSD. All other authors declare no competing interests.

Data sharing
Data will not be made available for others according to Danish data protection legislation.

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