FamilyCoviDD19: results of a cross-sectional study—long-term outcomes of infected and uninfected household members

ABSTRACT

Objective In this study, we aimed to compare long-term physical and mental health outcome between SARS-CoV-2 infected and uninfected household members to differentiate between infection-related and pandemic-related outcomes after about two and a half years of the pandemic. Furthermore, possible differences in the outcome of adults and children and young people (CYP) were of interest.

Design In a cross-sectional study design, we compared the long-term physical and mental health outcome between infected and uninfected as well as between adult and CYP (household members).

Setting The FamilyCoviDD19 study—a serology study in households—was initially conducted to evaluate virus transmission in a close contact setting focusing on households with children and adolescents in Germany. At least 1 year after initial infection in the respective households, a follow-up took place in which the prevalence and type of possible long-term consequences were surveyed on the basis of self-reported information on physical and mental health.

Participant In this study, a total of 533 household members of 146 families participated and responded to our survey, including 296 (55.5%) adults and 237 (44.5%) CYP.

Result The difference in frequency of reported symptoms between infected and uninfected individuals was very moderate, suggesting that the vast majority of reported symptoms were not attributable to a previous SARS-CoV-2 infection. However, regardless of age and infection status, this study showed overall high rates of self-reported symptoms with CYP having fewer long-term sequelae than adults one year after infection. Furthermore, over 50% of those reporting symptoms were not affected in their daily life, with CYPs reporting an even lower percentage compared with adults.

Conclusion CYP are at reduced risk not only to develop symptomatic infection or severe disease courses (previous analyses) but also to develop infection-associated long-term sequelae (this study). Independent of infection CYP reported high rates of neurocognitive, pain, somatic and mood symptoms, which makes the influence of the pandemic itself—including pandemic control measures—decisive.

INTRODUCTION

Since the beginning of the pandemic in December 2019, more than 35 million infections with the SARS-CoV-2 have officially been reported in Germany as of October 2022. The risk for severe acute COVID-19 and poor outcome has been well defined within the last 2.5 years and is mainly limited to the elderly and individuals with certain comorbidities. Children and adolescents usually have mild symptoms or are asymptomatic, with a low rate of hospitalisation, need for intensive care or death. Therefore, medium-term and long-term sequelae of SARS-CoV-2 infections—namely paediatric inflammatory multisystem syndrome (PIMS) and post-COVID-19—play a more important role in overall disease burden for the younger generation.
For adults, post-COVID-19 is defined as persistent or new-onset symptoms lasting for more than 12 weeks after an acute SARS-CoV-2 infection. In contrast to PIMS, for which the WHO has a well-defined case definition, even with numerous studies published on this topic, a clear case definition, reliable risk factors or biomarkers for Post-Covid-19 in children and adolescents are still lacking. There are many commonly described symptoms as headache, fatigue or sleep disturbance, but overall it is still a diagnosis of exclusion. Consequently, reliable estimators on the disease burden of post-COVID-19 are extremely difficult to obtain and control groups are needed to distinguish infection-related sequelae from pandemic-related morbidity and base rates of health problems in society. Literature shows that pandemic control measures (PCM), such as school closures and restrictions of social contacts, have an impact on children’s and adolescents’ mental health and well-being.

The distinction between infection-related and pandemic-related outcomes is essential and would ultimately lead to different prevention strategies or treatment approaches. Thus, the aim of this study was to compare long-term physical and mental health outcomes of SARS-CoV-2-infected (PCR-confirmed or serologically positive) and uninfected household members in our FamilyCoviDD19 study. Furthermore, differences in the outcome of children and young people (CYP) and adult family members were of interest to us.

METHODS

Study design

The FamilyCoviDD19 study is a serology study in households with at least one confirmed SARS-CoV-2 infection and was initially conducted in 2020/2021 to evaluate virus transmission in a close contact setting with focus on children and adolescents.

Participating households with an index infection till February 2021 were invited for follow-up between January 2022 and July 2022, at least 1 year after the infection of the index patient. At this follow-up, we aimed to compare the long-term physical and mental health outcomes between SARS-CoV-2 infected and uninfected household members. By using this cross-sectional study design, we provided data from individuals who experienced the same social and pandemic-related restrictions. Thereby, true infection-related sequelae could be observed more accurately. Additionally, possible differences between the outcome of adults and CYP could be analysed in the setting.

Inclusion criteria

(1) CYP≤18 years in the household and (2) at least one family member who tested positive for SARS-CoV-2 by PCR by the end of February 2021.

A total of 1156 persons matched the inclusion criteria. A total of 628 individuals were enrolled and agreed, the informed consent of our first round was sufficient for this follow-up study visit. After enrolment, participants received the link for an online survey. All questionnaires were age adapted, created with SoSci Survey, and answered online at home before the study visit. For children in secondary school and parents the online-questionnaire was self-reported, for younger children (elementary school or younger) it was parent proxy reported.

Exposure variable

The exposure variable in our study setting was a confirmed SARS-CoV-2 infection since the first study phase (positive PCR or positive serology).

Outcome variables

The outcome variables were mental and physical long-term sequelae, current quality of life and daily activity, as well as the occurrence of burn-out, fatigue and the self-reported state of health. To quantify the mentioned variables, we used several standardised questionnaires.

The long-term sequelae items were categorised into neurocognitive, pain and somatic symptoms, as well as mood, burn-out and quality of life symptoms occurring in the last 7 days. The specific neurocognitive items were: ‘difficulties concentration, memory loss, your mind going blank, listlessness and dizziness’. The pain items were: ‘headache, abdominal pain, myalgia/arthritis, chest pain’. The somatic symptom items were: ‘bowel problems, poor appetite, reduced physical capacity, altered sense of smell, altered sense of taste, sore throat, cough, shortness of breath, heart pounding or racing, trouble falling asleep, sleep that is restless or disturbed, awakening in the early morning’ and the mood symptoms were: ‘sadness, anger, happiness and tenseness’.

The majority of these items were taken from validated questionnaires—namely the Symptom Checklist-90-R (SCL-90-R), the Somatic Symptom Scale (SSS-8) and from a questionnaire about stress and stress management in CYP (SSKJ 3–8 R). Answers of the SCL-90-R were coded on a 5-point categorical scale from ‘not at all’ to ‘extremely’, the SSS also uses a 5-point-ctorial scale from ‘not at all’ to ‘very much’, and the questionnaire about stress and stress management is coded on a 5-point scale from ‘never’ to ‘always’, and the mood items as ‘never’, ‘once’ and ‘multiple times’.

To cover commonly reported infection-associated sequelae after a COVID-19 infection, we supplemented the validated symptom questionnaires with frequently mentioned infection-associated items—in accordance with the surveys of the Office for National Statistics (ONS) in the UK—and adapted the categorical answers of these self-created items.

To objectify fatigue, burn-out and quality of life standardised questionnaires were used. For burn-out, these were the Maslach Burnout Inventory (MBI) and School Burnout Inventory (SBI), for fatigue this was the Paediatric Quality of Life Inventory (PedsQL Multidimensional Fatigue Scale) and regarding the quality of life the Inventory for Evaluation of Quality of Life in Children.
and Adolescents (Inventar zur Erfassung der Lebensqualität bei Kindern, ILK) 26 and parts of the German Quality of Life questionnaire (Fragebogen zur Lebenszufriedenheit, FLZ) 29 30 —namely health, self, relationship with own children, income and partnership, were used. We used age adapted versions of the PedsQL Multidimensional Fatigue Scale and burn-out questionnaire (MBI, SBI).

The PedsQL Multidimensional Fatigue Scale is rated on a 5-point response scale. The items are reverse-scored and linearly transformed to a 0–100 scale, so that higher scores indicate a better quality of life. 31

The MBI is ranged on a 6-point scale 25 and the SBI is rated on a modified 5-point Likert-type scale ranging from ‘not at all’ to ‘very severe’. 26 The individual items of the Inventory for Evaluation of Quality of Life in Children and Adolescents (ILK) are rated on a 5-point scale 28 and the items of German Quality of Life questionnaire (FLZ) are rated on a 7-point scale. 29 30 32 Due to a different scaling and variable questions of these latter two age-adapted questionnaires, a direct comparison of results between CYP and adults was not possible.

In accordance with the ONS survey on self-reported post-COVID-19, we measured limitation of daily life on a 3-point scale—‘no activities limited’, ‘activities limited a little’ and ‘activities limited a lot’. 21 In addition, a self-created item was used to rate the overall degree of current mental distress on a scale similar to the Numerous Analogue Scale, ranging from 0 (‘not at all’) to 10 (‘totally stressed’).

Potential confounders
Potential effect modifiers could be sociodemographic variables (age and sex), comorbidities and body mass index (BMI) as well as SARS-CoV-2 vaccination.

Definitions
In the following, the terms ‘infected once’ and ‘infected twice’ were used for participants with one or two PCR positive SARS-CoV-2 infections and ‘not infected’ for participants who have not knowingly been infected with the novel COVID-19 (self-reported).

‘Infected once’ was used for index patients with an infection till the end of February 2021.

For participants ≤18 years of age, the term CYP is used. All participants >18 years of age were defined as adults.

Laboratory analysis
If desired, a second SARS-CoV-2 serological antibody test was performed at the follow-up visit. Participants were informed of their antibody test results after the study visit.

With the informed consent of the first study phase or after obtaining informed consent from all new participants of an already participating family and/or their legal guardian(s), a sample of peripheral venous blood was collected. SARS-CoV-2 IgG antibodies were detected in all samples by using a commercially available chemiluminescent immunoassay technology for the quantitative determination of anti-S1 and anti-S2 specific IgG antibodies to SARS-CoV-2 (Diasorin LIAISON SARS-CoV-2 S1/S2 IgG Assay).

Statistical analysis
All analyses were performed using Microsoft Excel 2016, IBM SPSS V.28.0 and GraphPad by Dotmatics. All statistical tests were conducted with p<0.05.

Results for continuous variables are presented as means with IQR and categorical variables as numbers with percentages, unless stated otherwise.

Answers to the categorised neurocognitive, pain and somatic symptoms items, as well as mood items, were dichotomised, enabling a comparison of the answer categories ‘none’/‘never’ (coded 0) against all other answer categories (‘any’/‘at least once’—coded 1) by using Fisher’s exact test (two tailed).

In a second step, the responses were evaluated according to their original scaling. Since all neurocognitive, pain, somatic and mood symptoms were planned to be ordinal scaled and not normally distributed, all symptom data were analysed by using non-parametric statistics.

In order to examine associations between potentially confounding variables (ie, age, sex, comorbidities) and the neurocognitive, pain, somatic and mood symptoms Spearman’s r bivariate correlations were performed. Spearman’s r bivariate revealed the expected correlation of age and sex as well as BMI, comorbidities and infection status with many of the queried symptoms (online supplemental table 1).

Non-parametric partial correlation analyses were then conducted between SARS-CoV-2 infection (PCR) and neurocognitive, pain, somatic and mood symptoms, adjusting for age, sex, BMI, comorbidities and vaccination status.

T-test (two tailed) was used to assess changes in the mean score of MBI, SBI, PedsQL, ILK and FLZ.

Comparison of infected and uninfected participants
Analysing the data with respect to the aspect of infection, we compared participants who were infected by the end of February 2021 to uninfected participants, separately for the age groups of CYP and adults. Responses were compared by Fisher’s exact test (two tailed) using dichotomisation. To control for confounding factors Spearman’s r bivariate correlations were performed as well as non-parametric partial correlations as described above. T-tests (two tailed) were used to detect changes in the mean score of MBI, SBI, PedsQL, ILK and FLZ.

Comparison of uninfected participants to those infected once or twice
The subsamples of once and twice infected participants were analysed comparing the results to those of never knowingly infected participants also regarding age group. We evaluated the responses with Fisher’s exact test (two tailed) using dichotomisation. T-tests (two tailed) were used to assess changes in the mean score of MBI, SBI, PedsQL, ILK and FLZ.
Overall comparison of results between CYP and adults
The outcome of reported symptoms was compared between CYP and adults, irrespective of their infection status. Their responses were dichotomised and analysed by using Fisher’s exact test (two tailed).

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS
Demographics
A total of 628 individuals were enrolled and agreed for this follow-up. A total of 95 participants, 25 adults and 70 CYP, were excluded, because they did not complete the questionnaire (figure 1). In total, 290/533 (54.4%) participants were female, 237/533 (44.5%) were ≤18 years of age. Median age of participants was 35 (IQR 13–45), median age of ≤18 years of age was 12 (IQR 8–16) and median age of adults was 44 (IQR 39–49). Of the 237 participants ≤18 years of age, 95 were ≤10 years of age (IQR 5–9) and 142 were >10 years of age (IQR 13–17). The median household size was 3 (IQR 2–4). Comorbidities were significantly less frequently reported by CYP 76/237 (32.1%) than by adults (166/296, 56.1%; p<0.001). 317/533 (59.5%) participants had at least one PCR-confirmed SARS-CoV-2 infection, 200/317 (63%) were infected early in the pandemic before the end of February 2021. A total of 216 participants (40.5%) had never knowingly been infected. Significantly more adults than CYP had a BMI ≥25 kg/m² (44.3% vs 5.5%; p<0.001). A total of 320 of all participants (60.0%) had been vaccinated at least once, 90/237 (38.0%) of CYP and 230/296 (77.7%) of the adults. Overall, 129/149 (87%) of CYP who had a serology at the follow-up were tested seropositive and 210/221 (95%) adults (for full demographics see table 1).

Table 1  Descriptive statistics of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>CYP</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>533</td>
<td>237 (45%)</td>
<td>296 (55%)</td>
</tr>
<tr>
<td>Age, median</td>
<td>35 (IQR 13–45)</td>
<td>12 (8–16)</td>
<td>44 (39–49)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>290 (54%)</td>
<td>123 (52%)</td>
<td>167 (56%)</td>
</tr>
<tr>
<td>Households</td>
<td>146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household size median (IQR)</td>
<td>3 (2–4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected</td>
<td>200</td>
<td>51 (22%)</td>
<td>149 (50%)</td>
</tr>
<tr>
<td>Once (till end of February 2021)</td>
<td>168</td>
<td>45 (19%)</td>
<td>123 (41%)</td>
</tr>
<tr>
<td>Twice</td>
<td>32</td>
<td>6 (3%)</td>
<td>26 (9%)</td>
</tr>
<tr>
<td>Uninfected</td>
<td>216</td>
<td>125 (53%)</td>
<td>91 (31%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>242</td>
<td>76 (32%)</td>
<td>166 (65%)</td>
</tr>
<tr>
<td>BMI ≥25 kg/m²</td>
<td>144</td>
<td>13 (6%)</td>
<td>131 (44%)</td>
</tr>
<tr>
<td>Vaccination</td>
<td>320</td>
<td>90 (38%)</td>
<td>230 (78%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CYP, children and young people.
Neurocognitive, pain, somatic and mood symptoms
Comparison of infected and uninfected participants

Comparing once and twice infected participants (n=200, infection before February 2021) with uninfected (n=216 participants), there was a 6.5% difference in reported symptoms (93.5% vs 87.0%; p=0.032). Regarding limitations through symptoms in their daily life, there was no significant difference detectable for infected and uninfected CYP (27.5% vs 20.8%; p=0.428) or adults (53.7% vs 50.5%; p=0.690).

Regarding each individual symptom, compared ‘none’ versus ‘any’ symptom, infected CYPs experienced significantly more ‘sore throat’ (19.6% vs 6.4%; p=0.013), ‘altered sense of smell’ as well as ‘altered sense of taste’ (11.8% vs 3.2%; p=0.036) and ‘altered sense of taste’ (11.8% vs 1.6%; p=0.008) than uninfected CYPs (figure 2). Comparing once infected CYPs with uninfected, all mentioned items were significant, as well as the item ‘reduced physical capacity’ (28.9% vs 14.4%; p=0.042).

Fisher’s exact test revealed no significant difference in all mood items (sadness (70.6% vs 70.2%; p=1.000), anger (66.7% vs 76.4%; p=0.192), happiness (100% vs 99.2%; p=1.000) and tenseness (68.6% vs 73.5%; p=0.576)) between infected and uninfected CYP. There was also no significant difference in all mood items for once infected CYPs compared with uninfected.

Partial correlation analyses, which were performed to test for age, sex, BMI, comorbidities and vaccination status independent effects of the analysed infection status, revealed a significant difference between infected and uninfected CYP for the items ‘altered sense of smell’ (p=0.037), ‘altered sense of taste’ (p=0.029) and ‘sore throat’ (p=0.016). All other tested items showed no significance after adjusting for confounders (online supplemental table 2).

Analysing individual symptoms for adults, infected participants reported significantly more ‘memory loss’ (59.2% vs 45.6%; p=0.045), ‘altered sense of smell’ as well as the ‘altered sense of taste’ (30.2% vs 14.3%; p=0.005 and 18.1% vs 7.7%; p=0.015) and ‘dizziness’ (28.2% vs 15.4%; p=0.027) (figure 3). For once infected versus uninfected adults only the items ‘altered sense of smell’ and ‘altered sense of taste’ were significant (29.3% vs 14.3%; p=0.013 and 17.9% vs 7.7%; p=0.042). Comparing once infected adults with twice infected, the items ‘your mind going blank’ (33.1% vs 57.7%; p=0.027) and ‘shortness of breath’ (21.2% vs 42.3%; p=0.026) were significant.

Analysing the mood items for adults according to infection, only the item anger showed a significant difference between twice infected participants and once infected participants (84.6% vs 59.2%; p=0.016). All other mood items showed no significant difference between infected and uninfected adults (sadness (61.2% vs 52.7%; p=0.227), anger (62.4% vs 61.5%; p=0.892), happiness (92.6% vs 92.3%; p=1.000) and tenseness (89.9% vs 81.3%; p=0.077)) as well as once infected versus uninfected adults.

Partial correlation analyses, which were also performed for adults to test for age, sex, BMI, comorbidities and vaccination status independent effects of the infection status, revealed only a statistical relation between SARS-CoV-2 infection and ‘altered sense of smell’ (p=0.010) as...
well as ‘altered sense of taste’ (p=0.015). There was no difference in all the other tested items (online supplemental table 3).

The symptom pattern and expression are different between infected CYP and adults. Infected CYP have compared with infected adults significantly more abdominal pain, but infected adults have compared with infected CYP significant more headache, heart pousing or racing, altered sense of smell and awakening in the early morning (figure 4).

Altogether, the overall difference in frequency of symptoms between infected and uninfected individuals was very moderate (around 6% (for CYP 9% and adults 3%)).

Overall comparison of results between CYP and adults
Overall, 482/533 (90.4%) of all participants reported symptoms during the last 7 days before completing the survey, with a moderate but significant difference between CYP and adults (86.9% vs 93.2%; p=0.012; table 2). Thirty-five (7.3%) of all participants reported only 1 symptom, 51 (10.6%) reported 2 symptoms, 41 (8.5%) reported 3 symptoms and 355 (73.7%) reported 4 or more symptoms. The most common symptom in CYP was in 67.9% ‘listlessness’, followed by ‘difficulties concentrating’ (59.7%), ‘sleep that is restless or disturbed’ (36.9%) and ‘trouble falling asleep’ (36.4%) (figure 2). Adults most commonly reported ‘sleep that is restless or disturbed’ (58.8%), followed by ‘difficulties concentrating’ (57.3%) and ‘listlessness’ (56.9%) and (figure 3).

Despite almost all participants reporting at least one symptom, only 64/237 (27.0%) of CYP and 156/296 (52.7%) of adults reported limitations in their daily life caused by these symptoms (p<0.001). The mean score of self-reported overall mental distress was 6.0 of 10.0, without a significant difference between CYP and adults (5.3 vs 6.6; p=0.721).

Regardless of infection status comparing CYP with adults, all mood items were significant. CYP reported significantly more sadness (70.7% vs 58.1%; p=0.003) and anger (73.9% vs 62.2%; p=0.005), but also happiness (99.6% vs 93.6%; p=0.001) compared with adults. Furthermore, they reported significantly less tenseness than adults (76.9% vs 87.2%; p=0.002) (table 2).

Fatigue, burn-out and quality of life questionnaires
Fatigue (PedsQL)
The PedsQL, which was used to screen for fatigue, detected no significant difference in both age groups (CYP and adults) comparing scales of infected with those of uninfected participants as well as those of once infected with uninfected participants. However, twice infected adults had significantly higher scores on the general fatigue scale (GFS) compared with uninfected adults (mean 49.4 vs 62.5; p=0.004). The PedsQL showed significantly higher scores on the GFS for adults than for CYP (mean 60.2 vs 75.1; p<0.001). Similar results were obtained for the sleep/rest fatigue scale (mean 66.0 vs
72.9; p<0.001) and for the Cognitive Fatigue Scale (mean 69.2 vs 77.2; p<0.001) (table 3).

**Burn-out (MBI/SBI)**

The standardised questionnaire for burn-out showed no significant difference for CYP and adults between infected and uninfected participants (SBI for CYP: EXH-subscale mean 7.6 vs 7.1; p=0.354; CYN-subscale mean 5.8 vs 6.2; p=0.492; INAD-subscale mean 3.8 vs 3.8; p=0.812. MBI for adults: EE-subscale mean 16.2 vs 15.4; p=0.431; DP-subscale mean 9.9 vs 9.7; p=0.839; PA-subscale mean 33.3 vs 33.0; p=0.757).

**Quality of life (FLZ/ILK)**

Regarding the standardised questionnaires for quality of life, for CYP the ILK and for adults the FLZ, we found no difference between infected and uninfected CYPs (≤10 years mean 1.2 vs 1.2; p=0.995; >10 years mean 1.2 vs 1.5; p=0.364). In the group of adults, there was no significant difference between infected and uninfected individuals regarding the scores on subscales for ‘self’ (mean 37.5 vs 37.7; p=0.753), ‘relationship with own children’ (mean 39.6 vs 38.8; p=0.361), ‘income’ (mean 38.1 vs 37.4; p=0.473) and ‘partnership’ (mean 37.0 vs 36.2; p=0.469). However, twice infected participants reported lower health scores compared with uninfected (mean 29 vs 36.5; p<0.001).

**DISCUSSION**

In this prospective study, we analysed the long-term sequelae of SARS-CoV-2 infections and PCM in 533 participants of the FamilyCoviDD19 study with either no, one or two confirmed infections. The long-term sequelae were grouped in neurocognitive, pain, somatic, mood, fatigue and burn-out and quality of life symptoms. When analysing data regardless of age and infection status, this study showed high rates of self-reported symptoms. Consistent with international studies, adults reported more symptoms than CYP.

Some symptoms occurred more frequently in infected participants, but the symptom pattern and expression is different between CYP and adults which is in line with data found in literature.
Carfi et al described that 2 months after an acute COVID-19 infection 87.4% of adult participants reported persistence of at least one symptom, most commonly fatigue (53.1%), which is in line with a systematic review and meta-analyses by Lopez-Leon et al identifying fatigue also as the most common symptom among adults (58%). In addition to fatigue or muscle weakness, Huang et al described sleep difficulties and anxiety or depression as most common symptoms 6 months after infection. In our study, significant infection-associated symptoms among adults were altered sense of smell, altered sense of taste and dizziness, which are also frequently reported in current literature.

Symptoms reported significantly more frequently by infected CYP in our study, for example, listlessness and abdominal pain, are consistent with data reviewed by Zimmermann et al. Asadi-Pooya et al reported fatigue, weakness, exercise intolerance and shortness of breath as most common symptoms among 6–17 years at least 3 months after acute COVID-19. The most common symptoms in a nationwide Danish cohort study lasting >4 weeks

<table>
<thead>
<tr>
<th>Item</th>
<th>CYP (%)</th>
<th>Adult (%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>31 (13.1)</td>
<td>206 (86.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>Any</td>
<td>206 (86.9)</td>
<td>20 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Limitation in daily life</td>
<td>173 (73.0)</td>
<td>64 (27.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>140 (47.3)</td>
<td>156 (52.7)</td>
<td></td>
</tr>
<tr>
<td>Concentrating difficulties</td>
<td>58 (40.3)</td>
<td>86 (59.7)</td>
<td>0.357</td>
</tr>
<tr>
<td>Any</td>
<td>134 (45.3)</td>
<td>162 (54.7)</td>
<td></td>
</tr>
<tr>
<td>Memory loss</td>
<td>87 (61.3)</td>
<td>55 (38.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>Any</td>
<td>144 (48.6)</td>
<td>152 (51.4)</td>
<td></td>
</tr>
<tr>
<td>Your mind going blank</td>
<td>100 (69.4)</td>
<td>44 (30.6)</td>
<td>0.335</td>
</tr>
<tr>
<td>Any</td>
<td>191 (64.5)</td>
<td>105 (35.5)</td>
<td></td>
</tr>
<tr>
<td>Listlessness</td>
<td>48 (33.3)</td>
<td>96 (66.7)</td>
<td>0.023</td>
</tr>
<tr>
<td>Any</td>
<td>133 (44.9)</td>
<td>163 (55.1)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>154 (65.0)</td>
<td>83 (35.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any</td>
<td>153 (51.7)</td>
<td>143 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>164 (69.2)</td>
<td>73 (30.8)</td>
<td>0.016</td>
</tr>
<tr>
<td>Any</td>
<td>233 (78.7)</td>
<td>63 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Bowel problems</td>
<td>189 (79.7)</td>
<td>48 (20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>186 (63.5)</td>
<td>108 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td>187 (78.9)</td>
<td>50 (21.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Any</td>
<td>261 (88.2)</td>
<td>35 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Myalgia/arthritis</td>
<td>159 (67.1)</td>
<td>78 (32.9)</td>
<td>0.072</td>
</tr>
<tr>
<td>Any</td>
<td>176 (59.5)</td>
<td>120 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Reduced physical capacity</td>
<td>191 (80.6)</td>
<td>46 (19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>153 (51.7)</td>
<td>143 (48.3)</td>
<td></td>
</tr>
<tr>
<td>Altered sense of smell</td>
<td>218 (92.0)</td>
<td>19 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>222 (75.0)</td>
<td>74 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Altered sense of taste</td>
<td>220 (92.8)</td>
<td>17 (7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Any</td>
<td>248 (83.8)</td>
<td>48 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>203 (85.7)</td>
<td>34 (14.3)</td>
<td>0.201</td>
</tr>
<tr>
<td>Any</td>
<td>241 (81.4)</td>
<td>55 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>177 (74.7)</td>
<td>60 (25.3)</td>
<td>0.542</td>
</tr>
<tr>
<td>Any</td>
<td>228 (77.0)</td>
<td>68 (23.0)</td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>209 (88.2)</td>
<td>28 (11.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Any</td>
<td>227 (76.7)</td>
<td>69 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>195 (82.3)</td>
<td>42 (17.7)</td>
<td>0.107</td>
</tr>
<tr>
<td>Any</td>
<td>226 (76.4)</td>
<td>70 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Heart pouncing</td>
<td>218 (92.0)</td>
<td>19 (8.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>215 (72.6)</td>
<td>81 (27.4)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>212 (89.5)</td>
<td>25 (10.5)</td>
<td>0.075</td>
</tr>
<tr>
<td>Any</td>
<td>248 (83.8)</td>
<td>48 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Trouble falling asleep</td>
<td>150 (63.3)</td>
<td>87 (36.7)</td>
<td>0.857</td>
</tr>
<tr>
<td>Any</td>
<td>184 (62.2)</td>
<td>112 (37.8)</td>
<td></td>
</tr>
<tr>
<td>Sleep that is restless or disturbed</td>
<td>151 (63.7)</td>
<td>86 (36.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>121 (40.9)</td>
<td>175 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Awakening in the early morning</td>
<td>166 (70.0)</td>
<td>71 (30.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>151 (51.0)</td>
<td>145 (49.0)</td>
<td></td>
</tr>
<tr>
<td>Sadness</td>
<td>68 (29.3)</td>
<td>164 (70.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any</td>
<td>124 (41.9)</td>
<td>172 (58.1)</td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>61 (26.1)</td>
<td>173 (73.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Any</td>
<td>112 (37.8)</td>
<td>184 (62.2)</td>
<td></td>
</tr>
<tr>
<td>Happiness</td>
<td>1 (0.4)</td>
<td>233 (99.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>19 (6.4)</td>
<td>277 (93.6)</td>
<td></td>
</tr>
<tr>
<td>Tenseness</td>
<td>52 (23.1)</td>
<td>173 (76.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Any</td>
<td>38 (17.8)</td>
<td>258 (82.2)</td>
<td></td>
</tr>
</tbody>
</table>

*p-value shows difference in frequency of reported symptoms, compares non vs. any, p<0.05 shows a significant difference CYP, children and young people.

<table>
<thead>
<tr>
<th>Item</th>
<th>CYP Mean</th>
<th>Adult Mean</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PedsQL GFS</td>
<td>75.1</td>
<td>60.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PedsQL Sleep</td>
<td>66.0</td>
<td>72.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PedsQL CFS</td>
<td>69.2</td>
<td>77.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value shows difference in the reported mean score of PedsQL (GFS, sleep/rest fatigue scale and Cognitive Fatigue Scale) for adults and CYP. p<0.05 shows a significant difference CFS, Cognitive Fatigue Scale; CYP, children and young people; GFS, General Fatigue Scale; PedsQL, Paediatric Quality of Life Inventory.
after acute COVID-19 were fatigue, loss of smell and loss of
taste, dizziness, muscle weakness, chest pain and respira-
tory problems. Ludvigsson, in his early case report and
systematic review, described that children still report
about fatigue, headaches, difficulties concentrating and
muscle weakness 6–8 months after infection.

However, the overall difference in frequency between
infected and uninfected individuals was very moderate
(around 6% (for CYP 9% and adults 3%)), suggesting
that the vast majority as well as the high levels of reported
symptoms is not attributable to a previous SARS-CoV-2
infection. This is also supported by our data showing
that the outcome of only a minority of queried symp-
toms was significantly associated with SARS-CoV-2 infec-
tion status. Particularly, after adjusting for confounders
there were barely infection associated symptoms. Similar
data was provided by Borch et al who described that symp-
toms as concentration difficul-
ties are not infection-associated symptoms or a mixture
of factors relating to the pandemic and lockdown as a
whole rather than the viral infection itself. Blankenburg
et al also reported on high levels of neurocognitive, pain
and mood items in CYP without significant differences
in the outcome of SARS-CoV-2 seropositive and seroneg-
ative participants, underlining the effect of pandemic-
related measures on adolescents’ well-being and mental
health. During the pandemic, there has been
emerging evidence that children’s and adolescents’
mental health decreased during the pandemic and that
CYP developed emotional and psychosomatic symptoms
due to pandemic factors such as PCM. Comparing
prepandemic data with pandemic data Ravens-Sieberer
et al showed in their COPSY-study that the pandemic
reduced the quality of life and mental well-being in chil-
dren and adolescents and increased the risk of mental
health problems. Further literature implied that CYP
showed symptoms of anxiety and depression as well as a
reduced quality of life, concerning the impact on daily life
for CYP and adults related to the COVID-19 pandemic and
PCM. Lemhöfer et al indicated in their cross-sectional
study that 49% of participants were still limited in their
daily life and had restricted activity 3 months after infec-
tion, but it seemed that in most cases this was not severe
and the impact on quality of life and vocational perfor-
mance was rather low. This is supported by our data on
overall mental distress score as a self-reported item, which
also suggested only a medium high burden (mean 6.0 of
10.0), without a significant difference between CYP and
adults.

Literature showed this as well, children were signifi-
cantly less likely than their parents to report worrying
frequently about the impact of the corona crisis and
many families coped relatively well with the time during
the pandemic. Overall, less than half of those who reported symp-
toms in our study, were affected in their daily life. This
was especially the case in CYP, of which less than a third
compared with more than half of the participating adults
experienced an affected daily life. In addition, infection
status had no significant influence on quality of life. It is
important to consider these aspects when interpreting
studies that rely mainly on self-reported symptoms
without making this distinction. Almost all participants
reported some kind of symptoms when specifically asked,
but only a fraction considers them severe enough to limit
daily activity.

Our results do not call the existence of post-COVID-19
in either CYP or adults into question, as also our data
showed that there are individuals who experience
infection-associated symptoms in the long term. However,
it remained very difficult to delineate post-COVID-19, as
it is still a diagnosis of exclusion with a very heteroge-
nous symptom picture. Regarding the questionnaires of
burn-out, fatigue and quality of life our data showed no
significant difference between all infected and uninfected
participants, regardless of their age—which is remarkable
because discussions repeatedly referred to these items
as long-term sequelae after acute COVID-19—especially
fatigue. Comparing once infected participants with twice
infected, only a few symptoms were significant and only
twice infected adults had significantly higher scores on
the GFS as well as lower health scores on the quality of life
questionnaire compared with uninfected adults, which is
probably caused by a shorter gap to the last COVID-19
infection. This suggested, however, that infection-related
symptoms were temporary and self-limiting in the majority
of cases.

Further studies including control group are needed to
distinguish between infection-associated and pandemic-
associated impacts, because prevention approaches are
very different, if not opposing.

This study is limited by several facts which may impact
the results. First, the questionnaire is based on self-
reported symptoms and is, regarding younger chil-
dren, parent-proxy reported. Second, the number of
participants was relatively small and only households
in and around Dresden, Eastern Saxony, Germany were
observed. Third, it is possible that some of the symp-
toms reported by the CYP group, such as listlessness,
headache or sleep problems are common in this age
group, which could be explained by unrelated external
or psychological factors. Further, it is possible that
the household setting can have an impact on reported
symptoms of family members in one family and that
these symptoms are mutually dependent. Also, we
cannot assume that all uninfected participants did not
have an infection. There will be a certain number of
unreported cases.

Because the results reported here were asked with
respect to the last 7 days before study visit, it is not
possible to describe any dynamics of symptoms during the
follow-up year. However, this method was used specifically
to reduce possible recall bias.

Another bias could be the low response rate of 43%
(553/1156), leading to an overestimation of self-reported
symptoms, as individuals without prolonged COVID-19
symptoms might have been less inclined to complete the questionnaire.

Spearman correlation analyses revealed significant associations between many of the questioned mental and physical symptoms and potential confounding factors, such as age, sex, BMI, comorbidities and vaccination status. Comparing the outcomes between infected and uninfected individuals were, therefore, adjusted for the above-mentioned factors. As we also found a significant difference between adults and CYP, regarding BMI, comorbidities and vaccination status, adults were potentially more affected not only because of their age but also because of pre-existing conditions and BMI.

Furthermore, it was difficult to rely only on serology results, as at that time point vaccinations were available for nearly all participants and because not every participant did a blood testing. Thus, our results are not depending on serology results, but on confirmed PCR results.

Overall, we found that CYP can experience long-term sequelae, but with fewer symptoms, less limitations in daily life and at a lower incidence than in adults. In both, CYP and adults, only a few symptoms were significantly associated with a positive SARS-CoV-2 infection status; this was the case even in twice-infected participants compared with uninfected or only once infected participants. Furthermore, we found higher rates on reported symptoms and limitations in daily life compared with preponderance data. These results underline the impact of non-infection-related factors such as the pandemic itself including PCM. The interval from the past infection plays a role in the severity and number of symptoms still present. To conclude, CYP are not only at reduced risk to develop symptomatic infection or severe disease courses but also to develop infection-associated long-term sequelae. Overall, independent of infection CYP reported high rates of neurocognitive, pain, somatic and mood symptoms, which makes the influence of the pandemic itself—including PCM—decisive.

Contributors TSH acquired participants, collected participants data, performed statistical analysis, wrote the manuscript and prepared tables 1, 2, 3, figures 1, 2, 3, 4 and supplement 1, 2, 3. JB acquired participants, collected participants data, helped with statistical analysis, helped with interpretation of the data and helped to write the manuscript. MD, SD, PC, JS and CG acquired participants and collected participants data. AB and MW helped with statistical analysis and helped with interpretation of the data. JPA designed and supervised the study, acquired funding and helped to write the manuscript. All authors reviewed and approved the manuscript before submission.

Funding This study was supported by a grant from the Federal State of Saxony, grant name PAE05AVCOVID.

Competing interests AD, RB and JPA report grants from Federal State of Saxony during the conduct of the study; A6 reports grants from the Deutsche Forschungsgemeinschaft (DFG) 2773 and 2698/2. The other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee of the Technische Universität (TU) Dresden (BO-EK-342072020). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified individual participant data will be available, in addition to study protocols, the statistical analysis plan and the informed consent form. The data will be made available on publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to corresponding author (theresa.horst@uniklinikum-dresden.de).

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Theresa S Horst http://orcid.org/0000-0003-1029-6689

REFERENCES


